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Economic consideration of the implementation of biotechnological therapies in chronic diseases

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Thank you words

The Department of Health Economics at the Corvinus University of Budapest was a wonderful research environment. During my PhD years I had the opportunity to work with an excellent team, which work -- and cooperation -- finally led to this PhD dissertation. I was excited by the tasks, challenges, collaborations with experts; these years were not a “usual Ph.D.-life”. I also had the pleasure to be invited to give presentations on conferences and publish papers in peer-reviewed journals.

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1 FOREWORD

My dissertation is focused on the economic consideration of the implementation of biotechnological therapies in certain chronic diseases, including their economic, financial and budgetary impact.

The purpose of this dissertation is to provide more knowledge and insight on this topic in the Central Eastern European (CEE) region, focusing mainly on Hungary, by exploring evidences using methods from the fields of health economics and health technology assessment (HTA). Furthermore, it provides evidence for further policy discussion on the implementation of these therapies. Although this dissertation is mainly focused on Hungary, its relevance is not exclusive for the Hungarian context; the topic is relevant for other countries facing similar challenges with introduction of biological treatment as well, especially in the CEE region.

The dissertation was written in manuscript based style and chapters are organised around the main objectives. The body of this dissertation comprises five autonomous publications. Chapters treat separate elements of my research program and include four discrete articles (which have been published in peer reviewed journals) (Baji et al, [2014]); (Balogh et al, [2014]); (Herédi et al, [2014]); (Brodszky et al, [2014]) and a book chapter (Balogh, [2014] In: Brodszky, [2014]), therefore it differs from the usual design that consists of Background, Objectives, Methods, Results and Conclusions. The first chapters (**Chapter 1, 2 and 3**) state the research questions and describe the theoretical background of the thesis and integrate the thesis across the different manuscripts. The purpose of this section is to draw out the importance of the topics, and the degree why this is relevant in the terms of global health. In **Chapter 4** I present a book chapter and an article, both of these deal with the statistical analysis of efficacy and safety of biologicals from a different point of view. **Chapter 5** presents a non-interventional, cross-sectional survey in the topic of economic burden regarding psoriasis in Hungary. **Chapter 6** continues with

the topic of psoriasis, analysing the relationship between utility and standard psoriasis related quality of life scales. **Chapter 7** presents data on the budget impact implied by the reimbursement of biosimilar infliximab over three years in six CEE countries. The last, concluding chapter (**Chapter 8**) includes a discussion on how the findings of the thesis provide a distinct contribution to knowledge in the research area.

It is important to note here that the methodological framework related to the economic effect of diseases is largely synthetised and can be considered standard, therefore I will not attempt to perform a critical analysis of these methodological tools. My dissertation is a niche work, taking a step back to connect the methodological questions regarding information needs in less researched fields of health care, while also taking a step forward to provide results regarding questions related to biological therapies which may arise during the registration of a new drug untill the sale. With this purpose, my dissertation is among the first papers to provide data about the implementation of biologicals in chronic diseases.

2 BACKGROUND OF THE DISSERTATION

2.1 RELEVANCE OF THE TOPIC

Biopharmaceutical drugs have been available for more than 20 years, the agents revolutionised the treatment of chronic diseases in several area of the medicine. However, these have an increased effect on the societies due to their high costs, thus the benefits also bring challenges and concerns about the value for money. There is an increased importance of health economic analysis to evaluate the unit expenses and also the unit health gain. Biologics represent about 2-5 percentage of the drug budget, but this is also a fast-growing segment of the pharmaceutical market. Biological treatments are usually expensive and lead to increasing pharmaceutical expenditures (Chen, [2006]). On one hand, there is a clinical demand for wider use of biologics, and thus preferences for the increasing use of these drugs. On the other hand, there is also certain limitation in terms of resource restrictions on financing (affordability) which means that the number of patients clinically eligible for biologic therapy is higher than the financing capacity of the funder. Therefore a gap exists between what is therapeutically possible and what is economically affordable.

Despite the centralised drug registration and clinical guidelines on the European Union level, there is variation in financing practices and treatment, and also in the patient's access to these agents across Europe (Laires, [2013]). The CEE region cannot be considered as a homogeneous group either from this perspective, but the financial burden of biological treatment puts a common pressure on the health care systems in these countries (Farfan-Portet, [2014]). Furthermore, the growth in the number of patients with chronic diseases is accompanied by the growth of the health care expenditures (Burisch et al, [2013]). Hence, health care systems have to live up to the challenges imposed by the continuously changing economic environment, which is becoming even more hectic in the recent years. The satisfaction of patients as conscious purchasers has become the main goal.

There is limited data on the above mentioned topics in Hungary and in the CEE region, and also the proportion of patients treated with biological vary significantly between the CEE countries. Therefore with this dissertation inter alia I would like to provide country specific data and analysis to expand the relevant literature. In order to plan interventions, data-supported facts derived from well-established, reproducible, reliable analysis are necessary.

2.2 THE SCOPE OF THE DISSERTATION

2.2.1 Biotechnological innovation in healthcare

Technological innovation has brought remarkable development in the health care sector over the past decades. Demand for health care services has increased (Davis et al, [2005]), but this growth and health care spending affects the economies in different ways. On one hand, the increased demand results in the rising of health care costs, and we can state that there is a gap between health, economic productivity and national prosperity. This situation even worsened during the economic crisis. On the other hand, in the recent years, breakthroughs in various fields have contributed greatly to the quality improvement in health care and the patient's conditions, including biological therapies. Now, we have found ourselves in the midst of yet another transformation in biomedical science.

We can observe differences between countries; this may be due to country specific features, for example different health care needs, economic conditions and structures of health systems (Shepherd et al, [2007]). Here should be mentioned that these conditions may result in suboptimal use of treatments and inequities in the patients' access, which means unnecessary expenditures and inadequate health outcomes. A tendency can be observed that the countries which have alredy finished the epidemiological transformation concentrate on layered medicine in the hope of successfully treating the growing burden of chronic disease (OECD, [2013]). Low and

middle income countries such as Hungary or certain countries from the CEE region tend to concentrate more heavily on efforts to control infections or common diseases (heart and vascular disease, obesity), therefore only richer countries can invest and benefit from the technological innovation.

2.2.2 Scarcity of resources, increasing pressure on the societies

Health policy makers try to maximise the utility in social level, subject to scarce resources. However, in the progress of health financing decisions, the use of evidence-based medicine and the exact results by researchers play an increasingly wide role. Furthermore, during the last decades health technology assessment developed as a tool to support this aim and encourage the efficient use of health technologies (Johnson et al, [1999]). The high societal costs of chronic diseases and new biological therapies have led healthcare payers and providers to increase their level of attention on this condition, particularly in the current period of increasing budget constraints. Economic and cost-effectiveness evaluations became important features.

Technology became manageable in a way to support health care while health policy makers, payers, leaders have a demand for well-founded information about whether and/or how to develop technology (Sorenson et al, [2008]). In order to plan interventions, data-supported facts derived from well-established, reproducible, reliable analysis are necessary, HTA can reflect to this demand. Beyond economic reasons, clinical practice also plays a key role in biologics' access. Most countries have issued clinical guidelines for treatment of the diseases, defining which patients are eligible for the use of biologics. It is not our task to make decisions, the aim is to provide accurate, cost effective and reliable data. This is crucial in the field of financing as well. Health economic research should provide and adapt the results to local health care settings. More and more information is required about clinical efficacy and safety of a new medical technology: systematic reviews, meta-analysis, epidemiology of the given disease, disease burden, results from

health economics analysis and patient reported outcomes. Local data are required to be used in industry economic dossiers for submissions. However, there is a limited experience in most of the countries to analyse published randomised controlled trials (RCTs) or other results (patient level study data from trials is not required in CEE), therefore there is a shortage of input data to local health economics analysis (costs, unit costs, heath status, and quality of life).

2.3 THE IMPACT OF THE HEALTH SECTOR ON THE SOCIETY

2.3.1 Health care spendings

Total health care related spending as a proportion of gross domestic product (GDP) has started to increase during the last years, after a decrease in many OECD countries under the crisis. The rapidity of growth remains below the rates before the crisis in many countries (OECD, [2014]), reductions have been driven mostly by price cuts. In Europe, health spending continued to fall in 2012 in the CEE region; in South and South-West Europe equally.

Table 1. GDP and expenditure on health care in CEE countries, 2011

Country	GDP per capita (current US$)	Total health expenditure per capita (current US$)	Total health expenditure (% of GDP)	Public health expenditure (% of GDP)	Private health expenditure (% of GDP)	Out-of-pocket health expenditure (% of total expenditure on health)
Bulgaria	7,287	522	7.3	4	3.2	43.2
Czech Republic	20,580	1,507	7.4	6.2	1.2	14.7
Hungary	13,909	1,085	7.7	5	2.7	26.0
Poland	13,382	899	6.7	4.8	1.9	22.4
Romania	8,539	500	5.8	4.7	1.2	20.3
Slovak Republic	17,760	1,414	2.3	5.6	2.3	22.5

Source: The World Bank DataBank, available: 16/11/2013

http://databank.worldbank.org/data/home.aspx

Overall health spending accounted for 9.3% of the GDP on average across OECD countries in 2012 (OECD, [2014]). The spending on health care varies among individual CEE countries (see Table 1) in 2011. There are countries such as Hungary with high per capita pharmaceutical expenditure (Gulácsi et al, [2014]pp2). Yearly growth rate was high in Romania from 2007 to 2008. Both per capita expenditure and its growth rate were stable in the Czech Republic in this period. Poland started from a low spending level and in 2011 its drug budget was still much lower compared to other CEE countries. Trends regarding Bulgaria are difficult to analyse due to lack of data (World Healthcare Outlook, [2013]).

Health care is a very costly industry sector. Estimations by the OECD states that global health care spending will be on average 10-11% of the global GDP in 2014 (OECD, [2014]). As it was alredy mentioned, the main cause contributing to the growth of health care expenditures is due to various tendencies such as demographical change, i.e. aging of the industrialised world; rising incidence of chronic diseases; growing expectations of patients. The demand for growth in health care expenditures will place high pressure on governments. Despite the economic stabilising period in Europe there is a need for continuing debt reduction in some of these markets. It is important to note that the effects of health care costs on one sector are likely to affect outcomes in other sectors (Sommers et al, [2005]).

The rising health care costs can cause reduction in the health care spending by raising taxes or reducing investments (Pauly et al, [2003]). Governments, particularly in Europe have attempted to apply various tools, e. g. reference pricing, positive or negative lists or volume contracts (Gulácsi et al, [2004]). This can be attributed to the fact that decisions about pricing and purchasing are now taking place in the context of cost and value rather than demand for innovation (Kobelt et al, [2009]). New and especially expensive technologies must demonstrate the benefits which can be gained by their usage more clearly. This is why it is so important to provide updated information regarding the mentioned biological therapies in all fields, such

as effectiveness, cost-effectiveness and quality, efficacy, safety (Boncz [2006]).

Here should be mentioned that health care spending also has a positive effect on the societies by raising incomes and by increasing the labor market productivity of workers in case of well-informed health policy makers and knowledge of local and country-specific data (Murphy et al, [2006]).

2.3.2 Biological drugs in Hungary

Taking into account Hungary, as an example, analysis of the first five years (2006-2010) of reimbursed biological treatment based on the National Health Insurance Fund Administration (NHIFA) database[i] revealed important economic aspects (patient numbers, costs, market share, and first choice treatment) of biological uptake in the country. The number of patients being treated with biological therapy showed a remarkable growth. While in 2003 there was only one patient and less than one thousand in 2006; in 2010, 5994 patients were treated with biologicals. In case of disease types we can see increasing numbers (see Table 2). However, a compulsory systematic data collection (electronic patient registry on the national level) monitoring clinical aspects and employment status of patients with biological treatment was introduced only in 2012 and results have not been published so far. According to a presentation held by a Deputy Head of Department from the NHIFA[ii] 11,665,920,003 HUF (39,545,491 €)[iii] was spent on biological therapies in outpatient care during the first six months in 2012. Further information is required regarding treatment with biologicals.

[i] http://www.oep.hu/pls/portal/docs/PAGE/SZAKMA/OEPHUSZAK_EUSZOLG/TIBI%20EGY%C3%89B/SZAKMAI%20ELLEN%C5%90RZ%C3%89S/BIOL_TH_2006_2010_PUBLIKUS4.PDF

[ii] http://teteles.oep.hu/downloads/orszagos_130528_karsay.pdf

[iii] 1 EURO= 295 HUF Source: http://www.mnb.hu/arfolyam-tablazat?query=daily,2012-06-11

Table 2. Number of patients with autoimmune diseases treated with biological drug between 2006 and 2010

	2006	2007	2008	2009	2010
Psoriasis	27	67	154	428	682
Arthiritis psoriatica	53	121	239	431	644
Spondilitis ankylopoetica	151	318	540	843	1082
Rheumatoid arthritis	629	1188	1946	2450	3148

Source: NHIFA 2012[iv]

Thus, it can be stated that despite the widespread availability of biological treatments, there is a shortage of health economics analysis in this field. Furthermore, data on chronic diseases is lacking in the CEE region. Due to the lack of data based on national studies, CEE countries are absolutely dependent on results from abroad.

Therefore, in my dissertation I will focus on the economic evaluation of applied biological therapies in chronic diseases in the CEE region mainly in Hungary.

[iv] http://www.oep.hu/pls/portal/docs/PAGE/SZAKMA/OEPHUSZAK_EUSZOLG/TIBI%20EGY%C3%89B/SZAKMAI%20ELLEN%C5%90RZ%C3%89S/BIOL_TH_2006_2010_PUBLIKUS4.PDF

2.4 APPROPRIATE DECISION-MAKING IN THE MARKET OF HEALTH CARE

2.4.1 Rising demand for data

Today's healthcare organisations are plagued by rising costs; hence risks and opportunities are changing. There is a need and also a pressure for more effective decisions by governments and by decision makers (Bouckaert [2008]). Government leaders and health-policy makers have to implement measures to boost efficiency and manage funds better while ensuring superior quality of care and patient satisfaction (Boland et al, [2000]).

The demand for greater performance and accountability is a key issue nowadays. The phenomenon of aging, when people require more and longer care (Laires et al, [2013]); the problems related to chronic diseases among patients from all generations such as diabetes, heart disease and asthma is one of the most critical issues for health care systems (Farfan-Portet et al, [2014]). At the same time, more new treatments appear than ever before. These pressures all lead to one outcome: escalating costs (Busse et al, [2002]). Several methods regarding performance, operation and clinical evidence are available; however, we can observe significant difference in the number of separate systems, and country specific conditions— patient admissions and discharges, financial, human resources (Gulácsi et al, [2012b]).

With measuring the inputs and outputs as far as possible from grassroots, taking into account health system features, applied methodology, institutional structure (Pawson-Tilley, [2007]), patient's expectation and preferences; in the given society better access and complex understanding can be provided. (Rossi, [2004]). Providing stakeholders with better information, linking financial and clinical planning is crucial (Bouckaert, [2008]). Treatments need to be based on local, up-to-date and real time data – that is, as quickly available as it is needed for better decision-making.

2.4.2 How can we provide accurate and reliable country specific data?

Within the last decades, many European countries established HTA programmes to inform decision makers (Hutton et al, [2006]). The main aim is to provide policy-makers and other key decision-makers with evidence-based information regarding medical, social, economic and ethical issues including costs (Anis et al, [1998]), cost consequences and benefits of new and existing treatments with available alternatives, based on a systematic and multidisciplinary assessment process.

This can help to maximise health for a given health budget, and to make the best treatment choices. (Cutler et al, [2001]). Applying the methods and assessments which are offered by HTA we can support those services that offer the greatest value for money and impact on health outcomes. Furthermore, when international decisions or guidance may not be relevant to local circumstances, HTA should be addressed in order to achieve the best result (Goldman et al, [2005]). It is not our task to make decisions, but we can support it with reliable data on a local level.

The type and quality of evidence required and reviewed varies across countries. Some bodies require only effectiveness data, while others also need cost–effectiveness evidence (Martelli et al, [2007]). In 2004 in Hungary the Transparency Secretariat (TS) was formed at the NHIFA and Ministry of Health to assess the therapeutic value or clinical benefits of drugs and to compare the results with already existing therapies so as to prepare decisions on reimbursement applications (Gulácsi et al, [2009]). The majority of European countries apply the method established by the National Institute for Health and Care Excellence (NICE). This means that a medicine can become financed if it fulfils a financial threshold expressed in cost/quality-adjusted life-year (see in 2.6.3).

In Hungary, the Office of Health Technology Assessment (OHTA) has the task of providing an organisational framework for technology assessment that

serves as the basis for the medicine subsidy approval policy of the NHIFA (Hevér – Balogh, [2013]pp17). In 2012, OHTA became part of the National Institute for Quality and Organisational Development in Healthcare and Medicines and was re-named Technology Appraisal Head Department (TAHD) (Gulácsi et al, [2014]). TAHD carries out assessment, a formal procedure including the evaluation of the submitted economic dossier which is a legally required as part of each company's submission. To summarise, it can be established that using HTA process results in greater efficiency in decision-making.

2.5 THE CONCEPT OF ECONOMIC EVALUATION AND PHARMACOECONOMIC EVALUATION AS A TOOL OF PERFORMANCE MANAGEMENT

Until now I aimed to collect the main problematic issues of health economics related to the implementation of a new technology in the field of biologics, and provided a short and concise theoretical background supporting the understanding of the concept of my dissertation and highlighting its actuality. However, there are some definitions which are required to be defined in order to develop a common conceptual framework.

Traditionally, welfare analysis is the basis for economic evaluation. While the individuals want to maximise their utility, the social systems and governments operate as a welfare maximiser. Under perfect conditions and competitive market, the allocation of the resources would be satisfying (Cunningham et al, [2001]). However, in the market of health care services the existence and increased appearance of the scarcity is prominent. Many options are available to decrease the scarcity in the health care systems (Drummond et al, [2005a]): rationing, increasing expenditure, greater efficiency, voluntary restraint and inactivity.

Pharmacoeconomic assessments are always comparative; the product in question is compared with some comparators. The cost-effectiveness method

was developed as a primarily used approach in the field of health economics (Drummond, [2005b]). It proved to be successful in limited budget setting of the health care systems. In this way pharmacoeconomic assessment operates as a tool of performance management.

With the development of evidence-based medicine more and more reliable methods became available. Economic evaluation in health care consists of the analysis of efficacy, effectiveness, efficiency and availability. Analysis of efficiency is often called as the economic analysis. As it was already mentioned, this refers to the comparison of alternative technologies in terms of costs and consequences and the goal is to maximise the utility. The advantage is that with these information we can inform policymakers (Briggs, [2000]), participants and steakholders in the health care system. Clinical significance and relevance of the outcome indicators should be established and, if necessary, supported with data.

2.6 METHODS OF ECONOMIC EVALUATION USED IN THE THESIS AND THEIR THEORETICAL BACKROUND

Nowadays, the focus of health economics decision-making has shifted from a one scale approach to multiple scale approaches. There is a variety of approaches to economic evaluation. It is rarely possible or necessary to identify and quantify all costs and all benefits, and the units used to quantify these may differ (Briggs-Sculper, [1995]). While the costs exceed the available resources, we need information as an input for resource related decisions, which are intended to provide the highest achievable health related gain. Two questions should be mentioned regarding this. Is it affordable to financing a given technology? Using this technology can we reach the efficient resource allocation? Cost-effectiveness analyses addresses which technology can produce one unit of a given outcome at the lowest possible price. Budget impact analyses examine the financial burden and gain in connection with a given technology. A cost-effectiveness analysis

would typically assess ‘value for money’, providing data for resource allocation decisions; while a budget impact analysis would assess affordability and issues relating to financing the service.

2.6.1 Types of economic evaluation

In the market of health care the resources to spend are scarce. From 2004, since joining the EU, there is health care regulation in place requiring to present cost effective results. Therefore there is a need for more and better information. To provide this information we use one of the existing economic-analysis. (Drummond, [1992]). When we arrive to a decision we are communicating information to resource allocation related issues (Weinstein et al, [1990]). Main types of economic analysis include the following (Tarricone et al, [2006]):

- Cost-minimisation analysis: a determination of the least costly among alternative interventions that are assumed to produce equivalent outcomes
- Cost-effectiveness analysis (CEA): a comparison of costs in monetary units with outcomes in quantitative non-monetary units (Towse et al, [2002])
- Cost-utility analysis (CUA): a form of cost-effectiveness analysis that compares costs in monetary units with outcomes in terms of their utility, e.g., in QALYs
- Cost-consequence analysis: a form of cost-effectiveness analysis that presents costs and outcomes in discrete categories
- Cost-benefit analysis (CBA): compares costs and benefits, both of which are quantified in common monetary units

Table 3. Different Types of Economic Analysis

	Valuation of costs		Valuation of outcomes
Cost Minimisation	€	vs.	Assume same
Cost Effectiveness	€	÷	Natural units
Cost Utility	€	÷	Utiles (e.g., QALYs)
Cost Benefit	€	÷ or -	€

Source: Gulácsi, 2007

Below I list and define the different types of economic evaluation. The suitability of any of these depends upon the purpose of an assessment and the availability of data and other resources (Goodman, [2004]). In this field we mostly assess the cost-effectiveness of a medicine or intervention by comparing the costs and outcomes with a relevant comparator (Weinstein, [1996]). In addition, cost-utility analyses, and cost-benefit analysis are the most discussed forms of analysis; therefore I will briefly provide information about these as well.

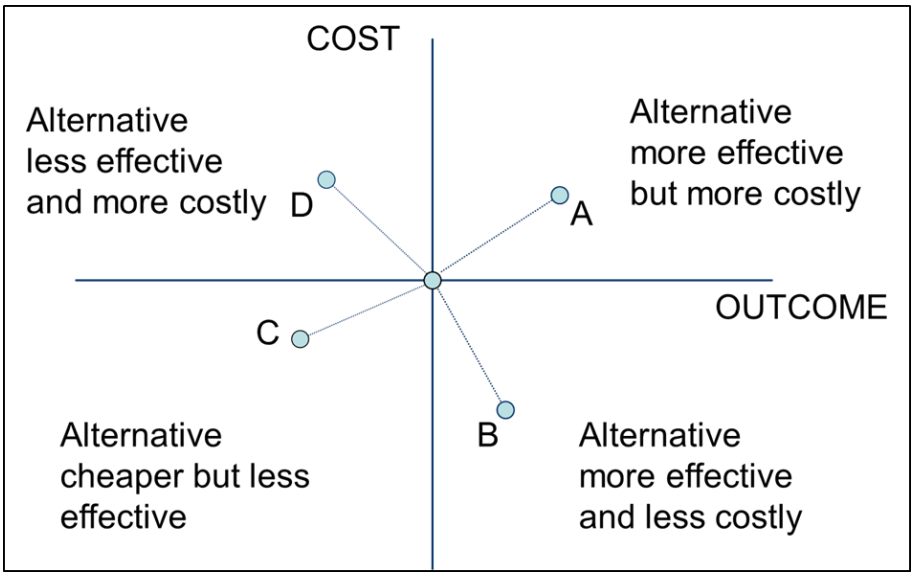
- Cost-effectiveness analysis (CEA): In CEA the outcomes of the alternative treatments are measured in the same non-monetary (natural) unit (e.g. life-years gained, reduction in diastolic blood pressure), so the input and output related to a 'new' and 'current' health technology are compared, i.e. comparing costs of the technologies with their consequences (Eddy et al, [1992]). Results are expressed in terms of an incremental cost-effectiveness ratio (ICER) which shows the incremental costs for one unit outcome gain:

$$ICER = \frac{Costs_{new} - Costs_{current}}{Outcome_{new} - Outcome_{current}}$$

The result of a CEA can be plotted on the cost-effectiveness (CE) plane (see in Figure 1). The plane is divided into four quadrants indicating four possible situations in relation to the additional costs and additional health outcome effects of a new therapy compared to the standard therapy (Drummond, [1996]).

- If a new therapy is cheaper and more effective than the other (quadrant South-East on the CE plane), then it is clearly the treatment of choice and is said to be dominant.
- If a new therapy is more expensive and less effective than the other (North-West quadrant on the CE plane), the situation is clear again, the new therapy is dominated by the other.
- However, if a new therapy is more costly but also more effective than the other (North East quadrant on the CE plane) then the decision is no longer clear. A decision must be made concerning whether the cost difference between two health technologys is justified by the difference in effectiveness.
- If a new therapy is cheaper but less effective than the other (South-West quadrant on the CE plane) then the question arises whether a certain efficacy loss is worth to sacrifice in order to gain some cost saving (especially if the loss is insignificant or small).

Figure 1. The cost-effectiveness plane



Source: Drummond, 2009

The incremental cost-effectiveness ratio can then be compared with a threshold incremental cost-effectiveness ratio, which reflects the maximum cost per unit of outcome that a health care payer is willing to pay for a medicine. Below the threshold, value is likely to be accepted by a payer (Drummond, [2009]).

- Cost-utility analysis (CUA): a form of cost-effectiveness analysis that compares costs in monetary units with outcomes in terms of their utility, usually to the patient, measured, e.g., in QALYs. CUA is a type of cost-effectiveness analysis that incorporates both quantity and quality of life by estimating the cost per QALY gained as a result of a treatment. QALYs are calculated by weighting time (years of life) with a quality adjustment, called 'utility' which represents the relative preference that individuals or society place on different states of health (Gulácsi, [2012a]). CUA has two major advantages compared to other types of economic evaluation: besides combining life expectancy and overall quality of life aspects, the use of a standard outcome measure makes it possible to compare treatments in

different disease areas that may have quite distinctive clinical outcome measures (Kobelt, [2002]). A health care will need to compare different treatments to make expenditure and prioritisation related decisions within its budget, across diseases and indications. That is why organisations in countries where economic evaluation is used to provide information for decision-making prefer cost-utility analysis to other types of analysis. Economic evaluation in itself does not give a value of the benefit but only estimates the relative inputs required to reach a given outcome – comparison is an essential feature of resource allocation.

- Cost-benefit analysis (CBA): is also a comparative assessment of all the benefits and all the costs regarding a technology. CBA estimates the equivalent money value of the benefits and costs to the given technology to establish whether they are worthwhile. The valuation of benefits and costs should reflect preferences revealed by choices which have been made. The unit of measure in the field of healt-economics is the quality-adjusted life-years (QALY).

2.6.2 Cost input for economic evaluations

For the evaluation of the above mentioned analysis, we need cost data. Accordingly, economic evaluations include two main components: (1) inputs defined as resources used or lost (e.g. direct and indirect costs); (2) outcomes measured as health improvements which can be expressed as (a) disease measures such as events avoided (e.g. stroke or death in cardiology), patients successfully treated (e.g. number of cancer patients in complete remission); (b) survival measured in terms of lives saved or life-years saved; (c) quality-adjusted survival, expressed as quality-adjusted life years (QALYs); (d) monetary value, expressed as willingness to pay for the improvement (Gulácsi, [2012a]). In the subsequent part I will discuss the theoretical background of cost data.

2.6.2.1 Measuring cost-of-illness

Cost-of-illness (COI) was the first economic evaluation technique used in the field of health economics (Drummond, [2009]). COI studies evaluate the economic burden, cost drivers, resource categories in which costs are congregated by a health problem caused on the population and are useful for public health as they can provide information about the importance of a given disease (Arrow-Lind, [1970]), which must be considered by all stakeholders, including patients, clinicians, and third-party payers when deciding on the allocation of scarce resources (Mihaylova et al, [2010]). For employers and patients, these can show which diseases have an especially large impact on their projected expenditures.

It should be noted that cost of illness studies serves a different purpose than other health economic evaluations (e.g. CEA, CBA) which are focused on evaluating the costs of interventions rather than estimating the cost of a particular disease. Furthermore it can be a good basis for further CEA or CBA. The disease burden or cost of disease analysis is the most commonly used health policy analysis method. It always presumes the hypothesis that the emerging cost is the expenditure that resurfaces as profit in case of a positive result (Gulácsi, [2007]). With these data we can inform pharmaceutical reimbursement decisions.

2.6.2.2 Types of costs related to illnesses

Scarcity of resources forces us to choose; a situation arises where we must decide which interventions to finance. During cost calculation, we take into account all the identified changes in resources, their measurement and definition of value, that will be used (Mihaylova et al, [2010]).

Costs can be categorised in the following way:

- Direct costs: resources used during healthcare service that have direct costs during the attendance (Hoffmann et al, [2002]). Direct costs can be further divided into direct healthcare and direct non-healthcare costs.

  a. Direct medical costs: direct healthcare resources that are directly necessary for the healthcare intervention. Direct costs (resources) are costs emerging and used during the process of healthcare servicing, such as laboratory costs, tools, equipment, medicine, salary of doctors, visits, the daily costs of the maintenance of hospital beds (Smith et al, [1996]).

  b. Direct, non-medical costs: direct, non-healthcare type resources that are necessary for healthcare interventions (Brouwer et al, [1997]). Traveling and accommodation costs of patients emerging during the use of healthcare services and the costs of tending children and the sick at home, or transforming one's apartment in case of disability all fall into this category. Costs of special diets in case of sickness also belong here (Gulácsi et al, [2005]).

- Indirect costs: resources in this group are not directly induced by the use of healthcare services (Liljas et al, [1998]), but they derive from patients' changed circumstances due to their condition (Lofland et al, [2004]). Patients' time, their absence from paid or non-paid jobs and the value of free time and its expression in terms of money (Brouwer et al, [1999]). Different methodological approaches calculate the length of being away from work in different ways (human capital approach, friction cost approach) (Koopmanschap et al, [1996]) however, there is an international consensus about the cost of absence from work per unit of time: the calculation takes the average great gross income of the given year (Koopmanschap et al, [1995]) (average gross income plus the taxes and contributions paid by the employer).

- Emerging future costs: costs emerging in the future due to the healthcare intervention, such as permanent damage to health following medical therapy, costs of following lawsuits and insurance.

2.6.3 Estimating utility in economic evaluations

In connection to the possible consequences of an illness, there are two major factors that must be considered: how does it affect lifetime and the quality of life? (Mason et al, [1994]) At health economic evaluation, the same question emerges, first in connection to the benefits expected from different therapies (healing and preventive procedures, screenings): does it provide a longer life span and will concerned parties feel better? (Ubel et al, [2000])

In economically developed countries, the chance of survival has increased in illnesses that used to end in early death (such as infectious diseases), and the population's life expectancy at birth has become higher and is continuously increasing. People live longer and many of them spend years suffering from a chronic disease. This is why the analysis of the society's state of health and quality of life related to health has become more accentuated besides mortality indexes. In case of therapeutic interventions we can also see that besides life-saving, life span increasing procedures, researches aimed at improving quality of life related to health are gaining more territory. Methods are needed with which health related quality of life benefits can be measured reliably.

The most commonly used method in the field of health related quality of life (HRQL) is the QALY approach (Fitzpatrick et al, [1992]). There is no doubt that a life year spent in perfect health is more valuable to people (1 life year spent in perfect health = 1 QALY[v]) than a life year spent not completely

[v] QALY (Quality-Adjusted Life Years) is the universal measurement tool of health benefits that enables us to compare different diseases and health technologies. It unifies lifespan (mortality) and life quality (morbidity) changes in one index. When calculated, health

healthy (Péntek, [2007]). QALYs can be compared across diseases and thus support choices for resource allocation within an overall health care budget. Economic evaluations require data on HRQOL on preference-based measures that capture preference weights (called utility, in terms of desirability) about values of different health states. Also, in many countries utility measures are required for reimbursement decisions. Consequently, QALYs are the outcome measure preferred by many government bodies and other authorities that require economic evaluation before recommending that be provided utilising public funds (Kobelt et al., [2002]).

2.6.4 Measuring efficacy for economic evaluations

Clinical trials may not always compare the relevant alternatives. This problem becomes acute when there are a number of new therapies for a given condition (van Houwelingen et al, [2002]). Mostly we do not have the appropriate head-to-head clinical trials of the therapies concerned. In this case we use meta-analysis. This is a statistical method to combine results of individual studies (Jones et al, [1992]). We often use meta-analysis to assess the clinical effectiveness of healthcare interventions; the methodology this by combining data from RCTs.

2.6.5 Affordability

The rapid biotechnological development resulted in a widening gap between what is therapeutically achievable and what is affordable. This affordability is a crucial issue for national health insurance funds. Budget impact analyses examine the financial burden and gain in connection with a given technology within a specific health care setting.

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benefits are corrected by quality weights, where 1 means complete health and 0 means death. (definition by ESKI)

Budget impact analysis (BIA) estimates the financial consequences of adoption and diffusion of a new health intervention within a specific health care setting or system context. In particular such analysis predicts how a change in the mix of pharmaceuticals or other therapies used to treat a specific disease will impact the trajectory of health spending on that condition. In contrast to a CEA, which measures the value of new interventions in terms of monetary units per additional unit of health benefit (e.g. dollars per quality-adjusted life year gained) to estimate their economic efficiency, BIA serves the very humble, pragmatic goal of examining “affordability”, the chief concern of health managers everywhere (Mauskopf et al, [2014]). A BIA usually applies narrow time perspective (3-5 years) and focuses on the financial consequences of the funder. Costs falling outside the scope of funder (e.g. in the social sector or on patients) and consequences in terms of production loss are disregarded in BIA.

3 RESEARCH OBJECTIVES

3.1 THE MAIN OBJECTIVES OF THE DISSERTATION

The main aims of the dissertation are formulated as follows:

Objective 1: Some biologicals have been approved by the European Medicine Agency (EMA) for the treatment of adults with severe, active ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Furthermore, in September 2013, the first biosimilar therapy, namely biosimilar infliximab was licensed in the EU for the first time for the treatment of AS. According to our knowledge, no meta-analysis have been published yet in AS, which compares the efficacy and safety of the biosimilar infliximab treatment to the original biological drugs indicated in AS. My first objective was to systematically review and analyse the available literature regarding the efficacy and safety of biological therapies in chronic diseases using literature search and meta-analysis. We compare infliximab and original biologicals in PsA in terms of efficacy and tolerability and compare the efficacy and safety of biosimilar-infliximab with other biological drugs for the treatment of active AS.

Hypothesis 1: a) In case of PsA, biologicals are nearly similar and tolerable, b) in case of AS, the efficacy and safety of the new and original drug are both more beneficial than the treatment with placebo.

Objective 2: Despite the widespread availability of biological drugs in psoriasis, there is a shortage of COI studies. My second objective was to assess the COI of patients with moderate to severe psoriasis in Hungary, based on a cross-sectional survey. We analyse the results of a self-designed non-interventional, cross-sectional questionnaire survey carried out in two academic dermatology clinics in Hungary.

Hypothesis 2: The treatment with biological therapies causes a significant financial burden to the society and the treatment of patients with these

agents results in higher financial costs compared to the case without biological therapy.

Objective 3: Economic evaluations require data on HRQOL on preference-based measures that capture preference weights (utility, in terms of desirability) about values of different health states. Furthermore, there is a growing interest in policy making for using utility measures and identifying algorithms to convert disease-specific measures into utilities. According to our knowledge there was no data based on empirical research from the CEE region regarding HRQOL in biologically treated patients in psoriasis. My third objective was to provide data regarding utility and quality of life of psoriasis patients, contributing to the international literature. Further objectives were to analyse the relationship between general and disease-specific outcome measures and to transform them alongside with key clinical, demographic, and health service utilisation variables into utility measures.

Hypothesis 3: Generic and disease specific quality of life scales and disease severity scores correlate with utilities.

Objective 4: The first biosimilar monoclonal antibody (biosimilar infliximab) was registered by the European Medicines Agency EMA in 2013 for the treatment of several inflammatory conditions including rheumatoid arthritis (RA) and AS. Biosimilar infliximab was first marketed in the CEE countries. My fourth objective was to build a model to perform a 3-year budget impact analysis of biological therapies in RA in six CEE countries.

Hypothesis 4: The introduction of biosimilar infliximab leads to substantial savings in health care budgets.

3.2 THE OUTLINE OF THE DISSERTATION

As presented in the the main objectives of the dissertation research questions, the outline of my dissertation is the following:

Chapter 1, 2 and 3: These chapters include a general introduction, provide the main background knowledge and describe the research questions and hypotheses.

Chapter 4: In this chapter, I present a book chapter and an article, both dealing with the efficacy and safety of biological therapies used in PsA and in AS. We conducted a quantitative analysis based on a systematic literature review for RCTs. Indirect meta-analysis and mixed treatment comparison was performed to compare the efficacy and safety of the substances of interest.

Chapter 5: In this chapter, I deal with a non-intervantional, cross-sectional survey in the topic of COI in psoriasis. We analysed the association between costs and types of treatment and disease severity with special interest in the effect of biological therapies for psoriasis. Moreover, we updated the literature search for COI studies in psoriasis in order to place our results in the context of the available publications.

Chapter 6: Continues with the topic of psoriasis, analysing the relationship between utility and standard psoriasis related quality of life scales. Hence, we analysed correlations between the widely used HRQOL and disease severity instruments of psoriasis and compared their capacity to distinguish among patients' severity groups. We also sought new possible predictors of the HRQOL to establish mapping models on EQ-5D score and visual analogue scale (EQ VAS).

Chapter 7: The chapter presents data on the budget impact implied by the reimbursement of a new biological drug. A model was developed to estimate

budget impact in RA over three years in six CEE countries, namely Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia.

Chapter 8: The main findings and conclusions of the dissertation are summarised with special emphasis on the added values achieved by the dissertation.

4 EFFICACY AND SAFETY OF BIOLOGICALS

This chapter draws upon:

Orsolya Balogh (2013): Clinical efficacy and safety of biologicals in Psoriatic Arthritis In: Valentin Brodszky: Systematic review and analysis of evidences on clinical efficacy and cost-effectiveness of biological drugs for the treatment of Psoriatic Arthritis: 13-38

ISBN 978-963-503-574-8

AND

Petra Baji, Márta Péntek, Sándor Szántó, Pál Géher, László Gulácsi, **Orsolya Balogh**, Brodszky Valentin (2014): Comparative efficacy and safety of biosimilar infliximab and other biological treatments in ankylosing spondylitis: systematic literature review and meta-analysis

Eur J Health Econ. 2014 May;15 Suppl 1:S45-52. doi: 10.1007/s10198-014-0593-5. Epub 2014 May 16.

First part: Clinical efficacy and safety of biologicals in Psoriatic Arthritis

4.1 EFFICACY OF BIOLOGICALS IN PATIENTS WITH PSORIATIC ARTHRITIS; A SYSTEMATIC REVIEW

Psoriatic arthritis (PsA) is a type of arthritic inflammation that occurs in about 15 percent of patients who have psoriasis. The disease can affect any joint in the body, and symptoms vary from person to person. Disability in the workplace inevitably has a significant impact on an individual's quality of life and financial status as well as society as a whole (Bansback et al, [2006]). There is increasing awareness that work disability in the form of absenteeism (time away from work) and presenteeism (reduced effectiveness at work) are important patient-centred, quality of life

outcome measures in arthritis (Tillet et al, [2012]). Furthermore, both psoriasis and PsA are associated with an increased cardiovascular mortality (Boehncke et al, [2012]).

The prevalence of PsA also shows similar variation, being highest in people of European descent and lowest in the Japanese. Although, study methodology and case definition may explain some of the variations, genetic and environmental factors are important (Mease, [2011a]). Overall, the available data suggest that the prevalence of psoriasis in the general population is approximately 2-3% (Catanoso et al, [2012]), with about a third of patients with psoriasis having arthritis. Therefore, PsA may affect 0.3-1.0% of the population.

Very few large-scale, prospective, observational studies have been conducted in PsA and only a few collected data on economic outcomes or patient utilities (Langham, [2011]). In Germany, mean annual per patient direct costs in PsA were €3156 and the indirect cost varied between €2414 and €7919 depending on the costing method used. Disease activity and physical function were the main cost drivers (Huscher, [2006]). Brodszky et al. conducted a study in Hungary (year 2008) involving patients with PsA. Mean direct medical, direct non medical, indirect and total costs were 1,876, 794, 2,904 and 5,574 €/patient/year, respectively. Total costs were in significant linear relationship with functional deterioration and skin severity (Brodszky, [2009]).

Scientific evidence suggests that infliximab and comparator biologicals (adalimumab, etanercept, golimumab) can improve the symptoms of the psoriatic arthritis (PsA) in all important outcomes. Safety profile of these biologicals is rather similar and tolerable. There is a shortage of studies published in Central and Eastern European countries however local data and local study results are more and more required in all CEE countries by the funders. More data about budget impact, costs, efficacy and safety outcomes and cost-utility is crucial in order to have better patient access to modern PsA therapy (Mease, [2011b]).

4.1.1 Main findings of the efficacy study of PsA

We conducted a quantitative review on efficacy and safety of the TNF-blockers in PsA based on 7 randomised controlled trials. Most studies were of good internal validity and each compared one TNF-blocker to placebo. TNF-blockers adalimumab, etanercept, golimumab and infliximab were found to be highly effective, achieving significant improvements in PsARC and ARC endpoints. Recently, five systematic reviews with meta-analysis have been published addressing the role of biologics in patients with PsA with similar conclusions. It may be concluded that present review on biologics in established PsA supported excellent efficacy and safety.

4.1.2 Objectives of the efficacy study of PsA

The main aims of this systematic review were: to identify all relevant literature on clinical efficacy and safety evidence for infliximab and comparator biological medications for PsA; to conduct an up-to-date meta-analysis on clinical efficacy and safety outcomes, and to generate an overview of recently published systematic reviews.

The main purpose of this review is to assist the infliximab with scientific evidences and to support it for reimbursement in 6 different Central European countries. Methods used in this analysis were fully corresponding to NICE Decision Support Unit's recommendations (Dias et al, [2008]) about the evidence synthesis and to Cochrane Handbook's (Higgins et al, [2009]) recommendations.

4.1.3 Methods of the efficacy study of PsA

4.1.3.1 Comparators

The following comparators were considered for this analysis: adalimumab, etanercept, golimumab and infliximab. The analysis compares each biological DMARD at licensed dose with placebo using follow-up data available at the end of the randomised, double-blind controlled period of the trial.

4.1.3.2 Search strategies

Medline database and references of retrieved articles were searched. The search was not restricted by publication date, but different search strategies were applied in two different time period. The Cochrane Highly Sensitive Search Strategy (Higgins et al, [2009]) was applied to identify randomised controlled publications and was combined with 'arthritis, psoriatic' MeSH terms and drug names. The search dates were January 1st 2010 to April 15st 2012. References of RCTs from earlier time period were taken from a meta-analysis published by Ash et al. (Ash et al, [2011]) and from our previously published systematic reviews (Brodszky et al, [2008]); (Koó et al, [2006]).

4.1.3.3 Data abstraction

Data was extracted and analysed by two independent persons and checked by a third reviewer. Any disagreement was resolved through discussion until consensus was reached. Data on the following outcome measures were included:

4.1.3.4 Quality assessment

The quality of selected studies was evaluated using the Jadad-score. (Jadad, [1996]) This score is the most frequently used scale in quality assessment of clinical trials. (Olivo, [2008]) The Jadad scale assesses the quality of published clinical trials based methods relevant to random assignment, double blinding, and the withdrawals and dropout of patients. Jadad score ranges from zero to five. Detailed description of scoring can be found in Appendix 10.2.

4.1.3.5 Comparisons

In PsA trials contrary to RA trials, quite homogenous inclusion criteria were applied. Prior treatment failures and administration were similar across trials. Trials included patients with prior inadequate response to conventional DMARD and biologics were used in combination with regular DMARDs. Therefore all trials were combined in the same comparison and subgroups of trials were not created as in our previous meta-analysis in patients with RA.

4.1.3.6 Meta-analysis

We have conducted a meta-analysis to compare the efficacy and safety of included biologicals. Two specific analyses were performed for this meta-analysis: direct comparison: a frequentist meta-analysis of study outcomes, a mixed treatment comparisons: combining direct and indirect evidence.

4.1.3.6.1 Direct comparison

Data were analysed using Review Manager 5 software. The Relative Risk (RR), Rate difference (RD), number needed to treat (NNT) and appropriate 95% CI were derived for each study according to the number of events reported in the original studies. Intention-to-treat analysis was conducted.

The denominators were the total number of patients randomised; missing values were considered treatment failures. The pooled RR and RD and 95% CI were calculated using a fixed effect model since no significant heterogeneity was detected. The chi-square test for heterogeneity was computed with a P-value set to 0.10 to determine statistical significance. In case of significant heterogeneity random effect model was applied.

4.1.3.6.2 Mixed treatment comparison

Traditional methods of meta-analysis do not permit indirect comparisons between drugs because they only allow us to pool studies with the same comparators. For our second analysis, we examined the relative effectiveness of each individual treatment using the Lu's method for combining direct and indirect evidence in mixed treatment comparisons, a Bayesian approach. A fixed effect statistical model developed by NICE Decision Support Unit (DSU) was used. We estimated the posterior densities for all unknown parameters using MCMC (Markov chain Monte Carlo) for each model in WinBUGS version 1.4.3. Each outcome measure was analysed using random effects models, which allowed for studies with 3 or more arms.

All MTC models used the odds ratio as the measure of relative treatment effect and assumed that treatment effects on the odds-ratio scale were multiplicative and exchangeable between trials.
Differences between treatments were considered significantly significant at the 0.05 level if the 95% CI around the odds ratio did not cross 1. Detailed description of methods and WinBUGS codes are provided in Appendix 10.3.

4.1.4 Presentation of results

We give a detailed description of the infliximab trials identified in the literature and also about the quality assessment of each trial. Outcomes of all published infliximab RCTs will be analysed and combined in one meta-analysis – in this way the key parameters of the "statistical infliximab trial"

will be provided. Results of the classical meta-analysis will then be summarised. In Appendix 10.4, the detailed results from classical meta-analysis will be presented as forest plots diagrams.

The Bayesian mixed treatment comparison will be introduced separately since it includes indirect comparisons of biologics. Results will be presented by outcome (e.g., PsARC, ACR improvement, serious adverse effect etc.).

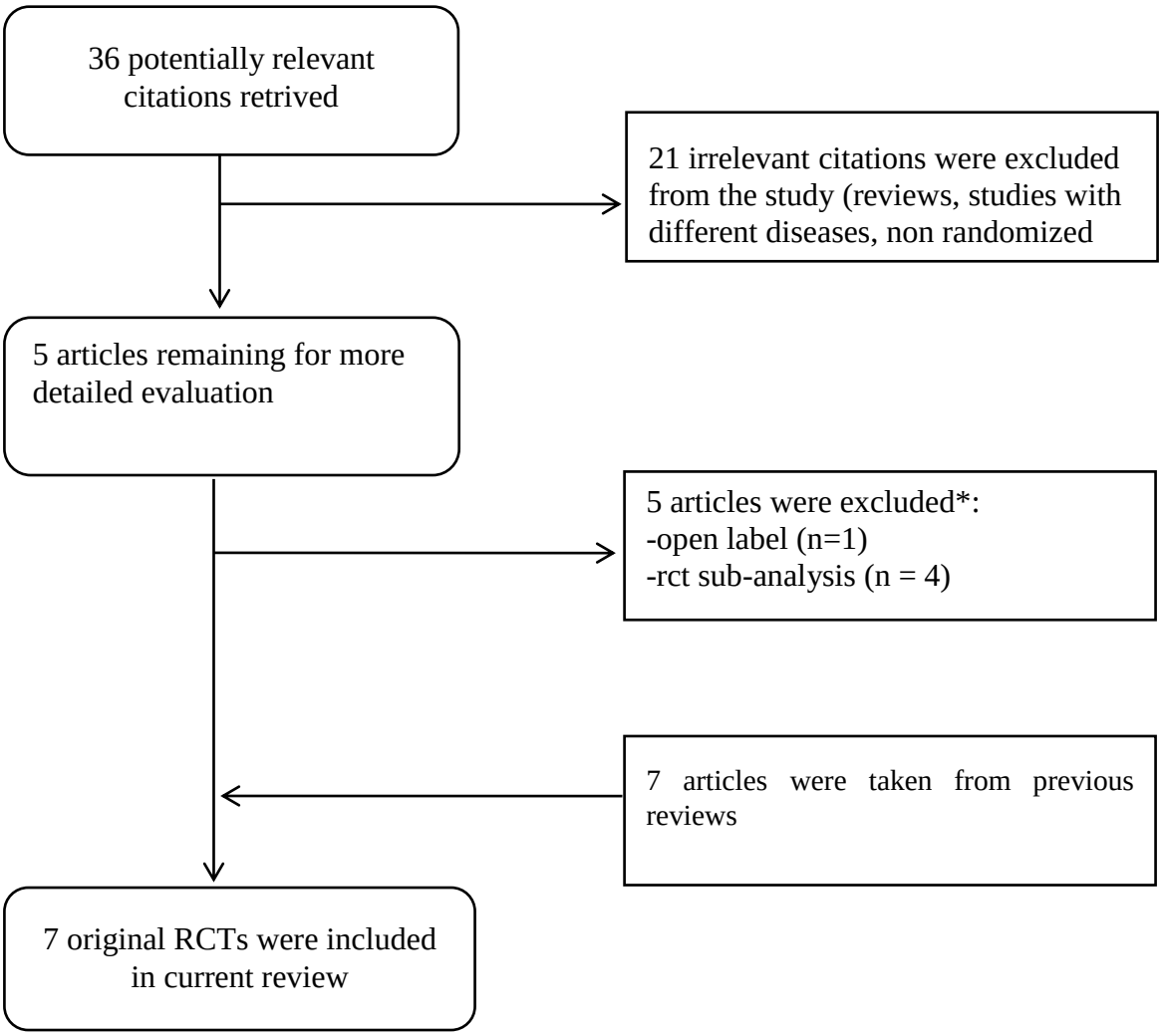
4.1.4.1 Results: meta-analysis of randomised controlled trials

4.1.4.1.1 Included studies

The search in MEDLINE (01.01.2010-15.04.2012) yielded 36 potential citations for randomised controlled trials examining the biologicals in PsA. Five RCTs in PsA were amongst them but all were excluded because of open label design or they were subanalysis of previously published RCTs (See

Figure 2 and its legend). In addition, seven references of trials were taken from previous systematic reviews (Ash et al, [2011]); (Brodszky et al, [2008]); (Koó et al, [2006]) Altogether 7 RCTs (Antoni et al, [2005a]); (Antoni at al, [2005b]); (Genovese et al, [2007]) ; (Kavanaugh et al, [2009]); (Mease et al, [2000]); (Mease et al, [2004]); (Mease et al, [2005]) were included. The number of trials in given comparisons might be different because of the distinct endpoints reporting across trials.

Figure 2 Quorum chart for identification of studies in the systematic review



4.1.4.2 Results from infliximab studies

4.1.4.2.1 Efficacy

There was a significant difference at 14-16 weeks in favour of the infliximab group compared to the placebo group with respect to the ACR20, ACR50, ACR70 and PsARC response (See Figure 3, Figure 4, Figure 5 and Figure 5). The NNTs were 2 (2-2), 3 (2-3), 5 (4-8) and 2 (2-2) treated patients to achieve one ACR20, ACR50, ACR70 and PsARC response, respectively.

Figure 3 Efficacy of infliximab 5 mg/kg on ACR20 response at week 14-16

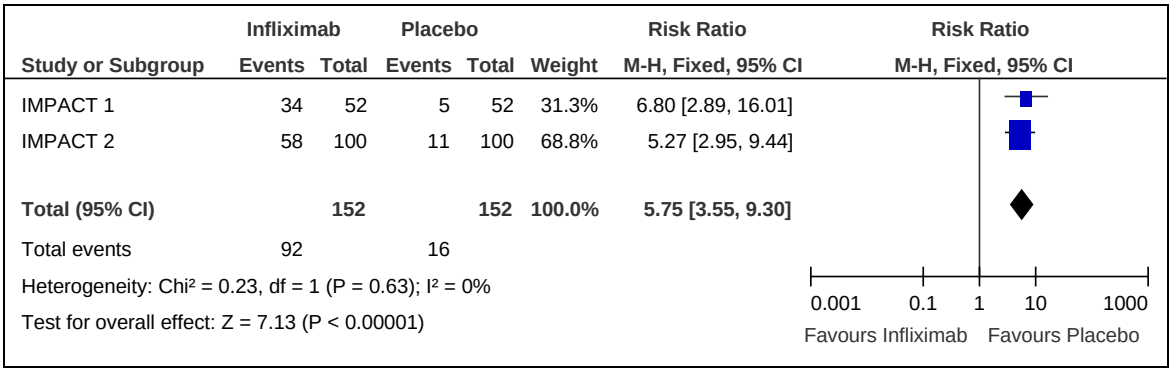


Figure 4 Efficacy of infliximab 5 mg/kg on ACR50 response at week 14-16

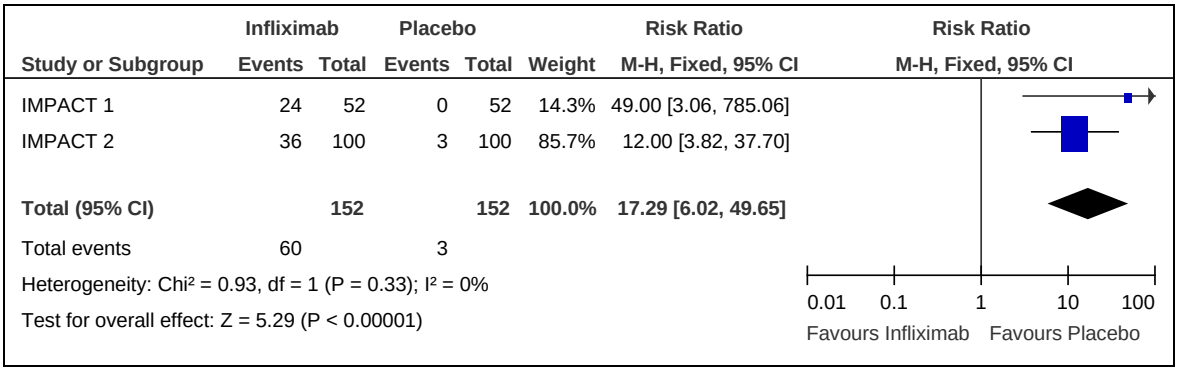


Figure 5 Efficacy of infliximab 5 mg/kg on ACR70 response at week 14-16

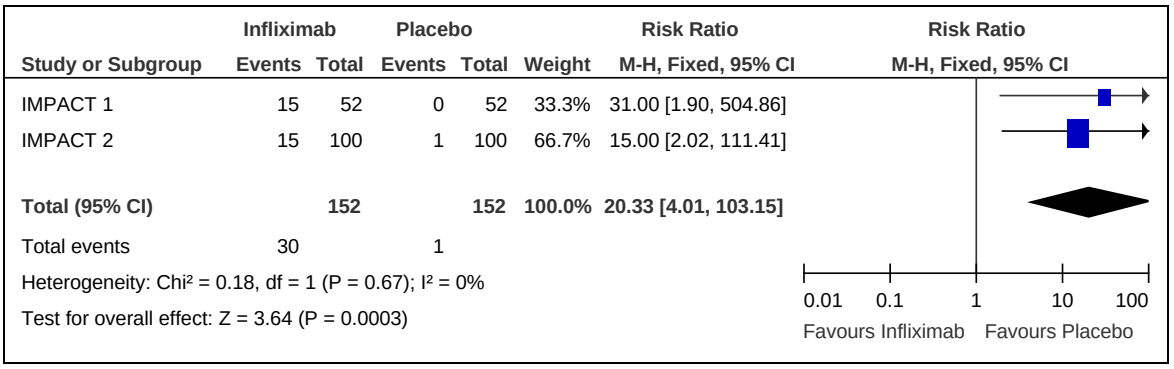
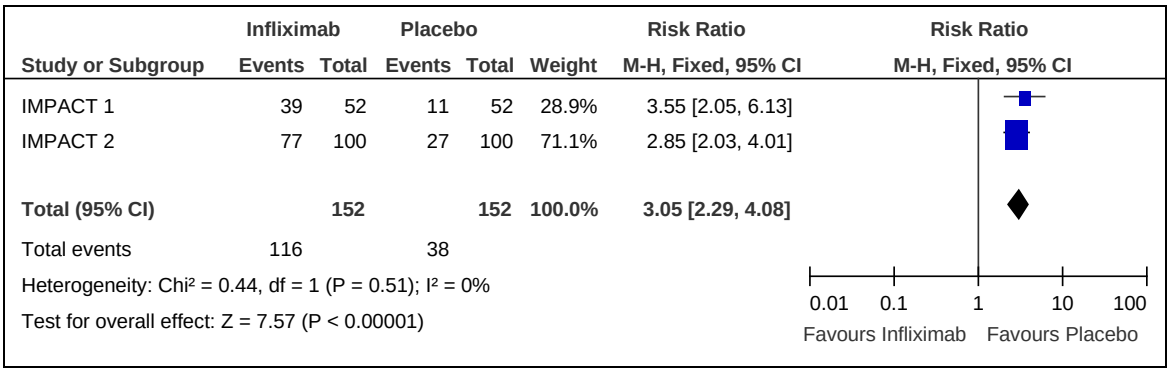


Figure 6 Efficacy of infliximab 5mg/kg on PsARC at week 14-16



4.1.4.2.2 Tolerability and safety of infliximab treatment

There were no significant differences between infliximab and placebo groups with respect to withdrawals due to any reason (Figure 7) and withdrawal due to adverse event (Figure 8). There were no significant differences between infliximab and placebo treatment with respect to any AE, serious AE and serious infections (See Figure 9 and Figure 10).

The NNH (number needed to harm) was 38 treated patients to cause one withdrawal due to adverse event. Similarly, NNHs were 22 and 38 patients to cause one AE and one serious AE respectively.

Figure 7 Tolerability of infliximab 5 mg/kg, withdrawal due to any reason at week 14-16

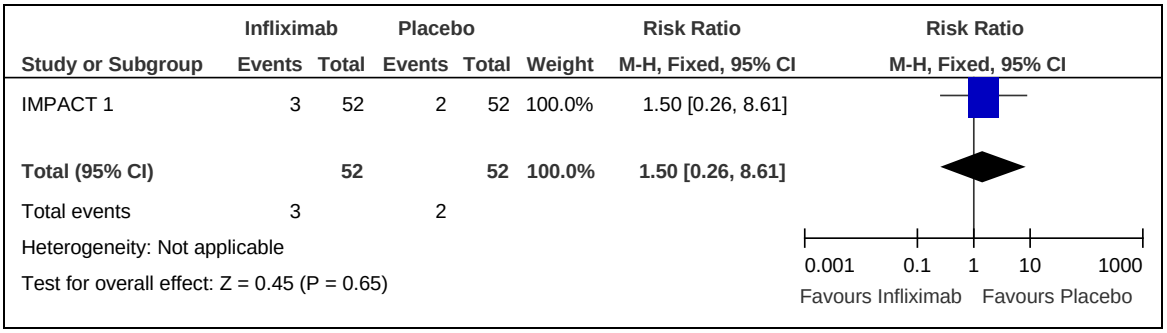


Figure 8 Tolerability of infliximab 5 mg/kg, withdrawal due to side-effect at week 14-16

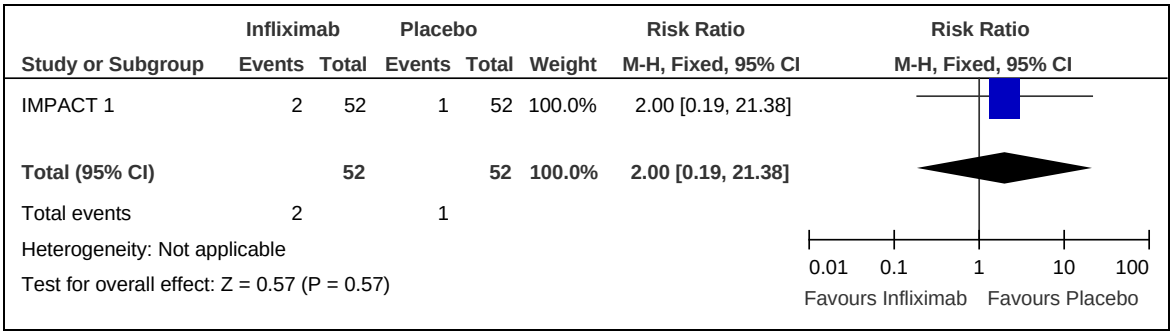


Figure 9 Safety of infliximab 5 mg/kg, any adverse events at week 14-16

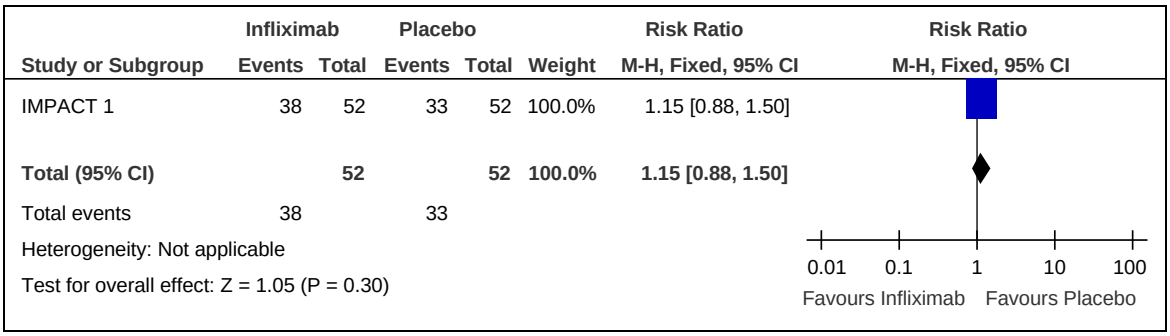


Figure 10 Safety of infliximab 5 mg/kg, serious adverse events at week 16

4.1.4.3 Classical meta-analysis: efficacy and safety of combination therapy

In total of 7 RCTs encompassing 1,241 patients with PsA were included in current meta-analysis. However, the number of trials in given comparisons might be different because of because of the distinct endpoints reporting across trials.

In this section we will present direct, head to head comparison between biologic + conventional DMARD vs. placebo + conventional DMARD for efficacy and safety endpoints.

4.1.4.3.1 Efficacy of biologics vs. placebo

Seven trials were included in this comparison. Global comparison of the PsARC efficacy of any TNF-blockers with placebo control showed a combined relative effect of 2.76 (95% CI 2.39, 3.20). The combined effect was 3.05 (95% CI 2.29, 4.08) for infliximab trials. Further analyses using ACR20, ACR50 and ACR70 efficacies similarly showed the statistically significant favourable efficacy of biologics compared to placebo, though the absolute values of effect estimates were greater with higher level of ACR improvement. Biologics were associated with a number needed to treat of 2 to 3 patients for ACR20 improvement. NNTs for ACR50 were 3 to 4 patients, for ACR70 were between 5-10 and for PsARC were between 2-3 patients.

4.1.4.3.2 Safety and tolerability of biologics versus placebo

Seven trials were included in this comparison. The number of trials in given comparisons might be different because of the distinct endpoint reporting across trials.

Biologics were well tolerated. Regarding withdrawals due to adverse events, we found no significant overall difference between the experimental and

control groups. Biologics were associated with less withdrawal due to any reason, therefore pooled number needed to treat for harm was not estimable.

There were no statistically significant difference between biologics and placebo with respect to any AE, serious AE and serious infections. The likelihood to experience an unspecified AE was slightly elevated compared to normal doses (RR=1.02; 95% CI: 0.89, 1.17). While the rates of serious AE and serious infections were the same or reduced.

4.1.4.4 Meta-analysis: mixed treatment comparison

Figures of this section present odds ratios between treatments A and B in the form treatment A - treatment B. Treatment A and B are biologics. To read the figures:

- for PsARC, ACR20, ACR50, ACR70, if the point estimate is greater than 1 then the first treatment in the sequence A-B is more effective (although not necessarily statistically significantly more effective)
- for adverse events and tolerability endpoints, if the point estimate is less than 1 then the first treatment in the sequence A-B is safer (although not necessarily statistically significantly safer)

Please note that the confidence intervals provide information on whether the difference between treatments is statistically significant. If the CI contains 1, the difference is not statistically significant.

4.1.4.4.1 Efficacy

Overall, results of mixed treatment comparisons indicate that efficacy does not differ substantially among TNF-blockers (adalimumab, etanercept, infliximab and golimumab), however certain comparisons showed significant differences between biologics (See Figure 11, Figure 12, Figure 13 and Figure

14). Point estimates of comparative PsARC responses significantly favour infliximab and golimumab over adalimumab (OR 2.29 and 2.39) while other comparisons showed no significant differences (See Figure 11). No significant differences in terms of ACR20, ACR50 and ACR70 improvements were observed between adalimumab, etanercept, golimumab and infliximab (See Figure 12, Figure 13 and Figure 14). The wider 95% CIs for higher ACR response rates due to the smaller effect size.

Figure 11 Indirect comparisons of biologics, PsARC at 12-16 weeks

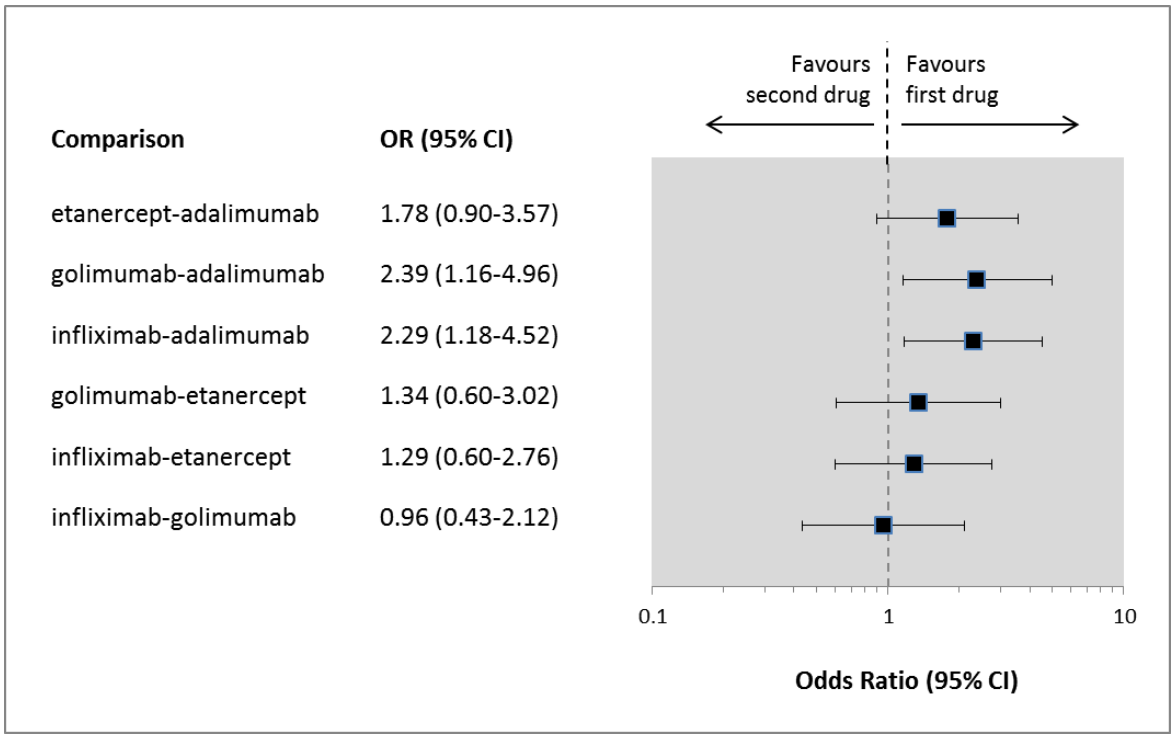


Figure 12 Indirect comparisons of biologics, ACR20 at 12-16 weeks

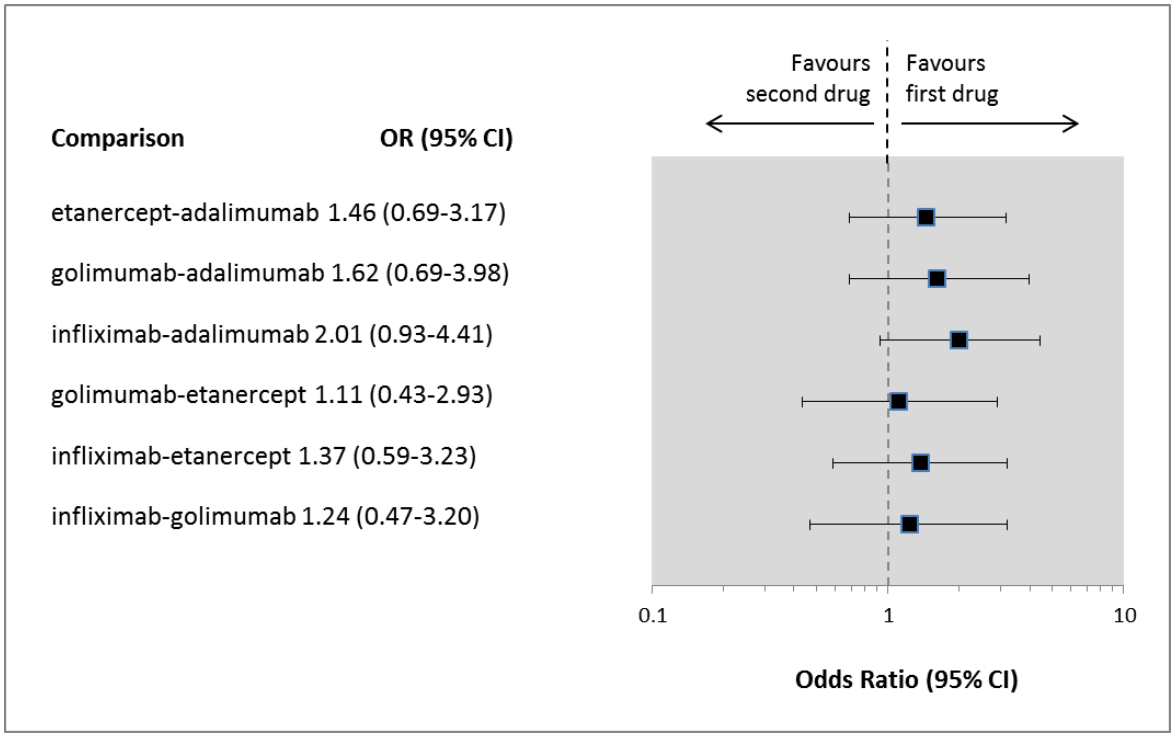


Figure 13 Indirect comparisons of biologics, ACR50 at 12-16 weeks

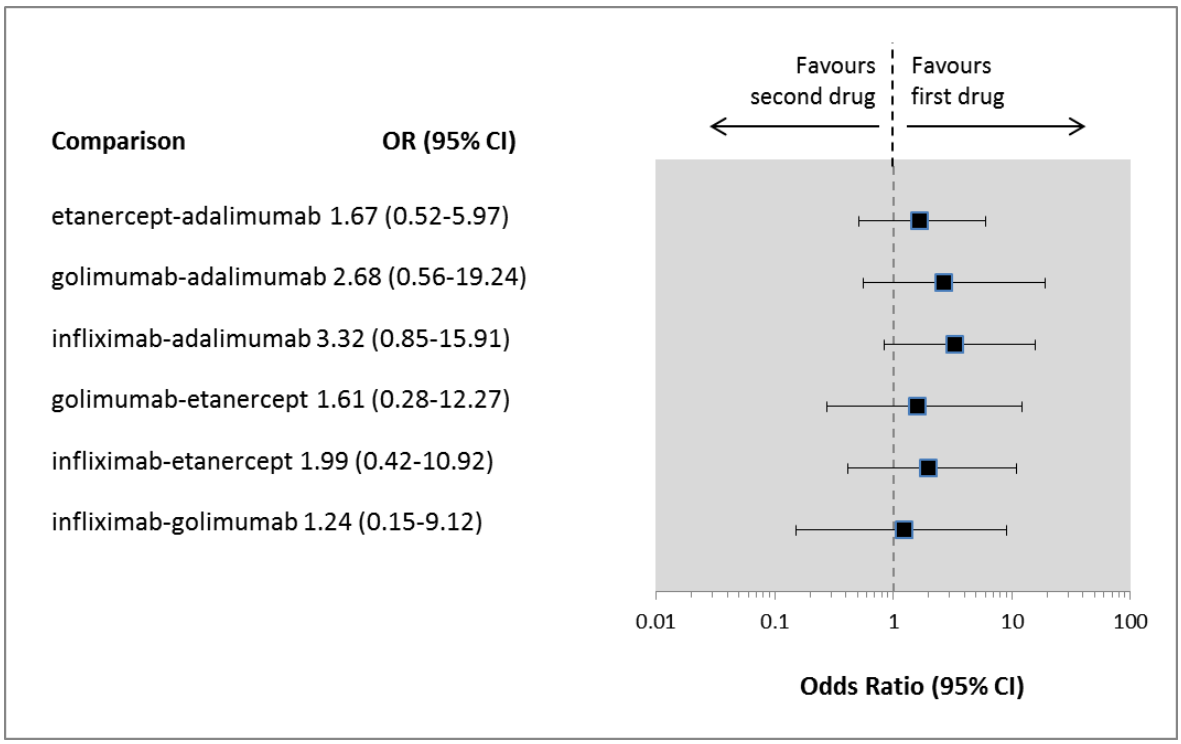
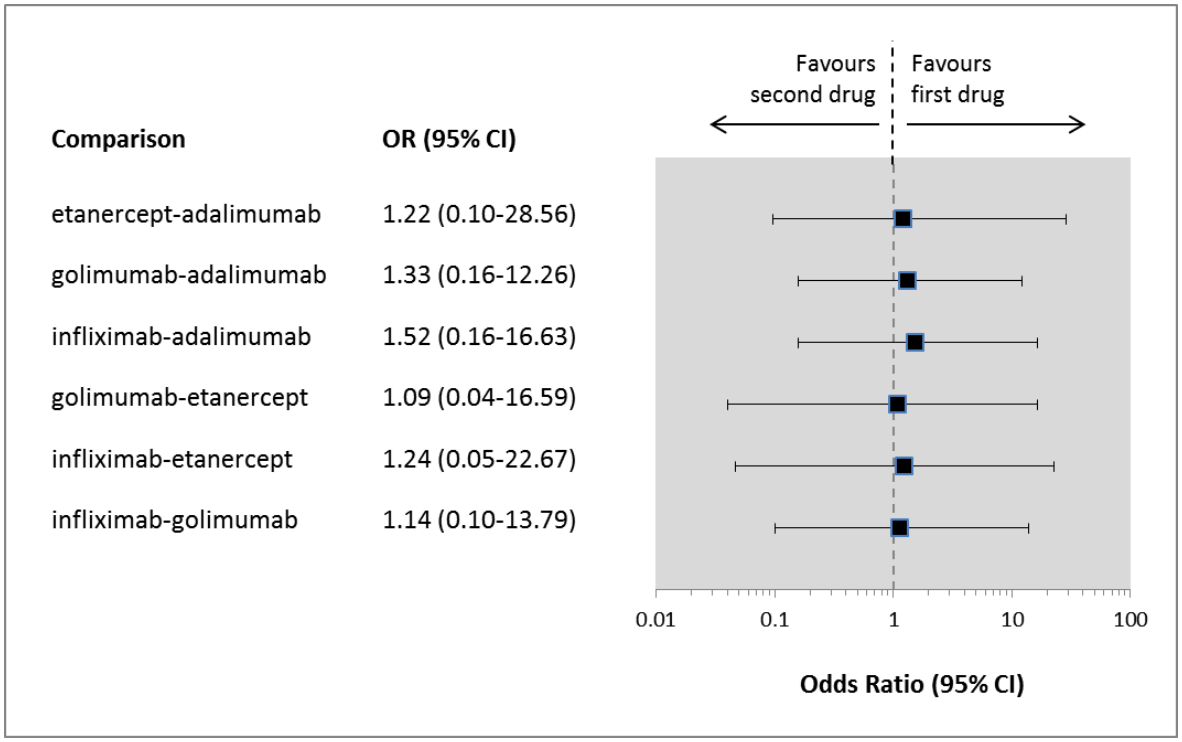


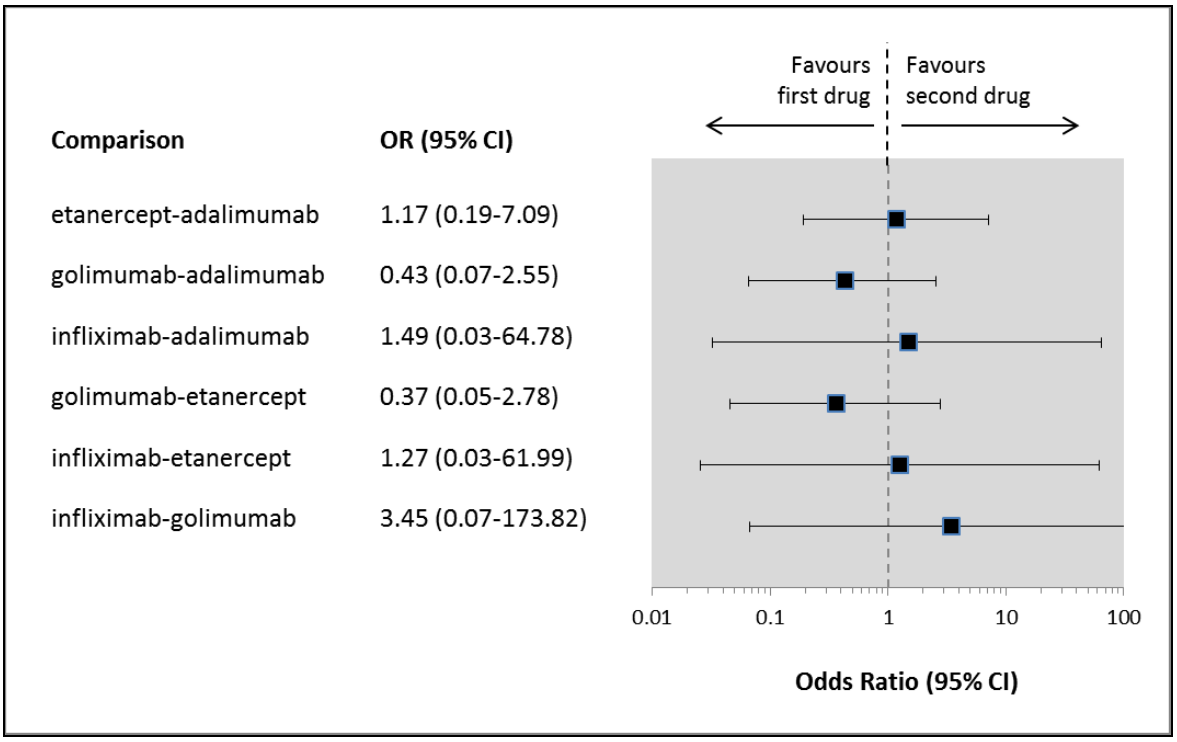
Figure 14 Indirect comparisons of biologics, ACR70 at 12-16 weeks



4.1.4.4.2 Safety

Important safety information as number of any adverse event or number of serious infections was provided not consistently across studies. Therefore we present in this section the indirect comparison of biologics according to the rate of serious adverse events, which was the most frequently reported safety endpoint. In the short term, we found no differences in rates of serious adverse event between biologics (See Figure 15).

Figure 15 Indirect comparisons of biologics, serious adverse event



4.1.5 Conclusions of the efficacy study of PsA

4.1.5.1 Efficacy and safety

Our quantitative review delivers both direct and indirect comparisons of the efficacy and safety of four biologics for PsA from double-blind, placebo-controlled trials. Firstly, a classical direct meta-analysis was undertaken to obtain summary estimates of clinical effectiveness and safety. Then, following recent NICE guidelines a mixed treatment comparison was undertaken allowing for indirect comparisons in the absence of a sufficient number of head-to-head trials.

We studied the efficacies of the TNF-blockers based on 7 trials fulfilling the required criteria for inclusion. Most studies were of good internal validity and each of them compared one TNF-blocker to placebo. In the present

quantitative review, the TNF-blockers adalimumab, etanercept, golimumab and infliximab were found to be highly effective, achieving significant improvements in PsARC and ARC endpoints. According to common primary endpoint across trials, PsARC, all four TNF-blockers were more efficacious than placebo with the estimates of risk ratios ranging from 2.33 (95% CI: 1.80-3.01) – 3.45 (95% CI: 2.39-4.99). Further analyses using ACR20, ACR50 and ACR70 efficacies showed very similar results. Safety endpoints were reported less consistently in PsA trials. Based on large a Cochrane meta-analysis of biologics in multiple diseases, infliximab showed similar safety profile than placebo.

Our Bayesian indirect comparison did not show any difference between infliximab, etanercept and golimumab on achieving PsARC, ACR20, ACR50 and ACR70 responses. However, adalimumab was significantly less effective on achieving PsARC response than infliximab and golimumab. The rate of serious adverse events did not differ significantly among TNF-blockers.

Recently, five systematic reviews with meta-analysis have been published addressing the role of biologics in patients with PsA. All the articles selected the same trials only different search dates might lead to differences. These previous systematic reviews came to very similar conclusions as we did.
It may be concluded that present direct and indirect comparisons of the marketed biologics in established PsA supported excellent efficacy and safety.

4.1.5.1.1 Limitations of the PsA study

A potential weakness of this meta-analysis arises from the fact that the trials from which data are combined are likely to differ in their design and patient population characteristics.

Second part of the chapter: Comparative efficacy and safety of biosimilar infliximab and other biological treatments in ankylosing spondylitis: systematic literature review and meta-analysis

4.2 EFFICACY OF BIOLOGICALS IN PATIENTS WITH ANKYLOSING SPONDYLITIS; A SYSTEMATIC REVIEW

4.2.1 Introduction to the efficacy study of AS

So far adalimumab, etanercept, golimumab and infliximab have been approved by the European Medicine Agency (EMA) for the treatment of adults with severe, active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

In September 2013, the first biosimilar therapy, namely biosimilar infliximab (CT-P13, trade names: Remsima and Inflectra) was licensed in the EU for the treatment of AS. The results of a Phase 1, multicenter, double-blind randomised controlled trial (RCT) with biosimilar infliximab (called the PLANETAS study) were published in May, 2013 (Park et al, [2013]). The trial was designed to demonstrate pharmacokinetic equivalence and efficacy and safety comparability of biosimilar infliximab (CT-P13) and the originator infliximab in active AS patients. The RCT was conducted at 46 sites across 10 countries in Europe, Asia and Latin America between November, 2010 and December, 2011. Altogether, 250 patients were enrolled in the study. Besides pharmacokinetics, proportions of patients achieving 20% and 40% improvement according to the Assessment of SpondyloArthritis international Society[6] response criteria (ASAS20 and ASAS40) at week 14 and 30 were the endpoints to assess efficacy (Sieper et al, [2009]). (See the definition of ASAS response criteria in the Methods section).

[6] Former ASessment in ankylosing spondylitis

No significant differences were found in the efficacy and safety of the originator infliximab and biosimilar infliximab. According to the study results ASAS20 and ASAS40 responses at week 30 were 70.5% and 51.8% for biosimilar infliximab and 72.4% and 47.4% for originator infliximab, respectively. The authors concluded that pharmacokinetic, efficacy and safety profiles of the biosimilar infliximab and the originator infliximab were equivalent in patients with active AS (Park et al, [2013]).

According to our knowledge, no meta-analyses have been published yet in AS, which compares the efficacy and safety of the biosimilar infliximab treatment to the other biological drugs indicated in AS. Thus, the aim of this study was to carry out systematic literature review and meta-analysis of published RCTs in order to compare the efficacy and safety of biosimilar infliximab to adalimumab, etanercept, golimumab and infliximab in AS[7].

Besides the PLANETAS trial, no other RCTs, presenting head-to-head comparison of biologicals, have been published yet in this diagnosis (Migliore et al, [2012]). Due to the difference in comparators across the trials biosimilar infliximab is compared to originator infliximab in the PLANETAS study, while other biologicals are compared to placebo), traditional methods cannot be applied for the comparison. Therefore, we used indirect comparison method, namely mixed treatment comparison (MTC) to evaluate the efficacy and safety of biological treatments. MTC permits indirect comparisons between study drugs with different comparators as well (Ades et al, [2006]; (Lu et al, [2004]).

[7] The search dates were November 1, 2009 to August 20, 2013. Certolizumab pegol was registered for the treartemnt of AS on 19 September 2013 thus it was not included in our analysis.

4.2.2 Methods of the efficacy study of AS

4.2.2.1 Treatments

In the current analysis adalimumab, etanercept, golimumab and infliximab are considered as comparators of biosimilar infliximab as these biologicals are recommended by the EMA for the treatment of AS. Only doses recommended by the EMA were considered in the analysis: adalimumab (40 mg every other week as subcutaneous injection);etanercept (25 mg twice weekly, or 50 mg once weekly as subcutaneous injection); golimumab (50 mg once a month as subcutaneous injection);infliximab (5 mg/kg at 0, 2, 6 weeks and then every 6 to 8 weeks as intravenous infusions over a 2 hour period) as biosimilar infliximab (CT-P13) (5 mg/kg at 0, 2, 6 weeks and then every 6 to 8 weeks as intravenous infusions over a 2 hour period).

4.2.2.2 Literature search

Electronic databases (Medline and Cochrane Library) as well as references of retrieved articles were searched. The Cochrane Highly Sensitive Search Strategy (Higgins et al, [2009]) was applied to identify randomised controlled publications and was combined with the disease (ankylosing spondylitis, ankylosing spondyloarthritis, spondyloarthritide) and drug names for adalimumab, etanercept, golimumab and infliximab [8]. We carried out the search for the period between November 1, 2005 and August 20, 2013. To identify RCTs from earlier years, we relied on the systematic review of McLeod et al. published in 2007, which assessed the comparative clinical effectiveness of adalimumab, etanercept and infliximab for the treatment of AS (McLeod et al, [2007]). A separate search was carried out to identify RCTs

[8] (“ankylosing spondylitis” OR “ankylosing spondyloarthritis” OR “spondyloarthritide”) AND ("adalimumab” OR "infliximab" OR "golimumab"OR "etanercept") AND ((randomised controlled trial[pt] OR controlled clinical trial[pt] OR randomised[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("2005/11/01"[PDAT] : "2013/08/20"[PDAT])

with the biosimilar agent, using its generic name (CT-P13) as search term, and in this case no further restrictions were applied.

4.2.2.3 Exclusion and inclusion criteria

Double blind RCTs in AS with parallel design, with full paper obtainable were included. Non randomised or uncontrolled studies, observational studies, case series, letters to editor, studies with no abstracts or with conference abstracts only were not included. Further inclusion criterion was that AS patients, diagnosed based on the modified New York criteria (van der Linden et al, [1984]), in at least one arm of the trial must receive adalimumab, etanercept, golimumab, infliximab or biosimilar infliximab treatment in the labelled dose. Studies which examined only off-label doses, or other than the suggested administration (e.g. infliximab combined with methotrexate) studies reporting solely on laboratory measures aimed at investigating disease, or treatment mechanisms and which do not report relevant clinical outcomes were excluded. Studies involving patients younger than 18 years were also excluded as well as pilot studies.

4.2.2.4 Data extraction

We used the same data extraction process and quality assessment of the RCTs as in our previous study in which we assessed the efficacy and safety of biosimilar infliximab in another inflammatory rheumatic disease, rheumatoid arthritis (RA). Details have been published elsewhere (Baji et al, [2014]). In brief, data on study design, patients' demographic and morbidity characteristics, treatment interventions, end-points and duration of follow-up were subtracted. The quality of selected studies was evaluated using the Jadad-score (Jadad, [1996]).

4.2.2.5 Endpoints

The proportions of patients with ASAS20 response at week 12 and 24 were used as efficacy endpoints in the meta-analysis of AS trials. The ASAS20 improvement criteria requires improvement of ≥20% and ≥1 unit in at least 3 of 4 well-defined specific domains (patient global assessment, pain, function and inflammation) on a scale of 10 and no worsening of ≥20% and ≥1 in remaining domain on a scale of 10 (Sieper et al, [2009]). To evaluate the safety of biological therapies, the occurrence of serious adverse events at week 24 was used as safety endpoint in the analysis. We could not carry out the safety analysis at week 12, as the biosimilar infliximab study presented safety results only at week 30. (Park et al, [2013])

4.2.2.6 Meta-analysis

Mixed treatment comparison (MTC) was applied in the analysis (Ades et al, [2006]); (Lu et al, [2004]). We estimated the posterior densities for all unknown parameters using MCMC (Markov chain Monte Carlo) for each model in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) We applied random effects model to estimate the odds-ratios (OR) as the measure of relative treatment effect. We also present the 95% credibility intervals (CI) which contains the true value of OR with 95% probability.

4.2.3 Results of the efficacy study of AS

4.2.3.1 Literature review

Our literature search for the period between November 1, 2005 and August 20, 2013 yielded 336 potential citations for RCTs. Among them seven RCTs in AS with the target drugs of our study were identified. Five of them met our inclusion criteria (Huang et al, [2014]; (van der Heijde et al, [2006]); (Barkham et al, [2010]); (Dougados et al, [2011]); (Inman et al, [2008]). One study was not enrolled as it examined off-label infliximab therapy (3mg/kg) (Inman et al, [2008]). To have comparable results, one study was excluded

as infliximab was given in combination with methotrexate (Marzo-Ortega et al, [2009]). Till November, 2005, nine RCTs identified by the systematic review of McLeod et al. (2007) were screened for eligibility. Seven of them met our enrollment criteria, and were included in the current meta-analysis (van der Heijde et al, [2006]; (Maksymowych et al, [2005]); (Gorman et al, [2002]; (Calin et al, [2004]; (Davis et al, [2003]; (Braun et al, [2002]; (van der Heijde et al, [2005]). (One study (Brandt et al, [2003]) was excluded as it examined the effect of etanercept at week 6, and another study was published later in a scientific journal by van der Heijde et al. in 2006, which was identified by our search as well in the Medline database). The search for biosimilar infliximab did not identify other RCT than the PLANETAS trial (Park et al, [2013]).

Thus, altogether 13 studies were included in the meta-analysis. Eight of them were 12-week trials: one with infliximab (Braun et al, [2002]), five with etanercept (Gorman et al, [2002]; (Calin et al, [2004]; (Barkham et al, [2010]; (Dougados et al, [2011]; (van der Heijde et al, [2006]) and two with adalimumab (Huang et al, [2014]; (Maksymowych et al, [2005]). Five of 13 studies were at least 24-week trials: one with infliximab (van der Heijde et al, [2005]), one with adalimumab (van der Heijde et al, [2006]), one with etanercept (Davis et al, [2003]), one with golimumab (Inman et al, [2008]) and one with biosimilar infliximab (Park et al, [2013]).

Table 4. Characteristics of included studies

Studies	N	Week	Treatment	Mean age, years	Mean disease duration, years	Baseline BASDAI score** (0-10)	JADAD score
Park 2013 PLANETAS	**250**	**30**	1) biosimilar infliximab 5 mg/kg at week 0, 2, 6, 14, 22 n=125 2) infliximab 5 mg/kg at week 0, 2, 6, 14, 22 n=125	38.0 38.0	NR	6.8 6.6	5
Braun 2002	70	12	1) infliximab 5 mg/kg at week 0, 2, 6 n=34 2) placebo n=35	40.6 39.0	16.4 14.9	6.5 6.3	5
Van der Heijde 2005 ASSERT	279	24	1) infliximab 5 mg/kg at week 0, 2, 6, 12, 18 n=201 2) placebo n=78	40.0 41.0	7.7 13.2	6.6 6.5	5
Adalimumab							
Huang 2013	344	12	1) adalimumab 40 mg eow n=229 2) placebo n=115	30.1 29.6	8.1 7.7	6.0 6.2	5
Van der Heijde 2006 ATLAS	315	24	1) adalimumab 40 mg eow n=208 2) placebo n=107	41.7 43.4	11.3 10.0	6.3 6.3	5
Maksymovich 2005	82	12	1) adalimumab 40 mg eow n=38 2) placebo n=44	41.9 40.0	14.5 12.1	6.2 6.5	4
Gorman 2002	40	16(four months)	1) etanercept 25 mg twice weekly n=20 2) placebo n=20	38.0 39.0	15 12	NR	5
Calin 2004	84	12	1) etanercept 25 mg twice weekly n=45 2) placebo n=39	45.3 40.7	15.0 9.7	61.0*** 58.6***	5
Davis 2003	277	24	1) etanercept 25 mg twice weekly n=138 2) placebo n=139	42.1 41.9	10.1 10.5	58.1*** 59.6***	5
van der Heijde 2006	356	12	1) etanercept 50 mg once weekly n=155 2) etanercept 25 mg twice weekly n=150 3) placebo n=51	41.5 39.8 40.1	9.0 10.0 8.5	62.4*** 59.4*** 61.1***	4

Barkham 2010	40	12	1) etanercept 25 mg twice weekly n=20 2) placebo n=20	40.8 39.4	11 20	6.1 5.5	4
Dougados 2011 SPINE	82	12	1) etanercept 50 mg once weekly n=39 2) placebo n=43	46.0 48.0	19 23	64.0 58.0	5
Inman 2008	35 6	24	1) golimumab 50 mg every 4 weeks n=138 2) golimumab 100 mg every 4 weeks n=140 3) placebo n=78	38.0 38.0 41.0	11.0 9.5 16.0	6.6 7.0 6.6	5

*median; ** Bath Ankylosing Spondylitis Disease Activity Index; ***Scale:0-100; NR=not reported; eow=every other week

4.2.3.2 Mixed treatment comparison meta-analysis: efficacy and safety

4.2.3.2.1 Efficacy

The biosimilar infliximab study and Inman et al. (2008) golimumab study presented ASAS20 results at week 14, and Gorman et al. (2002) etanercept study at week 16 (four months). These studies were pooled with trials presenting results for week 12. In this way, results of twelve studies involving 2,395 patients were analysed for ASAS20 endpoint at week 12. All biologicals were found to be significantly superior to placebo. Compared to placebo, infliximab showed the highest OR for ASAS 20 response at week 12, OR=6.74 [3.81-11.3], followed by biosimilar infliximab OR=6.39 [2.75-12.78] and golimumab OR=5.7 [2.88-10.44].

Four studies reported ASAS20 response at week 24. The infliximab-biosimilarbiosimilar infliximab RCT presented ASAS20 results at week 30. However, patients in this trial received the same number of infusions as patients in the 24-week infliximab study. Therefore, we pooled these five studies involving 1,337 patients in the analysis of ASAS20 response at week 24.
At week 24, infliximab showed the highest odds ratio compared to placebo (OR=7.2 [95%CI=3.68-13.19]), followed by infliximab-biosimilarbiosimilar infliximab (OR=6.25 [95%CI=2.55-13.14]) and adalimumab (OR=4.81 [95%CI=2.67-8.18]). All biologicals were found to be significantly superior to placebo.

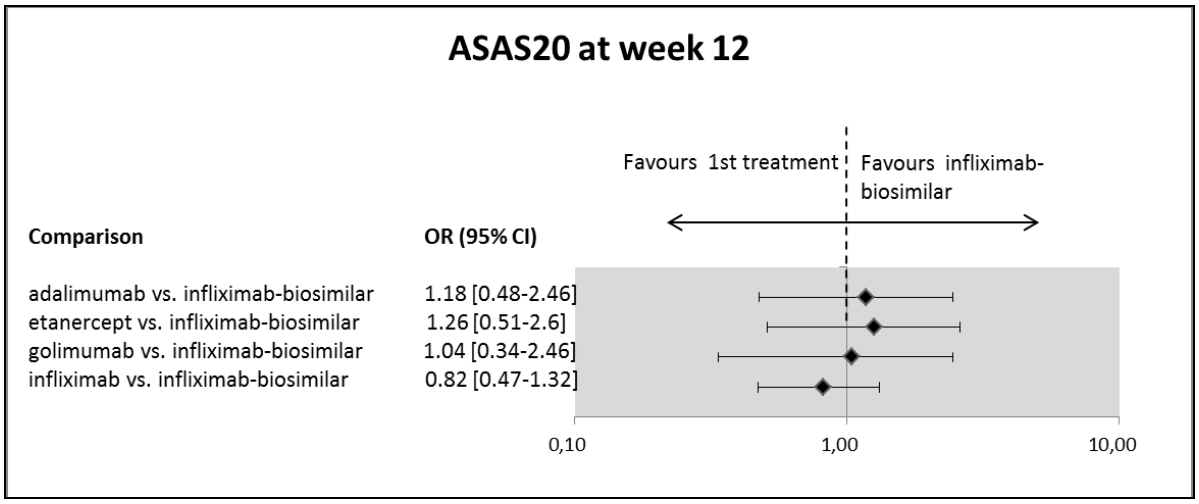
The results of the pairwise comparison did not show significant differences between the efficacy of infliximab-biosimilarbiosimilar infliximab and the other biologicals in terms of ASAS20 response neither at week 12, nor at week 24 (See Figure16).

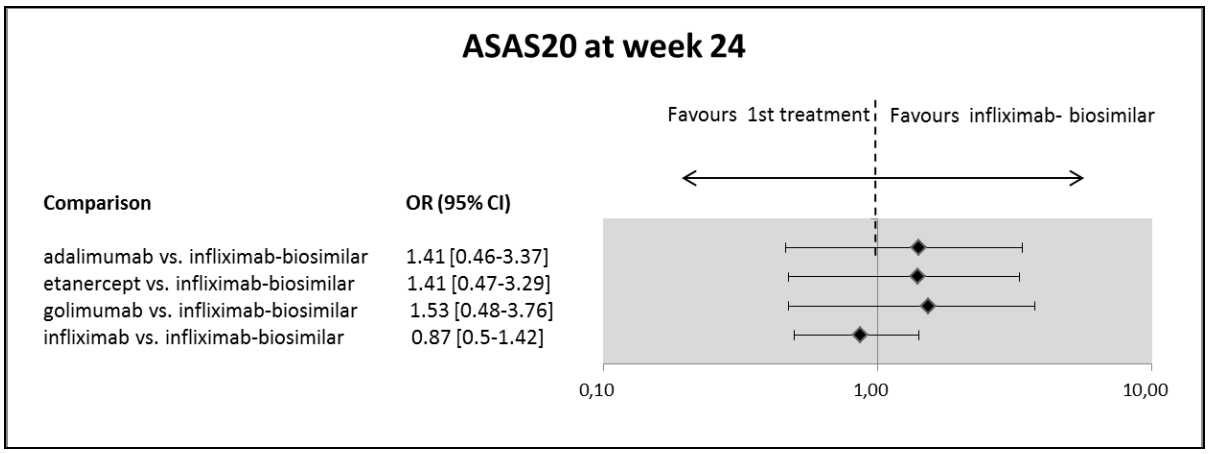
Table 5. Efficacy of biosimilar infliximab and other biologicals compared to placebo in AS, results of mixed treatment comparison

Substance	ASAS20 at week 12, odds ratio [95%CI]	ASAS20 at week 24, odds ratio [95%CI]	Serious adverse events OR [95%CI]
adalimumab	4.65 [3.29-6.43]	4.81 [2.67-8.18]	1,57 [0,27-5,72]
etanercept	4.35 [3.09-5.96]	4.76 [2.73-7.81]	2,36 [0,64-6,58]
golimumab	5.7 [2.88-10.44]	4.53 [2.32-8.22]	0,69 [0,14-2,1]
infliximab	6.74 [3.81-11.3]	7.2 [3.68-13.19]	2,71 [0,35-12,03]
biosimilar infliximab*	6.39 [2.75-12.78]	6.25 [2.55-13.14]	2,31 [0,17-11,43]

*Results for week 14 and 30 were available and considered for biosimilar infliximab.

Figure16. Efficacy of biosimilar infliximab compared to other biological in AS, results of mixed treatment comparison (ASAS20 response at week 12 and 24*)





*Results for week 14 and 30 were available and considered for biosimilar infliximab. Note: The figure presents odds ratios (OR) between treatments. If the point estimate is greater than 1, then the biosimilar treatment is more effective (although not necessarily statistically significantly more effective) compared to the originator biologicals. Credibility intervals provide information on whether the difference between treatments is statistically significant. If the CI contains the value 1, the difference is not statistically significant.

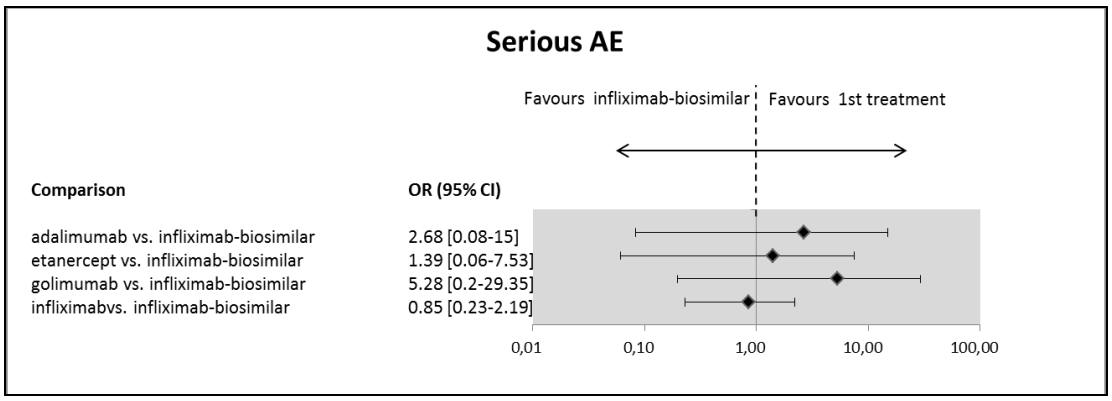
4.2.3.2.2 Safety

The occurrence of severe adverse events (AE) was examined at week 24. Five AS studies involving 1,337 patients reported the occurrence of severe AEs at week 24. In this endpoint the lower ORs are in favor of biologicals, as the lower OR, the lower the chance of the occurrence of serious AEs compared to placebo.

Golimumab gave the lowest odds ratio compared to placebo (OR=0.69 [95%CI=0.14-2.1]), followed by adalimumab (OR=1.57 [95%CI=0.27-5.72]) and biosimilar infliximab (OR=2.31 [95%CI=0.17-11.43]). We have not found significant difference between placebo and biological treatments regarding safety.

Regarding the pairwise comparison of the treatments, we found no significant difference in the safety of biosimilar infliximab and other biological treatments (See Figure17).

Figure17. Safety of biosimilar infliximab compared to other biological in AS: serious adverse events (AE)



Abbreviation: Results for week 30 were available and considered for biosimilar infliximab. Note: The figure presents odds ratios (OR) between treatments. If the point estimate is lower than 1 then the biosimilar treatment is safer (although not necessarily statistically significantly safer). Credibility intervals provide information on whether the difference between treatments is statistically significant. If the CI contains the value 1, the difference is not statistically significant.

4.2.4 Discussion of the efficacy study of AS

Our study based on the meta-analysis of available RCTs, involving 2,395 AS patients at week 12 and 1,337 AS patients at week 24, has demonstrated that there is no significant difference in the efficacy of biosimilar infliximab and other biological drugs in terms of ASAS20 improvement. The results showed no significant differences in the safety of biosimilar infliximab and biologicals either.

Some of the former meta-analyses synthetised the evidence of a single biological agent against placebo (Boyce et al, [2010]); (Poddubnyy et al,

[2011]); (Li et al, [2013]). All these studies concluded that biological agents were superior to placebo. Thaler et al. in their extensive review (year 2012) compared the efficacy and safety of 12 biologicals in seven inflammatory diseases, including AS, based on literature published between January, 2009 and October, 2011 (Thaler et al, [2012]). However, they have not presented results regarding the indirect comparison of available treatments in AS.

McLeod et al. assessed the comparative clinical effectiveness and cost-effectiveness of adalimumab, etanercept and infliximab for the treatment of AS. The authors carried out traditional direct and indirect comparisons of the treatments. Nine placebo-controlled RCTs were included in their meta-analysis. According to their findings the difference between biologicals was not significant. Mixed treatment comparison was used by Migliore at al. and Shu et al.

Shu et al. compared the effectiveness of different doses of adalimumab, golimumab and infliximab in terms of ASAS20 response at week 12. Fourteen RCTs were included in their analysis[9].All drug dosages applied in the RCTs were assessed, while we focused only on treatment arms with the doses recommended by the EMA. Nevertheless, authors came to the same conclusion as us, namely that infliximab 5mg/kg at 0, 2, 6 weeks was the best efficacious therapy (OR=6.53 (95%CI 3.35, 11.61) compared to placebo (Shu et al, [2013]). No significant differences were found between the biological treatments either.

Migliore et al. (2012) compared ASAS20 response at week 24 between biological agents. Three RCTs were included in their analysis as the 24-week golimumab RCT and the recently published RCT with biosimilar infliximab were not included (Migliore et al, [2012]). The authors found no significant differences when comparing directly one biological agent against another. When compared with placebo, infliximab increased the probability of response by 7-times (OR = 6.8), adalimumab by 4-times (OR = 4.4), and

[9] Shu et al.'s study included two additional RCTs, which were not included in our analysis– For further explanation, see the results section.

etanercept by 5-times (OR = 4.9). These results are in line with our findings, which confirms the validity of our study.

We have to acknowledge some limitations of our study. First, a potential weakness of this meta-analysis arises from the fact that the trials from which data are combined are likely to differ in their design. For example, the biosimilar infliximab study reports efficacy and safety results at week 14 and 30 while most of the others for week 12 and 24, that is biosimilar infliximab results are from two and six weeks later, respectively. However, we do not expect strong bias related to this difference as patients in the biosimilar infliximab study received the same number of infusions as patients in the infliximab study. Also, patient characteristics (age, disease duration, baseline BASDAI score) slightly varied across studies.

Furthermore, only the primary efficacy outcome was assessed in this analysis (ASAS20). Other efficacy endpoints were not investigated as on the one hand, some of the RCTs have not reported ASAS40. On the other hand, the biosimilar infliximab RCT did not assess another activity score, the 50% improvement of the initial disease activity score of the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI50). Also, the safety analysis was carried out only for the occurrence of serious adverse events at week 24, since the biosimilar infliximab study presented safety results only at week 30. In this way only five RCTs were included in the safety analysis. Despite these limitations we believe that our analysis contributes with important results to the evidence-based health care evaluation of AS that might support clinical as well as financial decision making.

In conclusion, biosimilar infliximab has recently been approved by the European Medicines Agency for the treatment of adults with active AS and this first meta-analysis suggests that it is similar in both efficacy and safety to other biologicals. Further head-to-head comparisons, continuous data collection and benefit-risk assessment might confirm our results.

5 COST-OF-ILLNESS IN PATIENTS WITH MODERATE TO SEVERE PSORIASIS; A CROSS-SECTIONAL SURVEY IN HUNGARIAN DERMATOLOGICAL CENTRES

This chapter draws upon:

Orsolya Balogh, Valentin Brodszky, László Gulácsi, Emese Herédi, Krisztina Herszényi, Hajnalka Jókai, Sarolta Kárpáti, Márta Péntek, Éva Remenyik, Andrea Szegedi, Petra Baji, Péter Holló (2014): Cost-of-illness in patients with moderate to severe psoriasis; a cross-sectional survey in Hungarian dermatological centres

Eur J Health Econ. 2014 May;15 Suppl 1:S101-9. doi: 10.1007/s10198-014-0599-z. Epub 2014 May 16.

5.1 INTRODUCTION OF THE COST-OF-ILLNESS STUDY IN PSORIASIS

Psoriasis is a chronic inflammatory condition affecting about 0.73% to 2.9% of the population in Europe (Parisi et al, [2013]). Skin disease with multiple different phenotypic variations and degrees of severity is the most prominent feature of psoriasis. Approximately 80% of patients with psoriasis have mild to moderate disease, whereas 20% have moderate to severe disease (Menter et al, [2009]). Classification of psoriasis severity takes into account not only the extent of body surface area involvement, but also the intensity of local signs and symptoms, history of previous treatments, disease duration, degree of disability and the impact of the disease on patients' quality of life (EMA, [2004]). Even a mild disease with limited extent can have a substantial psychological impact on one's personal well-being (Menter et al, [2011]). Psoriasis is associated with considerable co-morbid conditions and elevated mortality has been observed in severe psoriasis (Richard et al, [2013]), (Ogdie et al, [2014]). Epidemiological studies suggest that about 5-25% of patients with psoriasis also develop psoriatic arthritis (PsA) (Dhir et al, [2013]). While commonly

considered a non-life-threatening disease, psoriasis represents significant social and financial burden both for patients and the healthcare system. Owing to the persistent character of the disease patients with psoriasis usually need lifelong care which generates high continuing costs (Radtke et al, [2008]).

Highly effective and expensive biological therapies have increased interest in the cost-of-illness (COI) associated with psoriasis. A systematic literature review on the disease burden of moderate to severe psoriasis was published by Raho and colleagues covering the period between 2002 and 2010 (Raho et al, [2012]). They found altogether 7 COI studies from 5 countries (2 USA, 2 Germany, 1-1 Italy, Spain and Switzerland). Authors highlighted that patients' health related quality of life (HRQL) was affected by psoriasis to a degree comparable with diabetes or cancer. Treatment costs varied significantly across the studies. Direct costs were higher than indirect costs with hospitalization representing the most significant item. It is important to note, however, that there were no patient samples with biological treatment among the seven COI studies and none were from the Central and Eastern European (CEE) region.

The objective of our study was, therefore, to evaluate the disease burden of moderate to severe psoriasis in Hungary by assessing disease related costs from a societal perspective and patients' HRQL. Moreover, we updated the literature search for psoriasis COI studies in order to place our results in the context of the available publications. These data are required for health economic analyses and can provide a more complete picture to health care providers and policy makers on the economic implications of the disease.

Detailed analysis of HRQL related findings, including the mapping of EQ-5D utilities on disease-specific measures, are provided in another article in this Supplement (Herédi et al, [2014]). In this paper we present the main HRQL data and focus on COI results. Besides reporting summary results we

provide subgroup analyses in order to give an insight into the clinical and economic impact of different treatments. Thus, three subgroups were created after sampling based on patients' psoriasis treatment at the time of the survey: patients not receiving systemic therapy (NST); patients receiving traditional systemic treatment (TST) such as methotrexate, retinoids, cyclosporine or phototherapy; and patients on biological systemic treatment (BST), namely on adalimumab, etanercept, infliximab or ustekinumab.

5.2 METHODS OF THE COST-OF-ILLNESS STUDY IN PSORIASIS

5.2.1 Study design and patients

We conducted a non-interventional, cross-sectional questionnaire survey in 2 university dermatology clinics in Hungary. Patients with diagnosis of psoriasis, aged ≥18 years and who gave informed consent were consecutively enrolled between September 2012 and May 2013. Inclusion criteria were set up considering disease severity (assessed by the Psoriasis Area and Severity Index, PASI), health related quality of life (assessed by the Dermatology Life Quality Index, DLQI) and treatment history (Finlay et al, [2005]). (PASI and DLQI are introduced in the next section.) Patients were eligible for inclusion with either 1) PASI > 10 and DLQI > 10; or 2), traditional systemic treatment (TST) or biological systemic treatment (BST) at the time of the survey. Ethical approval was obtained from the national ethical committee (ETT – TUKEB 35183/2012-EKU).

5.2.2 Survey

Patients completed a set of questions (see Appendix 10.5) in which demographic data, employment status, disease duration, self-assessed

disease activity on a visual analogue scale (VAS) and related topical treatments were surveyed. Psoriasis related outpatient care utilizations (GP and dermatologist visits in the past 1 and 3 months, respectively), hospitalizations and transportation to attend medical care in the previous 12 months were recorded. Informal care was assessed for the past month (the number of hours per week provided by others to help the patient in his/her everyday activities). Patients were asked to indicate co-payments and full out-of-pocket expenditures as well.

Absence from work and reduced work productivity were captured by the Work Productivity and Activity Impairment questionnaire (WPAI) (Reilly et al, [1993]). A validated Hungarian version of the Dermatology Life Quality Index (DLQI) was used to assess disease-specific quality of life. The DLQI ranges between 0 (not affected) to 30 (extremely affected), the higher scores correspond to a more impaired quality of life (Finlay et al, [1994]). As a generic health status measure, the EQ-5D questionnaire was used which comprises a descriptive system (EQ-5D-3L) and a Visual Analogue Scale (EQ VAS). The responses to the EQ-5D-3L were converted to utility scores (ranging from -0.594 to 1.0) using the UK social tariffs (Kind et al, [1998]).

Participating dermatologists assessed disease activity on a VAS and disease severity by the Psoriasis Area and Severity Index (PASI) (Pathirana et al, [2009]). The PASI combines assessments of the extent of body surface involvement in four anatomical regions (head, trunk, arms and legs) and the severity of desquamation, erythema and plaque induration (thickness) in each region, yielding an overall score from 0 to 72. The PASI is part of most currently used classifications of disease severity in psoriasis and represents a necessary first step in selecting a treatment strategy. Moderate to severe disease is defined as a PASI score >10 (Pathirana et al, [2009]). Dermatologists categorised patients by the clinical features of psoriasis and provided data on current and previous systemic treatments

(both traditional and biological systemic treatments in the past 12 months).

5.2.3 Costs calculation

Data obtained from the questionnaire survey were used for the calculation of psoriasis related costs. Cost calculation was performed from a social perspective (including direct medical, direct non-medical and indirect costs) over a 12-months period. Hungarian official prices and tariffs were used and costs were presented in 2012 EUR rate (€1 = 285 HUF).The cost of outpatient care was calculated by multiplying the number of visits by the estimated unit prices (GP: €5.2/visit, specialist: €5.7/visit) (HCSO, [2012]); (NHIFA, [2012]). Cost of hospitalization was based on Disease Related Groups (DRGs) reimbursement list (€373.7/admission) (DRG, [2011]). Drug costs were calculated based on official national prices of pharmaceuticals (NHIFA, [2012]). Travel cost to attend health care due to psoriasis was calculated considering the number of visits, the mode of transportation used and the distance between the patient's residence and the dermatology centre (BKK, [2012]); (DKV, [2012]). In cases of ambulance transportation unit costs per km (€3.1/km) was applied based on official financing data (MOH, [2012]).Weekly cost of informal care was estimated by multiplying the average hourly net wage in Hungary (€3/hour) (HCSO, [2012]) with the number of hours per week, but it was capped at a maximum of 40 hours/week.

The costs of absence from work and disability pension due to psoriasis were calculated using both Human Capital Approach (HCA) (Koopmanschap et al, [1996]) and Friction Cost Approach (FCA) (Koopmanschap et al, [1995]) with six-month friction period. Average gross income (€1,054/month in 2012, including net wage, personal income tax, pension contribution, health insurance contributions, employer's contribution) was

used to estimate daily cost (€50/day) of productivity loss which was multiplied with the number of days of absence (HCSO, [2012]).

5.2.4 Statistical analysis

Statistical analysis of the data was carried out using SPSS Version 20.0 for Windows. Descriptive statistics were performed and analyses focused on the comparison between treatment subgroups (NST, TST, and BST). We present the mean with standard deviation, median and bootstrap confidence intervals (1,000 drawings) for each cost domain. Due to the skewed distribution of the cost data, subgroups were compared by non-parametric tests. The level of significance was set to 0.05.

5.3 RESULTS OF THE COST-OF-ILLNESS STUDY IN PSORIASIS

5.3.1 Socio-demographic and clinical characteristics

Altogether 200 patients completed the questionnaire, 68% were male. The mean age of the patients was 51 years (SD 13) and the disease duration was 22 years (SD 11). Main characteristics of the patients are presented in Table 6. The distance between the patient's home and the dermatology center was mean 51 (SD 57) km. Altogether 99 (50%) patients were working (fulltime 79, part time 20) at the time of the assessment, 16 (8%) were on disability pension due to psoriasis. Regarding the characteristics of subgroups, patients receiving biological drug (BST subgroup) were significantly younger than patients without systemic treatment (NST) and moreover, disease duration of patients receiving systemic treatment (BST and TST subgroups) had a significantly longer disease duration than NST patients ($p<0.05$).

Table 6. Main characteristics of the patients

Variables	All patients N=200; mean (SD)	NST N=36; mean (SD)	TST N=61; mean (SD)	BST N=103; mean (SD)
Descriptive statistics				
Females, N (%)	63 (32)	11 (31)	21 (34)	31 (30)
Age, year	51 (13)	56 (13)	52 (13)	49 (12)
Disease duration, year	22 (11)	18 (11)	23 (12)	23 (11)
Weight, kg	88 (18)	83 (15)	86 (20)	91 (18)
Height, cm	172 (9)	171 (9)	170 (10)	172 (9)
Body Mass Index (BMI)	29.85 (5)	28.38 (6)	29.75 (5)	29.55 (5)
Disease related variables				
PASI index	8 (10)	18 (11)	11 (10)	2 (5)
DLQI score	6 (7)	12 (6)	10 (8)	2 (4)
EQ VAS	64 (21)	55 (20)	59 (17)	70 (22)
EQ-5D score (-0,594-1)	0.69 (0.3)	0.65 (0.3)	0,62 (0.3)	0.75 (0.3)
Self-assessed disease activity VAS (0–100 mm)	35 (33)	60 (30)	49 (31)	18 (25)
Physician's global assessment VAS (0–100 mm)	23(28)	58 (24)	34 (28)	7 (14)

NST=no systemic treatment, TST=traditional systemic treatment, BST=biological systemic treatment

5.3.2 Health care utilizations due to psoriasis

Health care utilizations, medications and productivity loss are presented in Table 7. Altogether 105 patients (53%) have had biological treatment in the past 12 months and 7 switches occurred between diverse biological agents whilst 2 patients stopped biological treatment. Thus, altogether 103 patients (52%) were on biological treatment at the time of the survey and they were considered for the BST subgroup. Thirty six (18%) patients were in the NST subgroup and 61 patients (30%) were receiving TST.

Table 7. Annual utilization of health care services, drugs and productivity loss

Health care services	Total sample N=200		NSTN=36		TSTN=61		BSTN=103	
	N (%)	utilization, mean (events/days)	N (%)	utilization, mean (events/days)	N (%)	utilization, mean (events/days)	N (%)	utilization, mean (events/days)
Physician visits*								
GP visits	49 (25)	4.3	12 (33)	6.6	26 (43)	7.5	11 (11)	1.5
Dermatology specialist visit	159 (80)	6.3	24 (67)	9.5	49 (80)	7.6	86 (84)	4.5
Dermatological inpatient care	57 (29)	0.4	11 (31)	0.4	32 (53)	0.6	14 (14)	0.2
Transportation*								
Ambulance	10 (5)	0.2	-	-	3 (5)	0.4	7 (7)	0.3
Travel voucher	28 (14)	0.6	1 (3)	0.05	9 (15)	0.5	18 (18)	0.8
Travel cost	172 (86)	1.7	35 (97)	2.6	52 (85)	2.3	85 (83)	1
Productivity loss**								
Sick leave	18 (9)	2	4 (11)	1.4	8 (13)	3.6	6 (6)	1.3
Disability due to psoriasis	16 (8)	29	3 (8)	30	2 (3)	12	11 (11)	39
Pharmacotherapy***								
TST								
Methotrexate	86 (43)	226	7 (19)	136	38 (62)	216	41 (40)	252
Retinoids	22 (11)	151	4 (11)	151	16 (26)	164	2 (2)	47
Cyclosporin	16 (8)	189	3 (1)	233	10 (16)	223	3 (3)	30
Phototherapy	7 (4)	77	2 (1)	188	5 (8)	32	-	-
BST								
Etanercept	18 (9)	293	-	-	-	-	18 (17)	293
Infliximab	42 (21)	319	-	-	-	-	42 (40)	319

Health care services	Total sample N=200		NSTN=36		TSTN=61		BSTN=103	
	N (%)	utilization, mean (events/days)	N (%)	utilization, mean (events/days)	N (%)	utilization, mean (events/days)	N (%)	utilization, mean (events/days)
Adalimumab	35 (18)	300	-	-	1 (2)-	21-	34 (33)	308
Ustekinumab	17 (9)	260	-	-	1 (2)-	176-	16 (16)	265

* utilization of health care services for the total group

** the length of absence or disability (days)

*** drugutilization among active users of the given medication in the past 12 months (days of treatment)

5.3.3 Psoriasis related costs

The annual costs of all psoriasis related items are presented in Table 8. The mean annual total cost per patient with HCA and FCA was €9,254 (SD €8,502) and €8,305 (SD €7,705), respectively, with direct costs accounting for 86% and 96%. The main cost driver was the biological drug cost amounting to mean €7,339/patient/year in the total sample (N=200). Average total cost differed significantly between treatment subgroups (NST, TST and BST) both with HCA and FCA ($p<0.001$).

5.3.4 Disease severity and quality of life across treatment subgroups

Disease severity (PASI) differed significantly across the three subgroups as patients without systemic treatment (NST) were in the worst state whilst those on biological drug (BST) in the best state ($p<0.01$). HRQL (assessed by the DLQI) of patients with biological treatment was significantly better compared to the other two subgroups ($p<0.01$). The difference in health status utility (EQ-5D score) was significant only between BST and TST subgroups ($p<0.01$).

Table 8. Annual cost / patient (€)

Variables	Total sample N = 200		NST N=36		TSTN=61)		BSTN=103	
	mean (SD)	95% CI_b[3]	mean (SD)	95% CI_b	mean (SD)	95% CI_b	mean (SD)	95% CI_b
Direct medical costs **Physician visits**								
GP visits	22 (48)	16 - 28	34 (56)	16 - 55	39 (56)	24 - 54	8 (24)	4 – 13
Specialist visit	36 (60)	29 - 46	54 (95)	29 - 87	43 (74)	28 - 68	26 (23)	21 - 30
Inpatients care	136 (257)	103 - 172	156 (274)	68 - 249	239 (305)	167 - 328	69 (194)	33 - 105
Total	**195 (286)**	**156 - 235**	**244 (312)**	**152 - 358**	**321 (331)**	**244 - 408**	**103 (23)**	**66 - 148**
Systemic therapy								
Biological	7,339 (7,966)	6,229 – 8,460	-	-	333 (25,089)	0 – 1,088	14,053 (5,121)	13,152 – 15,183
MTX[4]	21 (39)	16 - 27	2 (4)	1 -3	40 (51)	27 - 53	17 (33)	11 - 24
Other systemic therapy	235 (825)	131 - 361	386 (952)	108 – 734	520 (1,238)	241 - 868	14 (96)	2-36
Total	**7,595 (7,791)**	**6,545 - 8,630**	**388 (952)**	**110 - 736**	**893 (2,727)**	**348 - 1,710**	**14,084 (5,099)**	**13,189 - 15,212**
Direct non-medical costs **Transportation**								
Ambulance	18 (117)	4 - 35	-	-	22 (145)	0 - 66	22 (119)	2 - 47
Travel costs	8 (14)	7 - 10	13 (20)	7 - 20	11 (17)	7 - 16	5 (6)	4 - 6
Travel voucher	5 (15)	3 - 7	0.4 (3)	0 – 1.5	3 (8)	0.8 - 5	8 (19)	4 - 12
Total	**31 (117)**	**17 - 48**	**13 (20)**	**8 - 20**	**36 (144)**	**12 - 77**	**35 (119)**	**15 - 58**
Informal care	**117 (610)**	**45 - 220**	**199 (687)**	**29 - 465**	**104 (464)**	**20 - 252**	**96 (659)**	**9 - 240**
Out-of-pocket expenditures								
OTC products	15 (32)	11 - 20	25 (46)	13 - 44	22 (41)	13 - 33	7 (13)	4 - 10

Variables	Total sample N = 200		NST N=36		TSTN=61)		BSTN=103	
	mean (SD)	95% CI_b[3]	mean (SD)	95% CI_b	mean (SD)	95% CI_b	mean (SD)	95% CI_b
Non- reimbursed services	45 (198)	22 - 74	55 (140)	16 - 106	52 (184)	18 - 113	38 (223)	6 - 91
Total	**60 (206)**	**35 - 91**	**80 (143)**	**38 - 134**	**74 (202)**	**35 - 138**	**45**	**13 - 95**
Total direct costs	**7,999 (7,680)**	**6,902 - 9,063**	**923 (1,312)**	**535 - 1,406**	**1,428 (2,832)**	**861 - 2,235**	**14,363 (5,036)**	**13,449- 15,455**
Indirect costs								
Productivity loss due to sick leave	307 (1,216)	152 - 497	208 (886)	16 - 573	545 (1,782)	171 – 1,034	200 (836)	57 - 380
Permanent work disability (HCA)	948 (3,339)	444 – 1,453	1,054 (3,545)	0 – 2,392	415 (2,271)	0 – 1,090	1,227 (3,762)	614 – 2,084
Permanent work disability (FCA)	0	0 - 0	0	0 - 0	0	0 - 0	0	0 - 0
Total indirect costs (HCA)	**1,255 (3,470)**	**785 - 1,781**	**1,262 (3,591)**	**275 - 2,568**	**960 (2,806)**	**332 - 1,745**	**1,427 (3,789)**	**738-2,182**
Total indirect cost (FCA)	**307 (1,216)**	**144 - 484**	**208 (886)**	**16 - 573**	**545 (1,782)**	**171 - 1,034**	**200 (836)**	**58-390**
Total costs (HCA)	**9,254 (8,502)**	**8,050 - 10,436**	**2,186 (4,165)**	**986 - 37,398**	**2,388 (4,106)**	**1,456 - 3,512**	**15,790 (6,016)**	**14,680 - 17,050**
Total cost (FCA)	**8,305 (7,705)**	**7,167 - 9,367**	**1,132 (1,734)**	**627 - 1,756**	**1,973 (3,585)**	**1,139- 3,035**	**14,562 (5,056)**	**13,674 - 15,662**

MTX=methotrexate; HCA=Human Capital Approach; FCA=Friction Cost Approach

CI=bootstrap confidence intervals of the mean costs

5.4 DISCUSSION OF THE COST-OF-ILLNESS STUDY IN PSORIASIS

This study provides data on COI and HRQL in patients with moderate to severe psoriasis in Hungary attending hospital based dermatology centres. The annual societal cost of psoriasis in patients with a mean age of 50 years and a disease duration since first medical diagnosis of psoriasis of 22 years is mean €9,250 per patient, and is primarily driven (86%) by direct medical costs.

The majority of the patients (N=103, 52%) were receiving biological agent at the time of the assessment. According to the latest available data of National Health Insurance Found Administration, in 2010 altogether 682 patients with psoriasis received biological treatment in Hungary thus our survey captured a substantial proportion of this patient group (Laki et al, [2013]). Analysis by treatment subgroups revealed that yearly average total costs differ significantly across NST (€2,190), TST (€2,388) and BST (€15,790) subsamples.

Significant differences were observed across treatment subgroups with regard to disease severity (PASI, DLQI) and patients' general health state (EQ-5D) as well. Patients with biological treatment had a significantly lower disease severity (PASI score) and better HRQL (DLQI score) than their counterparts with our without traditional systemic treatment. The EQ-5D indicated also the best health state in the BST subgroup, however, the difference was significant only compared to TST subgroup. When comparing EQ-5D utility weights to the age-matched population norm in Hungary (age group 45-54 years, mean 0.81) (Szende, [2003]) a lower average score was observed in each subgroup (NST: 0.65, TST: 0.62, and BST: 0.75) resulting in a difference of 0.16, 0.19 and 0.6, respectively.

Both the average direct medical cost (excluding biological treatment costs) and indirect cost were the lowest in the BST subgroup when applying the 6-month FCA. One reason for that is the rate of patients who went on sick leave due to psoriasis in the past 12 months was the lowest (6%) among the subgroup of patients with biological treatment. On the other hand, although the rate of disability pensioners was the highest in this same subsample (11%), all of them were classified as permanently unable to work before the time period considered for the friction cost calculation. As a consequence, when HCA was used to calculate productivity related costs BST subgroup ranked as the one with the highest indirect cost. Overall we can conclude that patients on biological treatment had the highest total costs but the lowest disease activity and best quality of life compared to their counterparts receiving conventional systemic treatment or no systemic treatment.

Presence of psoriatic arthritis (PsA) may represent additional burden in psoriasis although findings in the literature are contradictory (Ciocon et al, [2008]). In our study 57 patients (29%) were diagnosed with PsA (females 35%, age 54 years, psoriasis disease duration 23 years) and 52% of them received biological therapy. The mean EQ-5D score of patients with concomitant PsA was significantly lower (<0.01) than that of patients without PsA, nevertheless they were older as well (54 vs. 51 years, p=0.035). Cost of informal care was high (mean €314/patient/year) among PsA patients reflecting a high disability and dependence on others of this specific subsample. Mean annual cost (with HCA) of patients with PsA was €8,977 (SD9,488) per patient and total costs by NST, TST and BST subgroups were mean €1,729, €775 and €16,983, respectively.

For comparison, Brodszky and colleagues surveyed 183 patients with PsA in Hungary in 2007 with similar age (mean 50 years) and disease duration (mean 19 years) (Brodszky et al, [2009]). The rate of patients on biological treatment was much lower (6%) resulting in a somewhat lower total cost (mean €5,547/patient/year, on 2007 prices).Nevertheless, when patients

on biological treatment were excluded from the analysis total cost were much higher (mean €4,281/patient/year, on 2007 prices) than in the NST and TST subgroups of PsA patients in our current survey. These results seem to suggest that rheumatic features might add extra HRQL loss and increase in costs in psoriasis. Nonetheless, further direct comparative studies are needed to confirm our findings.

Taking into account that the first biological agent was registered for the treatment of psoriasis in 2004 we would have expected COI studies involving patients with biological treatment by the end of January 2010, the date when the last systematic literature review was closed (Raho et al, [2012]). Contrarily, no such studies had been published by that time. Therefore, we performed a literature search for COI studies for the period from January 2010 to December 2013 using the same search terms and databases as Raho and colleagues (Raho et al, [2012]).

Our search identified a further nine publications (Fonia et al, [2010]); (Driessen et al, [2010]); (Kimball et al, [2011]); (Gleason et al, [2013]); (Le Moigne et al, [2013]); (Levy et al, [2012]); (Ghatnekar et al, [2012]); (Tang et al, [2013]); (Steinke et al, [2013]), seven of which involved psoriasis patients with biological treatment. In the COI analyses conducted by Fonia and colleagues (UK) and Driessen and colleagues (the Netherlands) all patients were treated with biological drugs. The biological treatment rate was 16% in the study by Ghatnekar and colleagues (Sweden), 13% by Levy and colleagues (Canada), 6% by Steinke and colleagues (Germany) and 3.6% by Le Moigne and colleagues (France). Only one study by Gleason and colleagues (US) did not report the rate of biological therapy.

Studies that provided costs specifically for BST groups or subgroups were selected for comparison. Neither the study by Gleason et al. (US) nor the one by Levy et al. (Canada) reported costs data for BST group, therefore, these were excluded. Moreover, only 8 patients received biological agent in the study by Steinkeet al. (Germany) so this was not considered either.

Finally we compared our results to 4 studies: Fonia (UK, 2010), Driessen (the Netherlands, 2010) [29], Ghatnekar (Sweden, 2012) and Le Moigne (France, 2013). (Table 9)

Fonia and colleagues conducted a retrospective chart review involving 76 BST patients. Health care resource utilization data were collected 12 months before and after BST initiation. The viewpoint of cost calculation was the third party payer and only direct medical costs were collected. Total cost of psoriasis care prior to biological treatment was £4,207/patient/year (€4,742) while after the biological treatment was initiated total costs rose to £11,981/patient/year (€13,505).The cost of the biological treatment was the main cost driver. However the total cost of hospitalization decreased by £1,683/patient/year (€1,897) and PASI decreased by 8.9 points in the BST subgroup.

A similar study design was applied in the Netherlands. Driessen and colleagues collected health care resource utilization data 12 months before and after starting biologic therapy start based on retrospective chart review including 67 BST patients. Mean direct medical cost during the pre and post period was €10,146 and €17,712/patient/year, respectively. The costs of other drug treatments, outpatient visits and hospitalizations decreased during the year after the biological therapy was given. An improvement of skin manifestation was observed after BST initiation and PASI decreased by 12.6 points.

A retrospective health insurance claims database analysis was conducted by Le Moigne and colleagues among patients with moderate to severe psoriasis in France. Two cohorts of 69 BST and 1,855 TST patients were compared during a 6-months period. The mean total direct medical costs in BST and TST patient groups were €16,214 vs. €3,356/patient/year. All cost items were higher in BST subgroup and the largest difference was identified in the cost of hospitalization, as this cost item was €886/patient/year higher than in TST subgroup.

Table 9. Cost-of-illness studies of psoriasis, reporting costs of BST*, till December 2013 in comparison with results of the current survey

Study	**Method**	**Patients**	**N_{total}/ $N_{biologic}$**	**Mean direct cost/patient/year** TST / BST	**Mean indirect cost/patient/year** TST / BST	**Mean total cost/patient/year** TST / BST
Foniaet al. 2010, United Kingdom	retrospective chart review	severe psoriasis, 2 tertiary dermatology centers	76/76	€4,742 / €13,505	n.r.	n.a.
Driessenet a. 2010, The Netherlands	retrospective chart review	moderate to severe psoriasis, 1 tertiary dermatology center	67/67	€10,146 / €17,712	n.r.	n.a.
Ghatnekar et al. 2012, Sweden	follow-up study	severe psoriasis, 1 tertiary and 1 secondary dermatology center	164/27	€7,812/ €18,457	€5,208/ €2,051	€13,020/ €20,508
Le Moigne et al. 2013, France	insurance claim database analysis	general psoriasis population, all types of out-patient and inpatient providers in an administrative area	1,924/69	€3,356 / €16,214	n.r.	n.a.
Balogh et al. 2014, Hungary (current survey)	cross-sectional study	moderate to severe psoriasis at 2 tertiary dermatology centers	200/103	€1,428/ €14,363	€960 / €1,427	€2,388/ €15,790

n.r.: not reported; n.a.: not applicable

In Sweden, Ghatnekar and colleagues performed a 1-month prospective study in 2009 from the societal viewpoint. Altogether164 patients were involved and among them 27 (16%) patients received BST.For the whole study population the average total cost was €11,928/patient/year (when monthly costs are multiplied by 12) which is higher than in our study (€9,254/patient/year). The total cost of TST subgroup was €13,020/patient/year, which is much higher than our TST result (€2,388/patient/year).

The main direct cost drivers were the biological drugs, outpatient visits and phototherapy. The indirect cost (productivity loss) was 16% of the total costs, which is similar to our finding of 14% associated with indirect costs. In the BST subgroup the yearly average total costs were €20,508 whilst we reported €15,790 per patient in our study. The indirect costs were lower in BST than in TST subgroup (€2,051 vs. €5,208). Despite the €14,280/patient/year difference of drug costs for TST vs. BST, the difference in total cost between these two subgroups was only €7,476/patient/year due to the offsets from improved productivity. In our study the indirect cost of BST subgroup was higher (HCA) than in TST subgroup (€1,427 vs. €960).

The total costs of BST presented in three of the four studies (Fonia et al, [2010]); (Driessen et al, [2010]); (Ghatnekar et al, [2012]; (Le Moigne et al, [2013]) were higher compared to our results in Hungary. In three studies (Fonia et al, [2010]); (Driessen et al, [2010]); (Le Moigne et al, [2013]) the costs of hospitalization and out-patient visits were lower in BST subgroup, similarly to our findings. These studies were conducted in tertiary dermatology centres with a very similar methodology. Le Moigne et al. presented different results. In this study the cost of out-patient visit and hospitalization was higher in BST subgroup compared to other subgroups. Health care utilization data are greatly depending on the financing mechanisms, professional and financing guidelines, management,

standard care, referral system, unit costs and cost accounting approaches of the given country and vary substantially, so it is very difficult to make comparisons among countries.

Our study has some limitations. The survey was conducted in two university based dermatology centers involving psoriasis patients attending outpatient care. Patients with mild psoriasis were not selected and patients with severe psoriasis might be under-represented in the sample. We used a retrospective survey to assess health care utilizations, recall bias might occur. Another limitation is due to the cross-sectional design, the current treatment were used as a proxy to measure disease severity and costs. In this sample there is a mixed patient population in terms of severity of disease, patients with recently initiated or changed treatment where the full effect has not been achieved yet. Seasonal variations were not taken into consideration. Further research is needed involving representative samples and incidence follow-up cohorts to further assess the changes in costs and in quality of life in the long term.

Our study showed that the economic burden of psoriasis is considerable in Hungary and revealed that results from health economic studies in psoriasis in other countries cannot be adapted without adjustment. With this study we provided input for further health economic analyses and a baseline to evaluate the economic effects of psoriasis treatment in Hungary. In line with our hypothesis, biological treatment increased the direct costs associated with while considerably improving quality of life of patients. Our study was the first from the CEE region that provided COI data and had the largest sample size of biologic treated patients in Europe.

6 EXPLORING THE RELATIONSHIP BETWEEN EQ-5D, DLQI AND PASI, AND MAPPING EQ-5D UTILITIES: A CROSS-SECTIONAL STUDY IN PSORIASIS FROM HUNGARY

This chapter draws upon:
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6.1 INTRODUCTION TO THE UTILITY MEASURING

Psoriasis is a chronic immune-mediated inflammatory disease of (Parisi et al, [2013]) the skin with various presentations and clinical courses. It is estimated to affect approximately 0.73-2.9% of the population throughout Europe. Extra-cutaneous manifestations such as arthritis, cardiovascular diseases or mental disorders are often associated with psoriasis. To date, there was no definitive cure for the disease, and therefore, patients usually need long-term treatment. Severe psoriasis has a profound impact on patients' health related quality of life (HRQOL) encompassing physical, psychological, and socio-economic levels (de Korte et al, [2004]).

Economic evaluations require data on health related quality of life (HRQOL) on preference-based measures that capture preference weights (called utility, in terms of desirability) about values of different health states. Also, in many countries utility measures are required for reimbursement decisions. EQ-5D is the most commonly used utility measure in health economic

analyses, however, it is rarely administered in clinical trials. Therefore, there is a demand for cross-walking (or mapping) algorithms to estimate EQ-5D utility scores from other HRQOL measures.

In recent years, introduction of biological agents (adalimumab, etanercept, infliximab, and ustekinumab) opened up new horizons in the treatment of patients with severe psoriasis. Compared to standard treatment, they proved clinical efficacy, but their use is associated with much higher costs and societal burden as well (Ahn et al, [2013]) (Brodszky et al, [2013]). Due to biologicals, HRQOL measures should be able to face a new patient population with better health state, with currently unexplored possible predictors of HRQOL and with new expectations of treatment outcomes.

There have been continuous discussions concerning the most appropriate, valid, sensitive, and reliable HRQOL assessment tool in psoriasis (Bronsard et al, [2010]). Dermatology Life Quality Index (DLQI), Psoriasis Area and Severity Index (PASI), and Short Form-36 (SF-36) are the most widely used instruments in psoriasis. Although these are focusing on different aspects of HRQOL, several overlaps exist between them.

DLQI was the first disease-specific questionnaire in dermatology with 20 years' experience in clinical trials and in everyday clinical practice by now. It has been considered a simple, valid, and reliable outcome measure is psoriasis (Lewis et al, [2004]). Nevertheless, from the perspective of health economics, a major disadvantage of DLQI has to be addressed. Due to it is not a preference-based measure, it does not enable to calculate utilities for economic evaluations.

Over the past decade, the literature on mapping the general measure EQ-5D in different diseases has rapidly grown (Baran, [2010]). According to the University of Oxford HERC online database of mapping studies (Dakin et al, [2013]), only two papers and a conference abstract have been published about mapping EQ-5D in psoriasis, so far (Norlin et al, [2012]); (Blome et al,

[2013]); (Currie et al, [2007]). All these researches investigated the relationship between the dermatology-specific DLQI questionnaire and the EQ-5D index.

Recent evidences suggest a significant moderate correlation between EQ-5D and DLQI global scores (Norlin et al, [2012]); (Blome et al, [2013]); (Currie et al, [2007]); (Hjortsberg et al, [2011]). Prior mapping studies could explain only 27-31.3% of the variance of EQ-5D [8-10]. Consequently, almost 70% of the possible predictors of EQ-5D in psoriasis has still remained hidden.

The objectives of this present cross-sectional study are, at first, to analyse correlations between the widely used HRQOL and disease severity instruments of psoriasis and compare their capacity to distinguish among patients' severity groups; secondly to seek for new possible predictors of HRQOL to establish mapping models on EQ-5D score and on visual analogue scale (EQ VAS).

6.2 METHODS OF THE UTILITY MEASURING

6.2.1 Patients

Between September 2012 and May 2013 a cross-sectional questionnaire survey of consecutive adult psoriasis patients from two Hungarian university clinics was carried out. The number of participants was limited to approximately 100 patients from each clinic. Patients included were required to be 18 years or older and to have been diagnosed with moderate to severe psoriasis (PASI> 10 or DLQI> 10 or patient using systemic or biological treatment) 12 months or more before the inclusion to the study. Data were collected by dermatologists at Semmelweis University, Department of Dermatology, Venereology and Dermatooncology (Budapest) and at the University of Debrecen, Clinic of Dermatology. All patients were invited to participate by their physicians during outpatient visits and signed

an informed consent form. The study was approved by the national research ethic committee (ETT – TUKEB 35183/2012-EKU).

6.2.2 Outcome measures and assessment

All participants and their physicians were asked to complete a self-designed questionnaire. Patients' questionnaire concerned demographic data, general health state, quality of life (EQ-5D, EQ VAS, DLQI, self-assessed disease severity VAS) affected body sites, and disease duration. Dermatologists' questionnaire was based on the patients' clinical type of psoriasis, PASI, psoriasis treatments in the last 12 months, current clinical outcomes, and physician's' global assessment of disease activity visual analogue scale (PGA VAS).

Quality of life was captured by the validated Hungarian versions of EQ-5D questionnaire, by PGA VAS and by disease-specific DLQI. Clinical severity of psoriasis was assessed by using psoriasis Area and Severity Index (PASI-72) and patients' self-assessed disease severity VAS. Questions included if there were any GP visit(s) in the last months, dermatologist visit(s) in the last 3 months and hospitalisation(s) in the last 12 months. Necessity of home help (professional or informal, e.g. family members) in the last 1 month and work impairment due to psoriasis were also recorded.

EQ-5D consists of a five-item instrument to assess general HRQOL (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and of a visual analogue scale (EQ VAS). In the current survey, EQ-5D-3L version was used in which each dimension has three response levels (no problems, some problems, and severe problems), accordingly 3^5=243 combinations of health states are possible. Due to lack of evaluated Hungarian tariffs, the UK weights were applied to calculate global EQ-5D scores; thus utility outcomes can range from -0.59 to +1, where -0.59 is corresponding to the worst and +1 corresponding to the best possible quality of life (Dolan et al, [1997]). EQ VAS is a 20 cm long, vertical visual analogue scale with endpoints of '0'

(worst possible health state) and ‘100’ (best possible health state) recording patients’ self-rating of their overall health which as well enables determining utilities.

DLQI is a disease-specific self-assessment questionnaire validated for measuring HRQOL in psoriasis (Finlay et al, [1994]); (Basra et al, [2008]) The ten-item questionnaire’s scale range from ‘0’ to ‘30’, where higher scores indicate greater disability experienced by patients. Each questions of DLQI scores quality of life impairment due the dermatologic condition in a 4-point Likert scale, including aspects such as symptoms, side effects of treatment, daily activities, work or school, personal relationships, leisure activities, and feelings of embarrassment.

PASI-72 (hereinafter PASI) is quantitative rating scale for psoriasis based on the severity of the lesions and the size of psoriatic areas assessed by physicians. It is widely used both in clinical trials to measure clinical effectiveness and in routine care to evaluate treatment success. To calculate PASI scores, the body is divided into four sections based on the estimated area of the skin affected (head=0.1, upper extremities=0.2, trunk=0.3 and lower extremities=0.4). Each area is graded by itself from 0–6, depending on the estimated percentage of the psoriatic involvement (0=0%, 1≤10%, 2=10–29%, 3=30–49%, 4=50–69%, 5=70–89%, and 6=90–100%). Within each area, severity is judged by the presence of three clinical signs: erythema, induration, desquamation (measured on a scale of 0 to 4). Total PASI values range from 0–72, with higher scores indicating greater disease severity.

6.2.3 Statistical analysis

Spearman’s rank correlation was used to test associations between outcome measures. Mann–Whitney U-test was performed to compare the differences in the distribution of EQ-5D, DLQI, and PASI.

The known-groups method was applied to compare outcome measures ability to detect differences between groups with known attributes. Overall 11 categories, including clinical types, localisation and several medical records were selected to grouping variables. In each category we expected that patients responded 'Yes' to a question had worse scores in quality of life or in disease severity measures than those who responded 'No' (i.e. control group). To compare the means of the two groups, effect size (Cohen's d) was calculated by dividing the difference of the means by pooled standard deviation. The Cohen's d is considered small if 0.2–0.5, medium if 0.5–0.8, or large if> 0.8, respectively, where the measure with a higher value can better distinguish between groups (Cohen, [1992]).

To determine possible predictors of quality of life in psoriasis, age, disease duration, body mass index (BMI), and instruments that significantly correlated with EQ-5D, were enrolled as continuous variables. Additionally, those categorical variables were selected as possible predictors which proved significant EQ-5D difference between their two possible outcomes (e.g. presence or absence of a clinical type, symptom or treatment). From this point forward, negative EQ-5D values were truncated to 0. In a bivariate mapping model on EQ-5D score and on EQ VAS, only DLQI was included as an independent predictor of the target variables. Then, to find an optimal algorithm in a multivariate approach that can explain the highest proportion of variance, we included all the possible predictors which were found to be in a significant relationship with the target variable. Data were analysed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). All the applied statistics were two-sided with a significance level of $p<0.05$.

6.3 RESULTS OF THE UTILITY MEASURING

6.3.1 Patient characteristics

Altogether 200 patients participated in the survey. Patient characteristics are described in Table 10. The mean age was 51 years with male

predominance (68.5%). The mean disease duration was 22 years. Overall 159 (79.4%) of the participants were overweight (BMI≥25). The most frequent type of psoriasis was chronic plaque psoriasis with 126 (63%), followed by nail psoriasis 71 (35.5%), scalp psoriasis 69 (34.5%), psoriatic arthritis 57 (28.5%), inverse psoriasis 18 (9%), palmoplantar psoriasis 12 (6%), erythrodermic psoriasis 4 (2%), and guttate psoriasis 4 (2%) (combinations are possible). In total, 50 (25%) of the patients reported psoriasis involvement of the face, 36 (18%) of the neck and/or décolletage, 83 (41.5%) of the hands and/or palms, 69 (34.5%) of the hand nails, 110 (55%) of the forearms, and 134 (67%) of the lower extremity, respectively. At the time of the survey, 59 (29.5%) of the patients had no symptoms at all (i.e. PASI=0).

Table 10. Patient characteristics

	n	Mean	SD	Median	Range
Age (years)	200	51.24	12.9	53	21-85
Psoriasis duration (years)	200	21.96	11.67	20.5	1-63
BMI (kg/m^2)	199	29.89	5.44	29.41	16.45-46.81
EQ-5D score (-0.594 to 1)	192	0.69	0.31	0.73	-0.43-1
EQ VAS (0-100)	196	64.43	21.34	70.00	0-100
DLQI (0-30)	194	6.29	7.29	3.00	0-28
PASI (0-72)	200	8.01	10.01	3.45	0-49.5
Physician's global assessment VAS (0–100 mm)	189	23.39	28.24	7.00	0-100
Self-assessed disease severity VAS (0–100 mm)	199	34.84	33.33	20.00	0-100

Among the included patients, 103 (51.5%) received biological drug in mono- or combination therapy, 61 (30.5%) systemic non-biological therapy, and 30 (15%) only topical treatment at the time of the survey. The distribution of scores in the applied quality of life instruments were skewed, thus the median is considered a better measure for the centre. The medians of quality of life tools were 0.73 for EQ-5D, 70 for EQ VAS, 3 for DLQI global score and 3.45 for PASI, respectively. Frequencies of health service utilisation variables, including medical examinations, types of treatment,

and additional non-reimbursed services are described elsewhere (Balogh et al, [2014]).

6.3.2 Comparison

Results obtained from correlation analysis of the instruments are demonstrated in Table 11. EQ-5D score showed a moderate negative correlation with DLQI, PASI, PGA, and with patients self-assessed disease severity VAS (0.29 < Spearman's-rho < 0.5). Strong significant correlation was found between DLQI, PASI, PGA, and self-assessed disease severity VAS.

Table 11. Spearman's correlations between the outcome measures

	EQ-5D score (-0.59-1)	**DLQI**	**PASI**	**PGA VAS**
EQ VAS (0-100)	0.56*	-0.43*	-0.42*	-0.42*
DLQI (0-30)	-0.48*	-	0.81*	0.80*
PASI (0-72)	-0.43*	0.81*	-	0.92*
PGA VAS (0–100 mm)	-0.42*	0.80*	0.92*	-
Self-assessed disease severity VAS (0–100 mm)	-0.41*	0.78*	0.78*	0.79*

*significant p<0.05. For DLQI and PASI '0' and for all other measures, the highest value is the best possible outcome

The differences between known-groups are presented in Table 12. As expected, in each category patients with more severe disease (responded 'Yes') reported significantly worse quality of life than the control group (Mann-Whitney U test, p <0.05). EQ-5D revealed the highest effect sizes in 4 out of the 11 examined categories: GP visit(s) in the last month, necessity of home help in the last month, and in the clinical types of palmoplantar psoriasis and psoriatic arthritis. Nevertheless, it was the least effective tool in capturing the variables of hospitalisation(s) in the last year, biological therapy and the localisations of psoriatic lesions. DLQI and PASI were able to

discriminate between these groups better. Patients with visible lesions (on body areas uncovered by clothes - face, neck, décolletage, hands, palms, hand nails) reported poorer HRQOL than those without visible lesions measured with any instrument.

Table 12. Differences in effect size (Cohen's d) between outcome measures with the known-groups method

		EQ-5D**			EQ-5D VAS			DLQI			PASI		
		n	mean	Effect size	n	mean	Effect size	N	mean	Effect size	n	mean	Effect size
Clinical type of Psoriasis													
Palmoplantar Psoriasis	No	152	0.71(0.29)	**1.2**	162	63.59(21.08)	**0.63**	160	6.41(7.37)	**0.69**	162	8.03(9.47)	**1.04**
	Yes	12	0.36(0.39)*		12	50.33(21.42)*		12	11.42(6.82)*		12	18.38(16.04)*	
Psoriatic arthritis	No	118	0.77(0.24)	**1.03**	121	65.61(20.7)	**0.44**	119	5.57(6.98)	**0.51**	121	6.95(9.12)	**0.55**
	Yes	56	0.48(0.36)*		57	56.61(20.76)*		57	9.26(7.70)*		57	12.42(11.47)*	
Localisation of Psoriasis													
Visible lesions (on body areas uncovered by clothes)	No	71	0.79(0.24)	**0.54**	72	72.1(19.77)	**0.6**	72	1.49(3.98)	**1.25**	74	2.26(5.24)	**1.02**
	Yes	113	0.63(0.33)*		116	59.75(21.23)*		114	9.3(7.36)*		118	11.34(10.61)*	
Facial involvement	No	144	0.74(0.28)	**0.55**	147	66.82(20.73)	**0.46**	145	4.63(6.48)	**0.98**	150	5.65(8.0)	**1.04**
	Yes	48	0.57(0.37)*		49	57.23(21.75)*		49	11.2(7.38)*		50	15.1(12.01)*	
Neck and/or décolletage involvement	No	156	0.74(0.28)	**0.89**	160	67.75(20.26)	**0.9**	158	4.47(6.28)	**1.59**	164	5.37(7.63)	**1.77**
	Yes	36	0.48(0.34)*		36	49.65(19.97)*		36	14.28(5.95)*		36	20.01(10.89)*	
Psoriasis on hands and/or palms	No	111	0.75(0.26)	**0.46**	114	68.41(20.08)	**0.46**	113	3.96(6.38)	**0.83**	117	4.61(7.24)	**0.9**
	Yes	81	0.61(0.35)*		82	58.88(21.92)*		81	9.53(7.27)*		83	12.8(11.38)*	
Psoriasis on hand nails	No	127	0.74(0.28)	**0.46**	128	67.06(21.76)	**0.36**	128	4.58(6.7)	**0.73**	131	6.19(9.52)	**0.55**
	Yes	65	0.60(0.35)*		68	59.47(19.76)*		66	9.61(7.29)*		69	11.47(10.09)*	
Medical history													
GP visit(s) in the last month due to	No	145	0.77(0.27)	**1.05**	148	68.46(20.05)	**0.82**	146	4.67(6.37)	**0.98**	151	6.52(9.33)	**0.63**
	Yes	47	0.47(0.32)*		48	51.99(20.58)*		48	11.21(7.76)*		49	12.59(10.74)*	

		EQ-5D**			EQ-5D VAS			DLQI			PASI		
		n	mean	Effect size	n	mean	Effect size	N	mean	Effect size	n	mean	Effect size
Psoriasis													
Hospitalisation(s) in the last 12 months due to Psoriasis	No	138	0.74(0.28)	**0.5**	140	68.82(19.52)	**0.76**	138	4.76(6.36)	**0.77**	143	6.58(9.83)	**0.52**
	Yes	54	0.59(0.36)*		56	53.44(21.91)*		56	10.05(8.08)*		57	11.61(9.64)*	
Use of home help (professional or informal) in the last month	No	165	0.75 (0.25)	**1.45**	169	66.31(20.78)	**0.66**	167	5.09(6.66)	**1.3**	173	6.49(8.69)	**1.22**
	Yes	27	0.35(0.41)*		27	52.65(21.43)*		27	13.7(6.70)*		27	17.77(12.40)*	
Biological therapy	No	90	0.63(0.31)	**0.37**	93	57.46(18.35)	**0.66**	93	10.8(7.4)	**1.48**	97	13.87(10.72)	**1.39**
	Yes	102	0.75(0.31)*		103	70.72(21.96)*		101	2.14(3.92)*		103	2.5(4.91)*	

* significant ($p<0.05$) in Mann-Whitney U test;** Minimum important difference: 0.09 EQ-5D index score, Shikiar et al. 2006 [31]

6.3.3 Mapping EQ-5D

A simple linear regression of DLQI onto both EQ-5D score and EQ VAS was performed: EQ-5D = 0.8 – 0.02*DLQI (adjusted r^2=0.169, ANOVA p<0.001), EQ VAS = 71.23 – 1.07*DLQI (adjusted r^2=0.129, ANOVA p<0.001). Thus, DLQI global score explained 16.9% of the variance of EQ-5D and 12.9 % of the variance of EQ VAS.

In order to establish a multivariate function, only those variables were applied which were previously tested and showed significant correlation (continuous variables) or significant EQ-5D difference between their outcomes (categorical variables) with the target indices. Thus, overall 23 possible predictors of EQ-5D and 21 of EQ VAS were identified.

In the final stepwise multiple regression, 10 out of the 23 possible predictors of EQ-5D and 6 out of the 21 possible predictors of EQ VAS were enrolled (See Table 13). The models are explaining 48.8% of EQ-5D variance and 30.4% of EQ VAS variance (adjusted R^2=0.488 and 0.304, ANOVA p<0.001). Consequently, mapping functions of the two indices are more accurate than there were in our bivariate regressions. Three predictors were included in both target variables' model, hospitalisation(s) in the last 12 months, the GP visit(s) in the last month, and presence of palmoplantar involvement. Furthermore, we noted that global DLQI score did not have an impact on EQ VAS values. However, we found that patients' self-assessed disease severity is implied in the multiple model of EQ VAS with an unstandardised regression coefficient (ß) of -0.14. Hence, 1 point fall on the patients' self-assessed VAS eventuates 0.14 point fall in EQ VAS.

Table 13. Regression coefficients in the multivariate mapping on EQ-5D and EQ-5D VAS

	EQ-5D score			EQ VAS		
	Unstandardised regression coefficient (â)	Standardised regression coefficient	p	Unstandardised regression coefficient (â)	Standardised regression coefficient	p
Constant	**1.026**		**<0.001**	**110.588**		**<0.001**
Age	-	-	-	-0.350	-0.214	0.002
Gender (female)	-0.090	-0.145	0.014	-	-	-
BMI	-	-	-	-0.600	-0.157	0.025
Psoriasis duration	-0.004	-0.169	0.006	-	-	-
DLQI	-0.080	-0.190	0.023	-	-	-
Self-assessed disease severity VAS	-	-	-	-0.14	-0.218	0.004
Chronic plaque Psoriasis	-0.089	-0.151	0.029	-	-	-
Palmoplantar Psoriasis	-0.347	-0.269	<0.001	-12.570	-0.145	0.034
Scalp Psoriasis	0.152	0.252	0.001	-	-	-
Psoriatic arthritis	-0.134	-0.212	0.002	-	-	-
GP visit(s) due to Psoriasis in the last month	-0.160	-0.227	<0.001	-8.112	-0.167	0.022
Hospitalisation(s) due to Psoriasis in the last 12 months	-0.104	-0.160	0.013	-12.075	-0.253	<0.001
Use of home help (professional or informal) in the last month	-0.139	-0.160	0.021	-	-	-

6.4 DISCUSSION OF THE UTILITY MEASURING

In this present study, our first purpose was to analyse correlations between quality of life and disease severity measures, and compare their ability in detecting differences between known groups in a sample of 200 moderate to severe psoriasis patients of two Hungarian university clinics.
As a result of the correlation analysis we found the expected significant correlations between EQ-5D, DLQI, PASI, PGA, and self-assessed disease severity VAS. All the included outcomes correlated only moderately with EQ-5D (r_s=0.41-0.48, $p<0.05$). DLQI global score correlated stronger with PASI, PGA, and with self-assessed disease severity, than with EQ-5D.

To date, there are only a few cross-sectional studies in the literature reporting correlation results on outcomes measures in psoriasis. Similarly to our results, Norlin et al. in a sample of 2,450 patients across Sweden found EQ-5D and DLQI moderately correlated (r_s= -0.55, $p<0.001$). This is further supported by a survey including 273 patients from Finland where authors observed moderate correlation between EQ-5D and DLQI (r=-0.52, $p<0.001$). Hjortsberg et al. also pointed out that DLQI score was more highly correlated with patients' self-assessed disease severity than with the EQ-5D (r=0.71, $p<0.001$), likewise in our study (r_s=0.8, $p<0.05$).

Two observational studies reported a weak correlation between PASI and EQ-5D (r= -0.17, -0.25) (Norlin et al, [2012]); (Blome et al, [2013]). In contrast, we noted moderate correlation (r=-0.43) between these two measures. It is therefore, likely that different clinical protocols of the countries and different patient characteristics of the samples (e.g. psoriasis severity, rate of biological treatment) account for the imparity.

Despite prior evidences that found significant moderate correlations (r=0.51, 0.54) between PASI and DLQI, we observed strong correlation (r_s=0.81)

between these two instruments (Norlin et al, [2012]); (Mabuchi et al, [2012]). We assume that major reasons for the differences are the distinctions amongst the types of treatment (e.g. proportion of patients on biologicals) and psoriasis severity of the patients included. This assumption is confirmed by the evidence that we demonstrated stronger correlation between DLQI and PASI scores amongst the patients treated with biologicals (r_s=0.76 vs 0.53, p<0.001). Furthermore, possible difficulties were described in the comparison of DLQI records related to the patients' different cultural backgrounds. Findings of Nijsten et al. suggest that patients from different countries respond differently to a substantial proportion of DLQI items, although they have the same HRQOL impairment (Nijsten et al, [2007]).

A recently conducted systematic review examined the correlation between DLQI and PASI throughout clinical trials of biological agents (Mattei et al, [2013]). Based on 13 randomised controlled trials (RCT), the proportion of PASI improvement revealed a strong correlation (r=0.8) with DLQI from the baseline to the 10-16 weeks of treatment, confirming our findings, where more than half of the enrolled patients received biological therapy.

In our study, the highest correlation (r_s=0.92, p<0.05) was observed between PASI and PGA VAS. Both measures are commonly used in clinical trials. Our finding is consistent with a review based on 30 biological RCTs (Robinson, et al, [2012]). According to the results of Robinson et al. the two outcome tools, PGA 0,1 and PASI 75 were correlated very closely (r=0.9157 for study weeks 8 to 16; r=0.892 for weeks 17 to 24, and r=0.9559 for longer than 24 weeks, p<0.01) (Robinson, et al, [2012]).

In the comparison of outcome measures with the known-groups method, 11 aspects of psoriasis severity were involved, including clinical types, localisations, and health service utilisation variables. A similar method was applied by Revicki et al. validating the psoriasis symptom inventory (PSI) (Revicki et al, [2014]), by Dauden et al. validating the PSO-LIFE questionnaire (Dauden et al, [2012]), and by Brodszky et al. assessing the

Psoriatic Arthritis Quality of Life (PsAQoL) questionnaire and the Health Assessment Questionnaire (HAQ) in psoriatic arthritis (Brodszky et al, [2010]). Each of the evaluated tools (See Table 12) was found to be effective instruments, which are able to discriminate between these groups regarding the severity of psoriasis. Merely a modest effect size was found within the group of hospitalisation(s), similarly to prior results of a study conducted by Brodszky et al. with the same method in psoriatic arthritis, also in Hungary (Brodszky et al, [2010]).

The effectiveness of the four assessed tools in tackling QOL varies in different segments. EQ-5D was found remarkably effective from the viewpoint of general HRQOL grouping variables such as the necessity of home help, since the ability for self-care is one of the dimensions of the EQ-5D index. Focusing on strengths of the disease-specific measures, the discriminating power of DLQI proved the greatest or the second greatest in 9 out of the 11 implied categories. In addition, DLQI scores correlated stronger with PASI, patients' self-assessed disease severity and with PGA as well than EQ-5D.

Therefore, DLQI is an optimal choice to measure general HRQOL and skin-related symptoms assembled. Not surprisingly, PASI was found especially effective in the distinction of the aspects of visible lesions, localisation of psoriasis, palmoplantar involvement, and biological therapy, because these variables are directly related to disease severity. The presence of visible lesions was analysed with the same method, but with a different instrument (PSO-LIFE) by Daudén et al. (Dauden et al, [2013]). Similarly to our findings, the authors suggest that HRQOL impairment perceived by patients with visible lesions is greater than the effect reported by patients with less visible lesions (Dauden et al, [2013]).

Furthermore, we assessed HRQOL in patients with the presence or lack of lesions on certain body regions. The neck and/or décolletage involvement was associated with the greatest EQ-5D reduction, followed by the forearm,

and facial lesions. Also, the neck and/or décolletage involvement proved the highest effect size in DLQI scores, followed by the forearm, and the leg and/or shin lesions. Unexpectedly, the effect sizes of the facial psoriasis, which is likely the most bothersome localisation due to stigmatisation and cosmetic issues, were overtaken by the neck and/or décolletage measured by any examined outcome. We assume that this is due to the fact that in our sample the majority of the patients with neck and/or décolletage involvement (n=36) had lesions on two or more body sites, covering higher proportion of their entire body surface.

Our second aim was to investigate new possible predictors of EQ-5D score and EQ VAS, and seek for a mapping algorithm on these variables. Bivariate analysis on EQ-5D was previously published in two studies. A simple linear regression developed by Currie et al. amongst 94 patients could account for 27% of EQ-5D variance: EQ-5D=0.956–0.02548*DLQI [10]. The model of Norlin et al. was able to explain 28% of the EQ-5D variance (EQ-5D=0.8777-0.0196*DLQI) (Norlin et al, [2012]). Our model is in line with these two bivariate algorithms, the constant term is about 0.8 and one point increase in DLQI is expected to result in a reduction of 0.02 point in EQ-5D.

A study from Germany including 1,511 patients performed by Blome et al. could predict 24.2% of the variability of EQ VAS with the following mapping algorithm: EQ VAS=77.367-1.493*DLQI ($p<0.001$) [9]. Furthermore, these results were cross-validated by a database of 2,009 patients.

To develop our multivariate function, we explored 10 variables as possible predictors of EQ-5D: DLQI, gender, psoriasis duration, palmoplantar involvement, psoriatic arthritis, chronic plaque psoriasis, scalp psoriasis, necessity of home help in the last month, GP visit(s) due to psoriasis in the last month, and hospitalisation(s) due to psoriasis in the last 12 months. The clinical type of palmoplantar involvement had the greatest negative standardised regression coefficient. This finding seems to be consistent with earlier researches, which described that patients with palmoplantar

involvement have reported significantly greater physical disability, discomfort, and work or leisure impairment than those without palmoplantar involvement (Pettey et al, [2003]); (Sampogna et al, [2006]). In contrast, scalp psoriasis was the only variable with positive unstandardised regression coefficient (ß) involved in the model. This might be conceivably due to the high proportion of the less severe cases amongst the patients of our sample with scalp involvement (n=69), and therefore, this finding cannot be generalised.

In the multivariate approach of Norlin et al., in addition to DLQI (global score or single items) gender and age were found to be predictors of EQ-5D (Norlin et al, [2012]). Their model could explain 32% of the variance of EQ-5D. Blome et al. implemented a stepwise linear regression on EQ-5D as well as on EQ-5D VAS with powers of explanation of 27.9% and 31.3% (Blome et al, [2013]). Age, presence of active arthritis and concomitant diseases predicted both target variables. Gender, psoriasis duration, and nail involvement were also described as predictors of EQ-5D. Compared to our model, gender, psoriatic arthritis, and disease duration are common predictors. The regression coefficients of DLQI are higher in both the bivariate and the multivariate function of Blome et al. than in ours (Blome et al, [2013]).

It seems that gender is the only variable that was found predictor in the two referred multivariate mapping functions and also in our model (Norlin et al, [2012]); (Blome et al, [2013]). A literature review on quality of life in psoriasis patients points that there is no association between gender and HRQOL in psoriasis (de Korte et al, [2004]). However, a few authors have described higher HRQOL impairment in female patients, possibly caused by stigmatisation and additional mental disorders (Mabuchi et al, [2012]); (Sampogna et al, [2006]). Lesuis et al. also indicated that men more often had high PASI scores and women more often had high DLQI scores (Lesuis et al, [2012]). In our study we could not justify significant difference neither in DLQI nor in PASI index, nonetheless, median EQ-5D in female patients was significantly worse than in males (0.67 vs 0.8, $p<0.001$).

Mapping EQ VAS, we observed that self-assessed disease severity VAS overwhelmed DLQI as a possible predictor, and hence, confirmed the importance of self-assessed disease severity as an outcome measure, as earlier highlighted by Hjortsberg et al. also.
To summarise, the three cited bivariate models can predict greater proportion of the variance of EQ-5D or EQ VAS than our mapping functions. However, our multiple linear regression algorithm can predict 48.8% of EQ-5D scores, which is more accurate than in any previously published models.

Finally, a number of important limitations need to be considered. To our knowledge, HRQOL median values of our sample are reflecting better health states than in other previous cross-sectional surveys. This might be the result of the biological treatment received by about half of our patients and also due to the treatment institutions, which were two university clinics considered to offer higher quality of care. Additionally, several limitations of mapping should be noted. Sample size was relatively small, only the ordinary least squares method was applied and no cross-validation was conducted. A recently published study suggests that ordinary least squares method systematically underestimates mapping from disease-specific measures, like DLQI to generic measures such as EQ-5D (Lu et al, [2013]). Consequently, the developed mapping algorithm is probably not transferable to all Hungarian psoriasis patients, merely to subgroups of patients.

A more broadly survey including more variables not investigated in this study (e.g. time on biological treatment, comorbidities and concomitant medications, mental health, body image, coping mechanisms) is needed to reduce the uncertainties around the model and to determine the still unexplained 51.2% of EQ-5D. A detailed analysis in terms of the individual 5 dimensions of EQ-5D and of each DLQI questions or items might as well improve the predictive power of mapping (Brazier et al, [2010]).

This current study confirms previous findings about correlations between EQ-5D, EQ VAS, DLQI, and PASI. We provided the first evidence that visible

psoriatic lesions have a significant impact on HRQOL measured not only with DLQI, but also with EQ-5D, compared to non-visible skin lesions. We revealed new possible predictors of HRQOL, such as clinical types and localisation of psoriasis, and necessity of home help in patients with moderate to severe psoriasis. In clinical trials, when direct utility outcomes are not available, our mapping functions can contribute to the valuation of utilities. Notwithstanding the limitations listed above, predictors tested in a multivariate approach explained higher proportion of variance of EQ-5D in psoriasis than any other models before.

7 BUDGET IMPACT ANALYSIS OF BIOSIMILAR INFLIXIMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS IN SIX CENTRAL AND EASTERN EUROPEAN COUNTRIES

This chapter draws upon:
Brodszky V, Gulácsi L, Balogh O, Péntek M: Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis and Crohn's disease in six Central and Eastern European countries

Eur J Health Econ. 2014 May;15 Suppl 1:S65-71. doi: 10.1007/s10198-014-0595-3. Epub 2014 May 16.

7.1 INTRODUCTION TO THE BUDGET IMPACT ANALYSIS

Chronic inflammatory conditions such as different types of autoimmune arthritis, inflammatory bowel diseases and psoriasis lead to considerable functional disability, a lowered quality of life and work capacity as well as significant economic burden on the patients, families and society. Biological drugs developed over the recent decades provided a new highly effective but very costly treatment options (Sokka et al, [2010]). The high price created a barrier to access for patients in the Central and Eastern European (CEE) region and the utilization of biological drugs is still lower compared to high income countries (Laires et al, [2013]). Access to biological drugs varies greatly within CEE as well.

In September 2013, a biosimilar monoclonal antibody (mAb), infliximab (CT-P13) received market authorisation in Europe for the treatment of adult patients with rheumatoid arthritis (RA), ankylosing spondylitis, psoriatic arthritis, psoriasis, adult and pediatric ulcerative colitis and Crohn's disease. It is expected that the spread of biosimilar mAbs will lead to cost savings in health care budgets and along with it might improve the access to biological

therapies. However, the potential savings have not been studied yet. This study aimed to analyse the budget impact implied by the introduction of biosimilar infliximab for the treatment of RA in six selected CEE countries, namely Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia. RA was selected to estimate the budget impact, as this indication involves the largest number of patients treated with biological agents.

Budget impact analysis (BIA) is used to estimate the financial consequences of adoption and diffusion of a new health intervention within a specific health care setting or system context (Mauskopf et al, [2007]); (Orlewska et al, [2009]); (van de Vooren et al, [2014]). Besides cost-effectiveness analysis (CEA) BIA is required as part of the application dossiers of all new pharmaceuticals seeking for public funding in the CEE similarly to a number of other countries. However, despite the importance of BIA, there is a shortage of literature in this field compared to the large number of CEAs. In a systematic literature review by Orlewska and colleagues (2009), altogether 34 BIAs were identified in peer-reviewed journals irrespective of therapy type and geographical region. In a recent systematic literature review by van de Voorenand colleagues (2013), 17 BIA publications focusing on European countries were identified. Furthermore, both reviews pointed out that several studies fail to reach appropriate methodological quality. Amongst the publications included in these reviews only two BIAs dealt with biological treatments, both in RA (Launois et al, [2008]); (Sorensen et al, [2005]) and none of these studies was conducted in the CEE region. No studies have been published so far which focused on the expected budget impact of biosimilar drugs.

It is rather challenging to estimate the budget impact of a new biosimilar mAb drug in the CEE region for several reasons. First, data on current, available biological treatments (price and patient populations, practice of current biological use) are not always available or reliable for all CEE countries. Patient registries are scarce in CEE thus our knowledge is limited about size, disease severity and other characteristics of patients currently

using biological drugs as well as the pattern of biological treatment in this region. Second, we have to rely on assumptions regarding the future use of biosimilar drug (market share, interchanging or switching of biological therapies).

Thus, in this paper we estimated cost savings from the payer's perspective in six CEE countries considering two extreme biosimilar scenarios (BSc) depending on whether interchanging a biosimilar is allowed or not, compared to the reference scenario (RSc) where no biosimilar infliximab is available.

7.2 METHODS OF THE BUDGET IMPACT ANALYSIS

This BIA estimated the impact of biosimilar infliximab on the healthcare budget over a three-year time frame in six CEE countries. The model was constructed in compliance with the principles of good practice for BIA from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Mauskopf et al, [2007]).The perspective of analysis was that of a third party payer.

7.2.1 Modelling framework

A prevalence based country-specific budget impact model was developed for RA. The budget impact model evaluated the impact of introducing biosimilar infliximab into the current treatment mix of biological drugs available for the treatment of RA in the six countries by comparing total costs (drug, administration and monitoring) of scenarios where biosimilar infliximab is introduced (BSc1 and BSc2) to the total costs of the reference scenario (RSc, where no biosimilar agent is available). Since there is a great uncertainty in policy discussions around interchanging from originator infliximab to biosimilar infliximab (Tóthfalusi et al, [2014]) we decided to explore the budget impact in two extreme scenarios:

Biosimilar scenario 1 (BSc1): Interchanging originator infliximab with biosimilar infliximab is disallowed. Only patients who start a new biological therapy are allowed to use biosimilar infliximab.
Biosimilar scenario 2 (BSc2): Interchanging of originator infliximab with biosimilar infliximab is allowed after 6 months from treatment start, and originator infliximab is interchanged by biosimilar infliximab in 80% of patients. Also patients who start a new biological therapy are allowed to receive biosimilar infliximab as first line therapy.

The model tracked the movement of patients between different biological treatments. At the end of each model cycle patients could either remain on the original treatment, or switch to another biological treatment, or leave the model (switch to a conventional synthetic disease modifying antirheumatic drug – csDMARD - therapy). The model functioned in quarter year time cycles according to a three-month-long evaluation period. The number of RA patients treated with biological agents in any quarter year was the sum of the population in the previous quarter year and the estimated growth. The number of patients starting new biologic treatment (first drug or switch) was the sum of discontinuations from all causes in the previous quarter year and the estimated growth. New patients receiving biological drugs exactly compensated for patients exiting the model.

Total costs of scenarios were estimated as the aggregation of the product of patients in different model states and costs associated with these states. Incremental costs were calculated as the difference of biosimilar scenarios (BSc1 and BSc2) and reference scenario (RSc). Cost savings are reported in 2013 prices, no discounting was applied. Besides cost savings in monetary terms, we also provide estimations for gains in terms of possible number of new patients who could be treated additionally if the savings were reinvested in additional biosimilar infliximab treatment.

7.2.2 Patient population

The size of initial population (Table 14) in both the reference (RSc) and the two biosimilar scenarios (BSc1 and Bsc2) was set on the basis of real 2013 penetration data in the six CEE countries (i.e. the number of patients with RA treated with different biological drugs in 2013). The number of RA patients in the six countries treated with abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab were 153, 4,055, 1,376, 4,197, 860, 1,643, 3,098 and 1,944 respectively (Péntek et al, [2014]).The model also accounted for the possibility of patient number expansion. A future growth rate of treated patients was assumed to predict the number of treated patients over the three years. Also, budget impact estimates included calculations on the numbers of previously untreated patients who started new biological drugs. We made no restriction on the number of potential patients. Only, we assumed that growth in the number of patients treated with biological drug would not exceed the number of patients eligible for biological therapy on a three-year time horizon.

Table 14 Model parameters

Variable	Base case parameters	Source
Average body weight in RA (kg)	75	NHIFA 2010
Initial population on biologic in RA	17,257	Péntek 2014 [9]
Three months discontinuation probability after 6 months	0.049	literature review [11]
Biologic market yearly growth rate	10%	assumption
Biosimilar infliximab price in % of originator infliximab price	75%	assumption
Distribution of switches from TNF-inhibitor to		
another TNF inhibitor	60%	NHIFA 2013 [12]
abatacept	0%	NHIFA 2013 [12]
rituximab	7%	NHIFA 2013 [12]
tocilizumab	33%	NHIFA 2013 [12]
Distribution of switches from tocilizumab to		
another TNF inhibitor	89%	NHIFA 2013 [12]
rituximab	10%	NHIFA 2013 [12]
Probability of switches from rituximab to		
another TNF inhibitor	0.64	NHIFA 2013 [12]
tocilizumab	0.36	NHIFA 2013 [12]
Rate of interchanging by the physicians	0-80%	assumption
Probability of initiating biosimilar infliximab instead of starting originator infliximab	65%	assumption
Probability of initiating biosimilar infliximab instead of starting non-infliximab TNF-inhibitor	20%	assumption

* interchanging rate: the given rate is reached at the end of first year applying a linear growth; NHIFA=National Health Insurance Fund Administration

7.2.3 Costs associated with model states

Only direct costs of the drug treatment were considered, including the acquisition costs of drugs, the cost of administration and the cost of treatment related monitoring (laboratory test, rheumatology visits, X-ray, cardiology and pulmonology monitoring). The model accounted for those

biological agents which are reimbursed in a given country for the treatment of RA. (Table 15)

Table 15 Retail prices of biological treatments in euro

Brand name	Substance	Retail price (EUR)					
		BUL	CZE	HUN	POL	ROM	SLO
ORENCIA 1x250	abatacept	NR	420	342	NR	352	395
HUMIRA 2x40	adalimumab	1,262	1,006	957	1,056	1,037	1,119
CIMZIA 2x200	certolizumab	1,093	975	957	NR	931	1,043
ENBREL 4x50	etanercept	1,164	1,021	957	1,015	968	1,048
SIMPONI 1x50	golimumab	1,282	1,112	1,109	NR	1,067	1,646
REMICADE 1x100	infliximab	NR	609	534	537	481	617
MABTHERA 1x500	rituximab	1,255	1,275	1,257	1,553	1,309	1,406
ROACTEMRA 400	tocilizumab	1,255	846	728	NR	745	778
ROACTEMRA 200	tocilizumab	948	423	366	NR	380	411
ROACTEMRA 80	tocilizumab	479	169	148	NR	161	167

NR: not reimbursed; BUL=Bulgaria, CZE=Czech Republic, HUN=Hungary, POL=Poland, ROM=Romania, SLO=Slovakia; Sources: SLO: http://www.adcc.sk; BUL: National Health Insaurance Fund, Списък с лекарства, които НЗОК заплащапорединаНаредба № 10 от 24 март 2009г. зауслoвията и редазазаплащаненалекарственипродуктипочл. 262, ал.4, т.1 отЗаконазалекарственитепродукти в http://www.nhif.bg; CZE: State Institute for Drug Control, http://www.sukl.eu/; HUN: National Health Insaurance Fund www.oep.hu; POL: Ministry of Health, http://www.mz.gov.pl/; ROM: Ministry of Health, http://www.msf-dgf.roCatalogul National al preturil or medicamentel or de uzumanautorizate de punerepepiata - Ianuarie 2012

Drug acquisition costs were derived from official national price lists in each country. We used retail prices for the analysis. Retail price of biosimilar infliximab was assumed as 75% of originator infliximab in all the six countries. Drug acquisition costs were calculated on a quarterly basis for both the induction and maintenance periods for each drug (Table 16). The

doses and administration schedules for each biological agent were taken as provided by the European Medicines Agency summaries of product characteristics. The calculation took into account both induction and maintenance dosing schedule in the case of infliximab, certolizumab and abatacept. For these drugs different dosing schedule were used in the first and the subsequent quarter after starting the treatment. Furthermore, the dosage of some biological drugs (infliximab, abatacept and tocilizumab) depends on body weight. The average body weight of an RA patient was estimated at 75 kg (SD17) based on Hungarian survey among patients treated with infliximab (Laki et al, [2012]). If not a full package is used for one patient the rest dosage might or might not be used for others. The latter is considered as waste. We assumed that the rest dosages are administered to the next patients.

Table 16 Quarterly drug costs in rheumatoid arthritis in euros

Country	Inf			Adl	Crt		Etn	Glm	Abt	Rtx	Tcl
	Q1	Q2	Q_i	Q_i	Q1	Q_i	Q_i	Q_i	Q_i	Q_i	Q_i
Bulgaria	3,696	2,156	2,002	4,100	5,192	3,553	3,784	3,847	-	2,509	6,117
Czech R.	4,130	2,409	2,237	3,283	4,650	3,182	3,333	3,349	3,948	2,560	4,142
Hungary	3,695	2,155	2,001	3,189	4,660	3,189	3,189	3,411	3,280	2,577	3,639
Poland	3,721	2,170	2,015	3,522	-	-	3,387	-	-	3,188	-
Romania	3,273	1,909	1,773	3,395	4,455	3,048	3,171	3,226	3,325	2,638	3,659
Slovakia	4,168	2,431	2,258	3,635	4,953	3,389	3,407	4,937	3,702	2,811	3,795

Q: quarter year; Inf=original infliximab; Adl=adalimumab; Crt=certolizumab; Etn=etanercept; Glm=golimumab; Abt=abatacept; Rtx=rituximab; Tcl=tocilizumab

Monitoring and administration costs were estimated according to clinical guidelines. Tariffs from the National Health Insurance Fund Administrations (NHIFA) were used to assess monitoring (outpatient visits, lab tests, imaging), administration (visits to nurse, outpatients visit) costs. In the case of unavailable price data in a country, Hungarian tariffs were converted to estimate these costs.

7.2.4 Assumptions in model

Movements between model states: Based on the results of a previous review (Koncz et al, [2010]), we assumed that the three-month discontinuation probability is 0.049% for all treatments. The probabilities that a given biological drug will be selected as second line treatment are presented in Table 14. These rates were derived from the Hungarian NHIFA database (Laki et al, [2012]) and were applied each of the six countries.

Infliximab biosimilar as first and second line treatment: We assumed that in 65% of the cases when originator infliximab would have been selected as a first or second line treatment, the physician will prescribe biosimilar infliximab. Also an assumption was made that in 25% of the cases when a non-infliximab tumour necrosis factor inhibitor (TNF-inhibitor, namely adalimumab, certolizumab, etanercept and golimumab) would have been selected as a first or second line treatment, the physician prescribes biosimilar infliximab (linearly reaching these percentages till the end of the 1st year, and remain till the end of the 3rd year).

Interchanging: The rate of interchanging originator infliximab treatment with biosimilar infliximab treatment is 0% in BSc1 and 80% in BSc2 (linearly reaching 80% till the end of the 1st year, and remain till the end of the 3rd year). BSc1 is the strictest possible option, when interchangeability is not allowed at all, while BSc2 is a potential extreme case with 80% replacement of originator by biosimilar (e.g., in an extreme situation if the payer would oblige providers to replace the originator treatment.)

7.2.5 Sensitivity analysis

One-way sensitivity analysis was performed changing different parameters of the model by ±10%: the assumption on the acquisition cost of biosimilar infliximab, the size of the initial population and its growth rate over time,

the discontinuation rates of biological drugs and the rate of interchanging from infliximab to biosimilar infliximab.

7.3 RESULTS OF THE BUDGET IMPACT ANALYSIS

Results of the analysis are presented in Table 17. In 2013, approximately 17,300 RA patients were treated with biological drugs in the six CEE countries. Findings show that in BSc1 the introduction of biosimilar infliximab in the biologic treatment setting led to a total savings of €15.3 M in the first three years of its introduction. Allowing for interchanging from original infliximab to biosimilar infliximab had a significant impact on budget savings. In BSc2 the total saving was estimated to be €20.8 M over the three years.

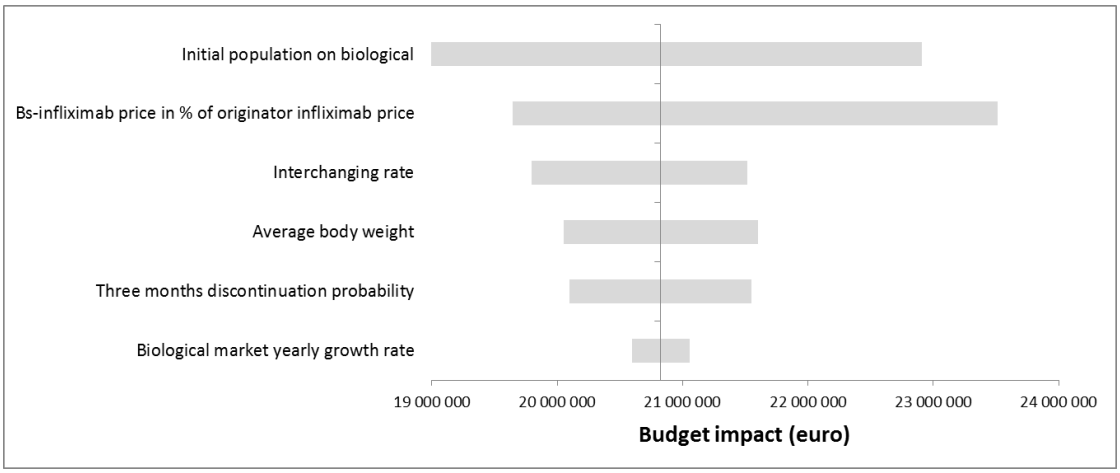
Table 17 Results of the scenario analyses

	Budget impact (euro)				Number of new RA patients on biological treatment if budget savings would be spent on biosimilar infliximab		
	year 1	year 2	year 3	Total	year 1	year 2	year 3
Biosimilar Scenario 1	-945,241	-4,782,462	-9,612,331	-15,340,034	165	672	1,205
Biosimilar Scenario 2	-2,394,545	-6,968,620	-11,463,059	-20,826,224	242	1,002	1,790

Biosimilar scenario1: interchanging of biosimilar and original biologicals is not allowed
Biosimilar scenario2: interchanging of biosimilar and original biologicals is allowed at least six months after treatment start

The cost savings may be reinvested to treat more patients with biological drugs. If all budget savings were spent on reimbursing biological therapy of new patients with biosimilar infliximab, additional 1,205 patients in BSc1 or 1,790 patients in BSc2 could be treated with biological drugs after three years. According to the results of the sensitivity analysis, the number of the initial population treated with biological agents and the assumption on the acquisition cost of biosimilar were the two main cost drivers (20.1% and 18.6%) in the model (Figure 18).

Figure 18 One-way sensitivity analysis results



Variables included in the one-way sensitivity analysis are listed on the vertical axis. The bars represent the budget impacts with the lowest and highest values of the given variable. The variables are ordered so that the widest budget impact interval appears at the top of the figure, the next largest appears second from the top, and so on.

7.4 DISCUSSION OF THE BUDGET IMPACT ANALYSIS

This is the first study to attempt to estimate the budget impact of introducing the first biosimilar mAb (infliximab) in the CEE countries. The analysis was carried out with multiple scenarios in order to evaluate various assumptions.

Our analysis has shown that introducing biosimilar infliximab as a treatment for RA might result in considerable budget savings. We demonstrated that the potential budget savings for the 6 countries are €0.9, €4.8 and €15.3 million in the first, second and third year of implementation in the strictest scenario (Bsc1), where the interchange from originator infliximab to biosimilar infliximab is not allowed.

Allowing for the interchange from original infliximab to biosimilar infliximab (BSc2) resulted in even more savings compared to the no interchanging scenario (BSc1). This increase was driven by a faster reduction of patient number on the more expensive originator infliximab. The one-way sensitivity analysis revealed that it was the acquisition price of biosimilar infliximab that had the greatest impact on budget savings. In contrast, the yearly growth rate of the total number of patients treated with biological agents had only a minor effect.

If the budget savings were reinvested in the treatment of additional patients with biosimilar infliximab, 1,205 and 1,790 additional RA patients could be treated in the two biosimilar scenarios, respectively. Thus, the implementation of biosimilar treatment may significantly improve the access to biological therapy in the CEE countries. As mentioned in the introduction, the utilization of biological drugs is significantly lower in the CEE countries compared to high income countries (Laires et al, [2013]). For example, in the review by Laires and colleagues the average access rate to biological treatment amongst RA patients was an average of 19.1% in 15 Western and Southern European countries (Laires et al, [2013]). In contrast, according to our estimations the average access rate in the six CEE countries was about 5.3%. Therefore, additional access to biologicals in these countries is particularly precious.

In recently published reviews (Orlewska et al, [2009]); (van de Vooren et al, [2014]) two budget impact analyses (Launois et al, [2008]); (Sorensen et al, [2005]) were identified in RA. Budget impacts calculated in our study can be

hardly compared directly with the findings of these analyses of biological treatments due to differences in settings and jurisdictions. However, comparison of relevant findings and conclusions might be meaningful. Launois and colleagues studied the budget impact initiated by the introduction of rituximab after failure of a TNF-inhibitor therapy from the perspective of the French health care system (Launois et al, [2008]). They estimated a total savings of €88 M (23%) over 4 years, deriving mainly from lower drug costs. The yearly acquisition cost of rituximab was 57% of the average acquisition costs of TNF-inhibitors. In comparison, in our model the yearly acquisition cost of biosimilar infliximab was assumed to be 75% of the originator costs.

In both analyses, what budget savings were the most sensitive to, was the changes in drug acquisition costs. Both studies similarly conclude that the implementation of biological agents with lower prices might lead to notable cost savings. In an earlier (2002) study by Sørensen and colleagues, the implementation of etanercept and infliximab in the Danish health care system was analysed. The setting of this study was considerably different from ours. The reference case was the csDMARD therapy which might result significantly higher incremental costs than our reference case. Sørensen and colleagues reported a €113 M and a €321 M budget increase over three years assuming a modest or a progressive market growth. They highlighted the financial challenges that when introduced these new treatment regimens will pose on healthcare systems.

7.5 LIMITATIONS OF THE BUDGET IMPACT ANALYSIS

Due to the number of limitations of this BIA, the results should be interpreted with caution. First, it should be taken in account, that any model is a simplification of the real treatment process. The model collected only resource use and costs for an average patient and did not consider other factors such as disease severity, patient characteristics or other disease-related factors. The model did not account for the changes in indirect societal costs arising from absence from work. Another limitation is that a dynamic cohort approach was applied in the study as in each model cycle some patients left the model while new patients entered it. Though, we were interested in the total budget impact for the whole population rather than in the individual patient patterns. Also, the model did not account for the potential decrease in the future drug costs (neither for biosimilar nor originator). However, it is possible that drug prices will decrease in the future due to increased market competition and the increased number of patients treated with biological agents. This might also lead to budget savings. Furthermore, the sensitivity analysis showed that the results are highly sensitive to changes in model parameters.

Several assumptions were made regarding the practice of available biological therapies based on data available from previous literature or from registers (e.g. discontinuation, switch). Since these data are not always available or reliable for every CEE country we made a great simplification that discontinuation rates and probabilities of taking up a given treatment are equal in each of the six countries.

Our assumptions about the future use of biosimilar infliximab (market share, interchanging or switching of biological therapies of the current biological) are even more uncertain due to the lack of empirical data on the use and experience with biosimilar treatments (interchangeability, market growth). However these parameters were tested in the sensitivity analysis.

7.6 CONCLUSIONS OF THE BUDGET IMPACT ANALYSIS

Based on the present analysis, the introduction of biosimilar infliximab as an alternative treatment option for RA in CEE is predicted to bring substantial cost savings to the national health care budget. The main drivers of budget savings were the current population treated with biological agent and the price of the new drug. Allowing interchange between biosimilar and originator biological drug might have substantial favourable effect on budget savings. Based on these results, the use of biosimilar infliximab appears to be economically attractive because it offers the potential to reduce the total expenditures or to increase the number of patients treated with biologicals.

8 DISCUSSION

In this dissertation, I aimed to synthetise the available knowledge and provided new, reliable data on health economics of the biological therapies in chronic diseases. Over four chapters I gave a detailed overview of the use of these agents and their effect on patients and economic impact on the society.

Given the complexity of the issue, the two main goals of the dissertation were (1) to show the experience with the implementation of biologicals; and (2) to expand the economic knowledge about these drugs and inform government leaders and health policy makers. The thesis also pays special attention to the current situation of and differences between the countries of the CEE region. The objective of each chapter was to provide new results; therefore, my dissertation elaborates four autonomous research questions in the field of health economics. Nevertheless, they shared a common goal, namely to provide valuable inputs and support decision making about health interventions in various levels within the reimbursement and financing mechanisms. In this chapter, I discuss how the findings of the thesis provide a distinct contribution to knowledge in the research area.

8.1 EFFICACY AND SAFETY OF BIOLOGICALS

Hypothesis 1: a) In case of PsA, biologicals are nearly similar and tolerable, b) in case of AS, the efficacy and safety of the new and original drug are both more beneficial than the treatment with placebo.

Some biologicals have been approved by the EMA for the treatment of adults with severe, active AS and PsA. Furthermore, in September 2013, the first biosimilar therapy, namely biosimilar infliximab was licensed in the EU for the first time for the treatment of AS. According to our knowledge, no meta-

analysis have been published yet in AS, which compares the efficacy and safety of the biosimilar infliximab treatment to the original biological drugs indicated in AS. Therefore we compared biosimilar and original biologicals in PsA and AS in terms of efficacy and tolerability.

Our Bayesian indirect comparison did not show any difference between the efficacy of infliximab, etanercept and golimumab treatments. At the same time, the finding of our quantitative review was that one biological (adalimumab) was significantly less effective on achieving clinical improvement (PsARC response) in PsA than the other drugs. Therefore, the first part of my hypothesis was partly right: all biologicals but one showed similar efficacy. Regarding the AS study, we should highlight that this was the first study to include a biosimilar drug in the meta-analysis of biological treatments in AS. The results have proven the similar efficacy and safety profile of infliximab-biosimilar compared to other biologicals, thus the second part of my hypothesis was also proved.

Policy implications: These studies are important in terms of health policy decisions, because transferability of efficacy and safety results from one country to another needs further considerations. This is especially relevant for the CEE countries that are characterised by different economic conditions, health and social care systems. It is worthy to point out that biosimilar infliximab has the same effect as the existing drugs, and it is also cheaper than the original biologicals in the market, which means that cost saving can be achieved, evidencing the appropriateness to choose this drug. Therefore, our results are important to the health financing institutes because applying biosimilars in the treatment cost savings can be achieved.

8.2 COST-OF-ILLNESS OF CHRONIC DISEASES

Hypothesis 2: The treatment with biological therapies causes a significant financial burden to the society and the treatment of patients with these agents results in higher financial costs compared to the case without biological therapy.

The appearance of new health technologies has led to the exponential growth of health care expenditures. The growing tension between 'technologically available' and affordable has brought the demand to measure efficacy, safety, cost-effectiveness or disease burden. Due to the scarcity of local data based on national studies, CEE countries are highly dependent on results from abroad. Despite the widespread availability of papers on biological drugs, there is also a shortage of COI studies in psoriasis in the CEE region. Therefore we made an empirical study to analyse the results from a non-interventional, cross-sectional questionnaire survey in 2 university dermatology clinics in Hungary. Before this survey, costs associated with psoriasis, the main cost factors and the size of disease burden to the society were unknown.

According to the results, the majority of the patients (N=103, 52%) in our sample were receiving biological agent at the time of the assessment. In 2010, altogether 682 patients[10] with psoriasis received biological treatment in Hungary, thus our survey captured a substantial proportion of this patient group. We observed that the mean annual total cost per patient with HCA and FCA was €9,254 (SD €8,502) and €8,305 (SD €7,705), respectively, with direct costs accounting for 86% and 96% of the total costs. Our hypothesis is

[10] http://www.oep.hu/pls/portal/docs/PAGE/SZAKMA/OEPHUSZAK_EUSZOLG/TIBI%20EGY%C3%89B/SZAKMAI%20ELLEN%C5%90RZ%C3%89S/BIOL_TH_2006_2010_PUBLIKUS4.PDF

fulfilled, as we found that the main cost driver was the cost of the biological therapy (€7,339/patient/year), and, furthermore, the average total cost differed significantly between treatment subgroups (NST: €2186/patient/year; TST: €2,388/patient/year; BST: €15,790/patient/year). Another important cost driver was the indirect cost (productivity loss), amounting to 14% of the total costs. We can also observe differences in indirect costs between the subgroups (BST vs. TST: €1,427 vs. €960).

Taking into account that the first biological agent was registered for the treatment of psoriasis in 2004, it is striking that no COI studies involving patients with biological treatment were carried out up to date of the last systematic literature review (January 2010). Therefore, we performed a literature search (up to December 2013) and identified further nine publications. Most of the analyses were performed in Western and Northern Europe or in the US. However, these regions and CEE differ significantly in a wide range of features such as GDP per capita, health and social care systems, demographics, health status of the given population, reimbursement mechanisms of medications and financing of health care institutions. Hence, the transferability of these health economic results to jurisdictions of CEE is rather limited. We fund that in France, the Netherlands and Sweden the total cost of treatment with biologicals were higher, whereas in the UK it was lower compared to our results in Hungary. Similarly to our findings, in France, the Netherlands, and the UK, the costs of hospitalisation and out-patient visits were reported to be lower in biologically treated subgroups. We can conclude that health care utilisation data are greatly dependant on the financing mechanisms, professional and financing guidelines, management, standard care, unit costs and cost accounting approaches of the given country and vary substantially. Therefore these factors hinder the comparison studies from these countries.

Policy implications: Our study indicated that the economic burden of psoriasis is considerable in Hungary, however, comparing to international data lower costs were observed. It is worth to point out that this was the first study from the CEE region that provided COI data and also had the largest sample size of biologically treated patients in Europe. We provided information on the health status of patients with psoriasis and disease burden, thus our findings will be useful for medical decision making, developing guidelines and in value based reimbursement. We saw that differences between countries (e.g. Europe, the US and the CEE region) emerges the need for country specific results.

8.3 RELATIONSHIP BETWEEN DISEASE SPECIFIC QUALITY OF LIFE SCALES AND UTILITIES

Hypothesis 3: Generic and disease specific quality of life scales and disease severity scores correlate with utilities.

Understanding disease-related quality of life issues are crucial in the management of chronic diseases for clinical and health policy decision making. Furthermore, economic evaluations require data on HRQOL on preference-based measures that capture utility of different health states. In many countries utility measures are required for reimbursement decisions. To provide country-specific data for Hungary regarding psoriasis patients treated with biologicals, we conducted a cross-sectional questionnaire survey on 200 consecutive adult patients in two Hungarian university clinics. We measured the relationship between the outcome measures with correlations and with the known-groups method, furthermore we formulated multivariate regression models to predict utility.

It should be taken into account that to date, there are only a few cross-sectional studies in the literature reporting correlation results on outcome measures on psoriasis. According to the results, our hypothesis is proven and we provided valuable information by explaining a higher proportion of EQ-5D variance than any previous findings in the literature. Moreover, we revealed several new possible predictors of HRQOL, such as clinical types and localisation of psoriasis. What indicates the importance of this issue is the fact that there has been an increasing number of health economic analyses estimating utilities from disease-specific instruments, but this remains a partially unexplored area in psoriasis. In our study, relations between EQ-5D and DLQI, PASI showed a moderate negative correlation, while strong significant correlation was found between DLQI, PASI and self-assessed disease severity VAS. Our mapping functions can contribute to the valuation of utilities in clinical trials, where preference-based outcome assessment is not available.

Policy implications: Utility measures are required for cost-effectiveness analysis of new interventions that can promote to reimbursement decision making. One of the best instrument to produce QALY, i.e. information about utility, is to conduct an analysis based on local data. According to our knowledge this was the first study from the CEE region reporting utility results of biological treated patients in psoriasis.

8.4 IMPACT ON THE HEALTH CARE BUDGET

Hypothesis 4: The introduction of biosimilar infliximab leads to substantial budget savings in health care budgets.

The first biosimilar monoclonal antibody (biosimilar infliximab) was registered by the EMA in 2013 for the treatment several inflammatory

conditions including RA and AS. Health care reimbursement bodies are facing a new challange, as biosimilar infliximab was first marketed in the CEE countries. The analyises of the expected changes in the expenditure of a health care system related to a new intervention are crutial. Furthermore, there is an expectation that biosimilar infliximab will lead to cost savings in health care budgets, however, the potential savings have not been studied yet, there is a shortage in the literature. To reduce this gap, we built a model to perform budget impact analysis of biological therapies in six CEE countries for 3 years within RA.

Our findings showed that this new drug can be economically attractive due to the potential of reducing health expenditures. Based on our results, the introduction of biosimilar infliximab in the biologic treatment setting can lead to a total saving of €15.3 M and €20.8 M over three years (in our scenarios). Furthermore, if all budget savings were spent on reimbursing biological therapy of new patients with biosimilar infliximab, an additional 1,205 and 1,790 patients could be treated with biological drugs over three years. Additionally, allowing switch from the originator biological drug to the biosimilar might have a substantially favourable effect on budget savings, therefore our hypothesis is proved. We also provided baseline data for further analysis.

Policy implications: The introduction of biosimilar infliximab as an alternative treatment option for RA in CEE is predicted to bring substantial cost savings to the national health care budget, and further savings are expected in other indications, where biosimilar medicines are implemented. It is worthy to point out that besides cost-effectiveness analysis, BIA is also required as part of the application dossiers of all new pharmaceuticals aiming for public funding in the CEE countries.

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10 APPENDIX

10.1 SEARCH TERMS FOR RCTS AND META-ANALYSES

RCT

"arthritis, psoriatic"[MeSH Terms] AND (adalimumab OR etanercept OR golimumab OR infliximab) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("2010/01/01"[PDAT] : "2012/04/15"[PDAT])

10.2 QUALITY ASSESSMENT OF INCLUDED STUDIES; DETAILED DESCRIPTION OF JADAD SCORE

Calculating Jadad score is based on a three-point questionnaire published by Jadad et al.(Jadad, 1996 #44). Each question can be answered with either a yes or a no. Each yes scores one point, each no zero points. The questions were:

- Was the study described as randomized?
- Was the study described as double blind?
- Was there a description of withdrawals and dropouts?

To receive the corresponding point, an article should describe the number of withdrawals and dropouts, in each of the study groups, and the underlying reasons.

Additional points were given if:

The method of randomisation was described in the paper, and that method was appropriate.

The method of blinding was described, and it was appropriate.

Points would however be deducted if:

The method of randomisation was described, but was inappropriate.

The method of blinding was described, but was inappropriate.

A paper reporting a clinical trial could therefore receive a Jadad score of between zero and five.

10.3 DESCRIPTION OF MIXED TREATMENT MODELS AND WINBUGS CODES

All MTC models used the odds ratio as the measure of relative treatment effect and assumed that treatment effects on the odds-ratio scale were multiplicative and exchangeable between trials. Each model was run with 3 chains and 10,000 burn-in iterations in order to limit the influence of the initial values on the simulated posterior distribution. A further 20,000 MCMC iterations were run, and the sampled values were used to estimate posterior means and 95% credibility intervals (CrIs). Credibility intervals are the Bayesian equivalent of classical confidence intervals.

Convergence was assessed based on Brooks-Gelman-Rubin (BGR) plot. The accuracy of the posterior estimates was done by calculating the Monte Carlo error for each parameter. As a rule of thumb, the Monte Carlo error for each parameter of interest is less than about 5% of the sample standard deviation. The overall residual deviance was compared to the number of independent data points to check if the model fit the data satisfactory. For a Binomial likelihood, each trial arm contributes 1 independent data point. Differences between treatments were considered significantly significant at the 0.05 level if the 95% CrIs around the odds ratio did not cross 1.

WinBUGS code for mixed treatment comparison

Biologicals for PsA Fixed Effect Modell

treatment 2 = adalimumab; 3 = etanercept; 4 = golimumab; 5 = infliximab

```
# Binomial likelihood, logit link
# Fixed effects model
model(                          # *** PROGRAM STARTS
for(i in 1:ns)(                 # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)       # vague priors for all trial baselines
   for (k in 1:na[i])(          # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
      rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
     )
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
    )
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt)[ d[k] ~ dnorm(0,.0001) )
# pairwise ORs and LORs for all possible pair-wise comparisons, if nt>2
for (c in 1:(nt-1))(
for (k in (c+1):nt)(
or[c,k]  <-  exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
)
```

10.4 DETAILED RESULTS FROM CLASSICAL DIRECT META-ANALYSIS

Figure 19 Forest plot of direct comparison: Efficacy of biological vs placebo at 12-16 weeks, outcome: PSARC

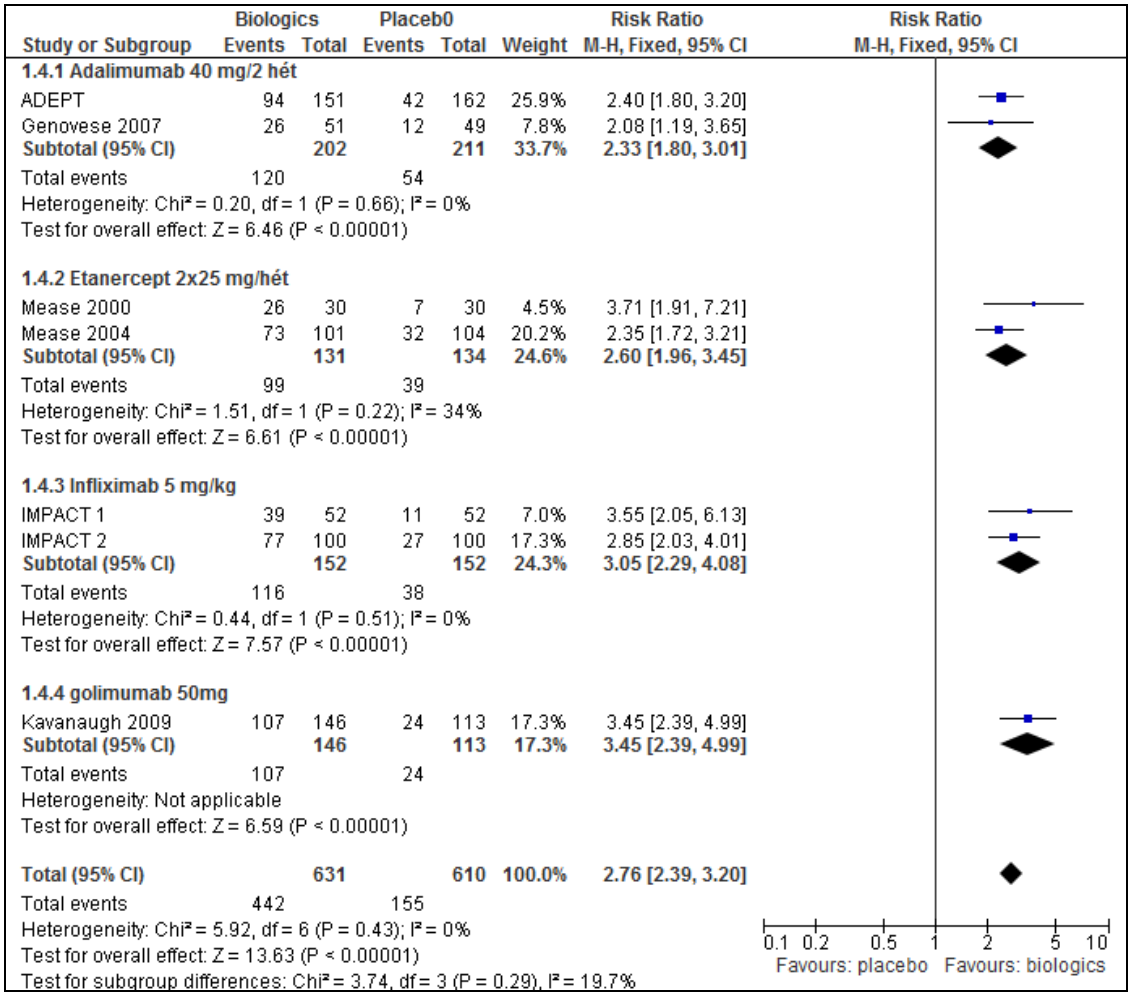


Figure 20 Forest plot of direct comparison: Efficacy of biological vs placebo at 12-16 weeks, outcome: ACR20 improvement

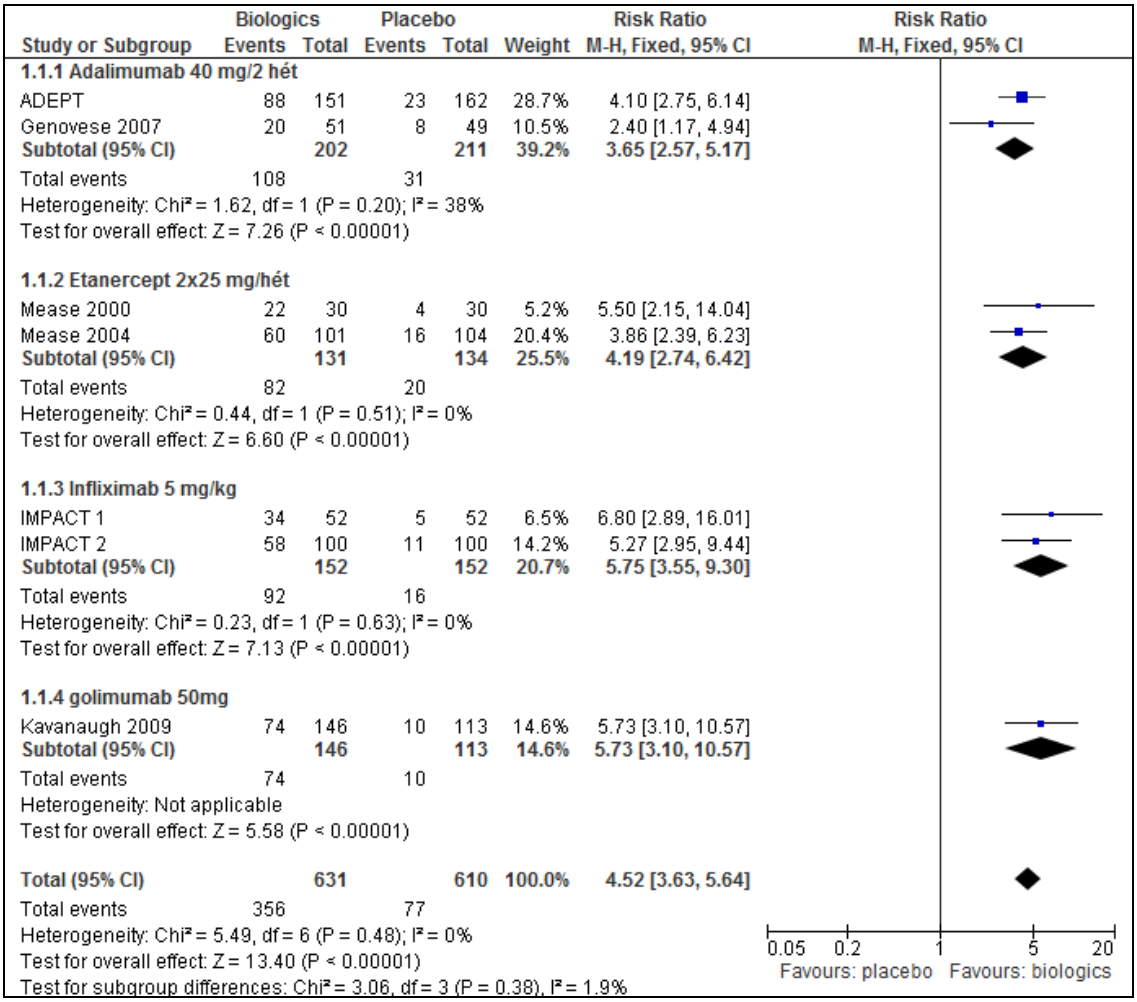


Figure 21 Forest plot of direct comparison: Efficacy of biological vs placebo at 12-16 weeks, outcome: ACR50 improvement

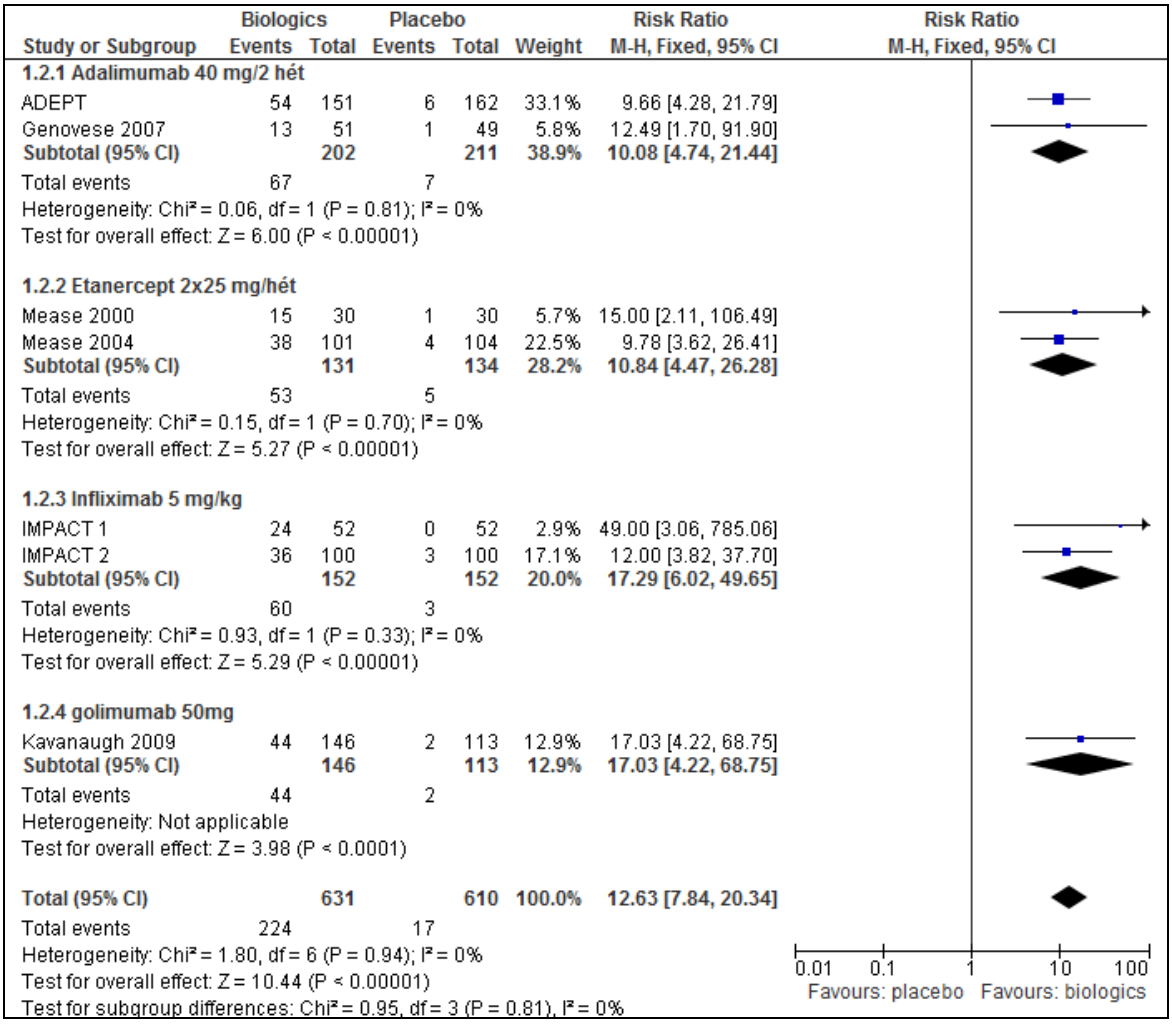
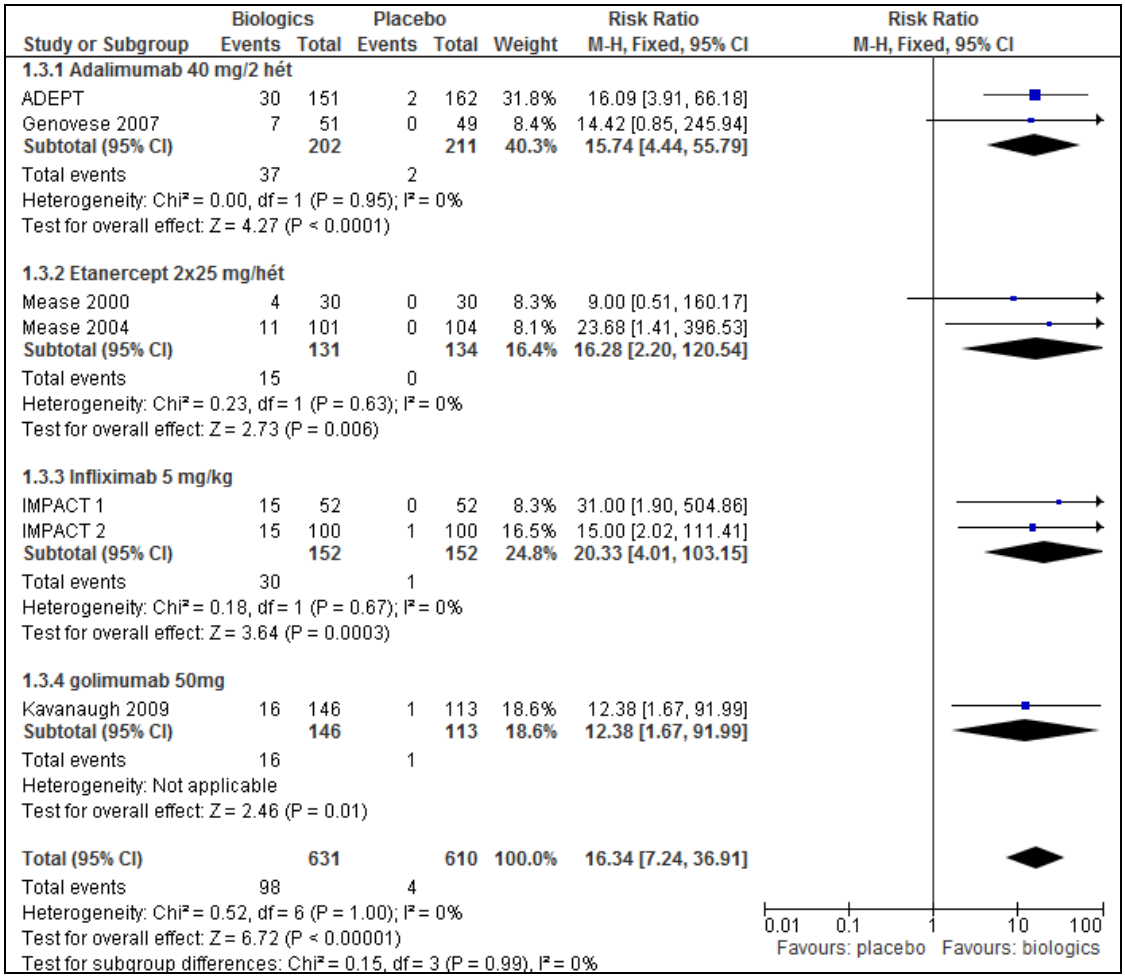


Figure 22 Forest plot of direct comparison: Efficacy of biological vs placebo at 12-16 weeks, outcome: ACR70 improvement



Életminőség és betegség-költség felmérés közép-súlyos és súlyos psoriasisban

A betegek egészségi állapotának, életminőségének, terápiájának vizsgálata és az egészségügyi ellátó hálózat igénybevételének felmérése Magyarországon

(Azonosító: 35183/2012-EKU)

Kérdőíves felmérés
2012

Vizsgálatban résztvevő intézmények:

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Semmelweis Egyetem Bőr-, Nemikórtani és Bőronkológiai Klinika, 1085 Budapest, Mária u. 41

BELEEGYEZŐ NYILATKOZAT SZEMÉLYES ADATOK GYŰJTÉSÉHEZ

a *M*agyarországi *P*soriasis *A*datgyűjtés kérdőíves felmérés keretében

Alulírott, belegyezem, hogy részt vegyek az „*Életminőség és betegség-költség felmérés közép-súlyos és súlyos psoriasisban*” című magyarországi kérdőíves felmérésben(A vizsgálat azonosító száma: 35183/2012/EKU). Hozzájárulok a kérdőív kitöltésével szolgáltatott adatok tudományos kutatás céljára való felhasználásához.

Kijelenti, hogy elolvasta a Tájékoztatót és kezelőorvosa megválaszolta a felméréssel kapcsolatban felmerült kérdésit. Kijelenti, hogy belegyezését önként, befolyástól mentesen adja, annak tudatában, hogy az bármikor, szóban vagy írásban, indoklás nélkül visszavonhatja.

Beteg neve: _____ anyja neve:_____

TAJ: _____ Születési hely, idő: _____

Lakcím:_____

Az egészségügyi intézmény neve: _____

A tájékoztatását végző személy neve:_____

Munkahelye és munkaköre: _____ _____

Dátum: 201__. _____

_____ _____

beteg aláírása tájékoztatást végző aláírása

Ez az oldal a vizsgáló centrumban marad!

Kitöltési Útmutató!

Kérem, tanulmányozza át figyelmesen az alábbi útmutatót, és ennek alapján töltse ki az alábbi kérdőívet a *M*agyarországi *P*soriasis *A*datgyűjtés részeként.

- Minden űrlapot golyóstollal töltsön ki. Írjon olvashatóan, és a tollat határozottan nyomja a papírhoz, hogy az összes adat olvasható legyen.
- Kerülje a megjegyzések írását a kérdőív szélére.
- Kérjük, kövesse az Általános kitöltési útmutatót.

	Példa:
Nyomtatott nagybetűvel írjon. Ne használjon rövidítéseket.	NAGYBETŰ
A **dátumok** kitöltésekor használja az éééé.hh.nn. **formátumot.** Használjon négy számot az év, két számot a hónap és két számot a nap jelölésére. Ismeretlen napok, illetve hónapok jelölésére használja "NI" jelzést (pl. 2007-08-NI vagy 2007-NI-NI).	**2 0 0 9 | 0 2 | 0 8** *éééé hh nn*
A megfelelő négyzetbe írjon **X**-et, vagy ✓**-t.**	**X** vagy ✓
A számértékeket úgy írja be a megadott négyzetekbe, hogy minden négyzetet töltsön ki, az egyébként üresen maradó négyzetekbe írjon 0-t.	**0 | 9 | 0**
Javítás: Ne használjon hibajavítót! A javítandó részt egyetlen vízszintes vonallal húzza át. A helyes adatot írja fölé. A javítást végző személy monogramját és a javítás dátumát írja a korrigált adat mellé.	09 ~~**0 | 8**~~ *NN* 2007-Júl-11
Kérem, töltsön ki minden négyzetet, a kérdőív minden oldalán. Amennyiben valamely kérdezett adat "nem ismert", "nem alkalmazható" kérem, használja a következő rövidítéseket:	**NI** ha nem ismert **NA** ha nem alkalmazható

A. Beteg kérdőív

I. Általános adatok

A kitöltés dátuma: ☐☐☐☐☐év ☐☐ hónap ☐☐ nap

Neme: férfi ☐ nő ☐

Születési dátum: 19 ☐☐ /év/

Testsúly: ☐☐☐ /kg/

Testmagasság ☐☐☐/cm/

Legmagasabb iskolai végzettsége

Általános iskola ☐
Középiskola ☐
Főiskola ☐
Egyetem ☐
Egyéb:_____

Családi állapota. Kérjük jelölje X-szel!

Egyedülálló (hajadon) ☐
Házas vagy élettársi kapcsolatban él ☐
Elvált ☐
Özvegy ☐

Mennyi az Ön nettó havi jövedelme? Kérjük jelölje X-szel!

0 – 75 000 Ft / hónap ☐
75 001 – 150 000 Ft / hónap ☐
150 001 – 250 000 Ft / hónap ☐
250 001 – 350 000 Ft / hónap ☐
350 001 – 450 000 Ft / hónap ☐
450 001 vagy több Ft / hónap ☐

II. A betegség jellemzői

Pikkelysömör megbetegedésének kezdete (első diagnózis)? (évszám): ☐☐☐☐

Fordult-e elő a családjában pikkelysömör betegség? Igen ☐ **Nem** ☐

Mi az ön véleménye betegségének aktivitásáról? Kérem, az alábbi skálán egy függőleges vonallal jelölje, hogyan ítéli meg betegsége aktivitását jelenleg. Minél enyhébbnek gondolja tüneteit, a jelölést annál közelebb tegye a skála tünetmentes végéhez. Minél súlyosabbnak gondolja betegségét, annál közelebb tegye a jelölést a skála igen súlyos tünetek végéhez.

tünetmentes igen súlyos tünetek

Van-e az Ön következő testrészein pikkelysömörös (psoriasisos) bőrelváltozás?

Arcon/homlokon jól láthatóan	Nem ☐	Igen ☐
Nyakon és ami az ingből kilátszik	Nem ☐	Igen ☐
Kézen, tenyéren	Nem ☐	Igen ☐
Alkaron	Nem ☐	Igen ☐
Kézkörmökön	Nem ☐	Igen ☐
Lábon, lábszáron	Nem ☐	Igen ☐

Az Ön véleménye szerint a külső megjelenés mennyire fontos része az egészségnek?

Egyáltalán nem fontos	☐
Egy kicsit fontos	☐
Közepesen fontos	☐
Meglehetősen fontos	☐
Nagyon fontos	☐

Ha Ön jelenleg NEM részesül biológiai terápiában (Enbrel, Humira, Remicade vagy Stelara), kérjük, ugorjon a 0. kérdésre!

A biológiai terápia eredményeképpen bekövetkezett javulás (Jelölje X-szel!)

a.) Általában – az egész testet figyelembe véve:

Most sokkal jobb, mint a biológiai terápia előtt…… ☐1

Most valamivel jobb, mint a biológiai terápia előtt…….. ☐2

Nagyjából olyan, mint a biológiai terápia előtt…… ☐3

Most valamivel rosszabb, mint a biológiai terápia előtt……. ☐4

Most sokkal rosszabb, mint a biológiai terápia előtt …….. ☐5

b.) Arcon

Most sokkal jobb, mint a biológiai terápia előtt…… ☐1

Most valamivel jobb, mint a biológiai terápia előtt…….. ☐2

Nagyjából olyan, mint a biológiai terápia előtt…… ☐3

Most valamivel rosszabb, mint a biológiai terápia előtt……. ☐4

Most sokkal rosszabb, mint a biológiai terápia előtt ☐5

c.) Nyakon és ami az ingből kilátszik -

Most sokkal jobb, mint a biológiai terápia előtt…… ☐1

Most valamivel jobb, mint a biológiai terápia előtt…….. ☐2

Nagyjából olyan, mint a biológiai terápia előtt…… ☐3

Most valamivel rosszabb, mint a biológiai terápia előtt……. ☐4

Most sokkal rosszabb, mint a biológiai terápia előtt …….. ☐5

d.) Alkaron -

Most sokkal jobb, mint a biológiai terápia előtt…… ☐1

Most valamivel jobb, mint a biológiai terápia előtt…….. ☐2

Nagyjából olyan, mint a biológiai terápia előtt…… ☐3

Most valamivel rosszabb, mint a biológiai terápia előtt……. ☐4

Most sokkal rosszabb, mint a biológiai terápia előtt …….. ☐5

e.) Kézkörmökön

Most sokkal jobb, mint a biológiai terápia előtt…… ☐1

Most valamivel jobb, mint a biológiai terápia előtt…….. ☐2

Nagyjából olyan, mint a biológiai terápia előtt…… ☐3

Most valamivel rosszabb, mint a biológiai terápia előtt……. ☐4

Most sokkal rosszabb, mint a biológiai terápia előtt …….. ☐5

f.) Lábon, lábszáron

Most sokkal jobb, mint a biológiai terápia előtt…… ☐1

Most valamivel jobb, mint a biológiai terápia előtt…….. ☐2

Nagyjából olyan, mint a biológiai terápia előtt…… ☐3

Most valamivel rosszabb, mint a biológiai terápia előtt……. ☐4

Most sokkal rosszabb, mint a biológiai terápia előtt …….. ☐5

Az elmúlt 4 hétben mennyire zavarta testi egészsége vagy lelki gondjai szokásos kapcsolatát a családjával, barátaival, szomszédjaival vagy másokkal? Jelölje X-szel!

Egyáltalán nem ☐
Alig ☐
Közepesen ☐
Meglehetősen ☐
Nagyon is ☐

Külső megjelenésében a psoriasisos bőrtünetek mennyire zavarják Önt?

Egyáltalán nem ☐
Alig ☐
Közepesen ☐
Meglehetősen ☐
Nagyon is ☐

Mennyire fontos Önnek a külső megjelenése?

Egyáltalán nem fontos ☐
Egy kicsit fontos ☐
Közepesen fontos ☐
Meglehetősen fontos ☐
Nagyon fontos ☐

Az <u>elmúlt 4 hétben</u> befolyásolta-e testi vagy lelki állapota személyes kapcsolatait (pl. barátok, rokonok meglátogatása stb.)

Mindvégig ☐
Az idő legnagyobb részében ☐
Az idő kis részében ☐
Az idő nagyon kis részében ☐
Egyáltalán nem ☐

III. Gondozás

Más személy segítségére szorult-e pikkelysömör betegsége miatt az elmúlt 1 hónapban? (vásárlás, házimunka, önmaga ellátása)

Igen ☐ Nem ☐

Ha igen, akkor hetente hány órában kapott segítséget családtagtól vagy más személytől?

Heti ☐☐ órát.

Hány alkalommal járt családorvosánál pikkelysömör betegsége miatt az elmúlt 1 hónapban?

Összesen ☐☐ alkalommal Egyszer sem ☐

Hány alkalommal járt bőrgyógyászati járóbeteg szakorvosi rendelésen pikkelysömör betegsége miatt az elmúlt 3 hónapban?

Összesen ☐☐ alkalommal Egyszer sem ☐

Hány alkalommal került pikkelysömör betegsége miatt kórházi felvételre bőrgyógyászati osztályra az elmúlt 12 hónapban? (Kérjük, írja be a felvételek számát!)

Összesen ☐☐ alkalommal Egyszer sem ☐

Hányszor vett igénybe az elmúlt 12 hónapban:

mentőszállítást ☐☐

utazási utalványt (egészségügyi) ☐☐

Milyen távolságra lakik az Önt rendszeresen ellátó szakorvosi rendeléstől?:……..km

Használt-e *<u>az elmúlt 1 hónapban</u>* a pikkelysömör miatt valamilyen külső kezelést?

igen ☐ nem ☐

<u>Ha igen, jelölje a készítmény típusát és a felhasznált egységek (tubus, üveg, alkalom) számát</u>

	Melyeket (jelölje „X”-el)	Mennyiség	Az Ön havi költsége Ft/hónap
Calcipotriol (Daivonex)	☐	☐☐	
Ditranol	☐	☐☐	
lokális szteroid készítmény	☐	☐☐	_____
UVB	☐	☐☐	_____
UV fésű	☐	☐☐	
fényterápiát	☐	☐☐	_____
TOMESA kezelést	☐	☐☐	_____
egyéb készítmény:			
_____	☐	☐☐	_____
_____	☐	☐☐	_____
_____	☐	☐☐	_____
_____	☐	☐☐	_____
_____	☐	☐☐	_____

Hány alkalommal vett igénybe <u>pikkelysömör betegsége miatt</u> társadalombiztosítás által nem térített ellátást (magánorvos, természetgyógyász, körmök manikűrös kezelése, nem receptes mosakodó krémek és kozmetikumok) az elmúlt 12 hónapban, és mennyit költött összesen ezekre az ellátásokra? (Kérjük írja be az alkalmak számát és az elköltött összeget!)

Egyszer sem ☐

	Ha igen, hányszor?	Összesen hány Ft-ot?
Magánorvosi vizsgálat	☐☐	
_____Ft		
Természetgyógyászati rendelés	☐☐	
_____Ft		
Gyógyüdülés	☐☐	
_____Ft		
Egyéb:_____	☐☐	_____Ft
Egyéb:_____	☐☐	_____Ft
Egyéb:_____	☐☐	_____Ft

V. Foglalkoztatottság, munkaképesség

A következő kérdések azzal foglalkoznak, hogy pikkelysömör tünetei milyen hatással vannak munkaképességére és napi tevékenységeire. *Kérjük, töltse ki a kérdőívet a megfelelő helyeken, vagy karikázza be a megfelelő számot*.

Dolgozik jelenleg? Kérjük, jelölje X-szel a megfelelőt! <u>Több választ</u> is megjelölhet!

Teljes munkaidőben dolgozom	☐
Részmunkaidőben dolgozom	☐
Rokkantnyugdíjas vagyok	☐
Nyugdíjas vagyok	☐
Tanuló vagyok	☐
Munkanélküli vagyok	☐
Háztartásbeli, egyéb	☐

<u>Ha rokkantnyugdíjas</u>,

Mióta? ☐☐☐☐**,** ☐☐ (évszám, hónap)

Psoriasis miatt Igen☐ Nem ☐

A következő kérdéseket csak abban az esetben válaszolja meg, ha a *„teljes munkaidőben dolgozom”* vagy a *„részmunkaidőben dolgozom”* válaszok egyikét megjelölte.

Ha NEM jelölte meg egyiket sem, ugorjon a 0. kérdésre.

A következő kérdések az **elmúlt hét napra** vonatkoznak, a mai napot nem számítva.

Az elmúlt hét nap alatt hány munkaórát mulasztott pikkelysömör betegsége miatt? *Számítsa bele azokat az órákat, melyeket betegállományban töltött, amikor későn ért munkába, korábban távozott, stb. egészségügyi gondjai miatt. Ne számítsa bele azt az időt, melyet azért mulasztott el, mert ebben a klinikai vizsgálatban vesz részt.*

_____ÓRA

Az elmúlt hét nap alatt, hány munkaórát mulasztott bármilyen egyéb ok miatt, mint például szabadság, ünnepnap, vagy a klinikai vizsgálattal munkaidőben eltöltött idő?

_____ÓRA

Az elmúlt hét nap alatt hány órát dolgozott ténylegesen?

_____ÓRA (*Ha“0”, ugorjon a 0. kérdésre.*)

Az elmúlt hét nap alatt, <u>munkája közben</u> mennyire befolyásolta pikkelysömör betegsége a munkavégzését? *Gondoljon vissza azokra a napokra, amikor kevesebb, illetve kevesebb fajta munkát tudott elvégezni, és azokra a napokra, amikor kevesebbet tudott teljesíteni, mint amennyit szeretett volna, vagy amikor nem tudta munkáját olyan gondosan elvégezni, mint máskor. Ha egészségügyi gondjai csak kis mértékben befolyásolták a munkavégzését, akkor válasszon egy kis számot, amennyiben egészségügyi gondjai nagymértékben befolyásolták a munkavégzését, válasszon egy nagy számot az alábbi skálán.*

Pikkelysömör tüneteim nem befolyásolták a munkavégzésemet.	0 1 2 3 4 5 6 7 8 9 10	Pikkelysömör tüneteim teljes mértékben megakadályoztak a munkavégzésemben.

KARIKÁZZON BE EGY SZÁMOT.

Az elmúlt hét nap alatt pikkelysömör betegsége mennyire akadályozta abban, hogy napi rendes tevékenységeit elvégezze, melyek nem függnek össze munkahelyi tevékenységével? *A napi rendes tevékenységeken azokat értjük, melyeket általában végez, mint például a ház körüli munkát, vásárlást, gyerekek ellátását, testgyakorlást, tanulást, stb. Gondoljon vissza azokra az időkre, amikor kevesebbet, illetve kevesebb félét tudott tenni, és azokra a napokra, amikor kevesebbet tudott elvégezni, mint amennyit szeretett volna. Ha egészségügyi gondjai csak kis mértékben befolyásolták napi rendes tevékenységét, akkor válasszon egy kis számot, amennyiben egészségügyi gondjai nagymértékben befolyásolták a napi rendes tevékenységeit, válasszon egy nagy számot az alábbi skálán.*

Pikkelysömör tüneteim nem befolyásolták a napi rendes tevékenységeimet.	0 1 2 3 4 5 6 7 8 9 10	Pikkelysömör tüneteim teljes mértékben megakadályoztak a napi rendes tevékenységeimben.

KARIKÁZZON BE EGY SZÁMOT.

VI. Életminőséggel kapcsolatos kérdések, EQ-5D kérdőív

Az alább szereplő kérdéscsoportok mindegyikébe tegyen keresztet azon válasz melletti négyzetbe, amely legjobban jellemzi **az Ön mai egészségi állapotát**

Mozgékonyság

Nincs problémám a járással ☐
Némi problémám van a járással ☐
Ágyhoz vagyok kötve ☐

Önellátás

Nincs problémám önmagam ellátásával ☐
Némi problémám van a tisztálkodással és az öltözködéssel ☐
Képtelen vagyok önállóan tisztálkodni vagy öltözködni ☐

Szokásos tevékenységek (pl. munka, tanulás, házimunka, családi vagy szabadidős tevékenységek)

Nincs problémám a szokásos tevékenységeim elvégzésével ☐
Némi problémám van szokásos tevékenységeim elvégzésével ☐
Képtelen vagyok elvégezni szokásos tevékenységeimet ☐

Fájdalom/Rossz közérzet

Nincs fájdalmam vagy rossz közérzetem ☐
Mérsékelt fájdalmam vagy kissé rossz közérzetem van ☐
Nagyon erős fájdalmam vagy rossz közérzetem van ☐

Szorongás/Lehangoltság

Nem szorongok vagy nem vagyok lehangolt ☐
Mérsékelten szorongok vagy lehangolt vagyok ☐
Nagyon szorongok vagy nagyon lehangolt vagyok ☐

Az elmúlt 12 hónap során tapasztalt általános egészségi állapotomhoz képest egészségi állapotom ma:

Kérjük, tegyen keresztet egy négyzetbe

Jobb ☐
Többnyire ugyanolyan ☐
Rosszabb ☐

EQ-5D skála

Azért, hogy az emberek könnyebben ki tudják fejezni, egészségi állapotuk mennyire jó vagy rossz, egy skálát készítettünk (amely leginkább egy hőmérőhöz hasonlít), amelyen az elképzelhető legjobb egészségi állapotot „100”, az elképzelhető legrosszabb egészségi állapotot pedig „0” jelöli.

Kérjük, jelölje be ezen a skálán, hogy véleménye szerint mai egészségi állapota mennyire jó vagy rossz. Ezt úgy tegye, hogy az alább szereplő négyzettől (melyben „Az Ön mai egészségi állapota” - kijelentés olvasható) húzzon egy vonalat a skála azon pontjáig, amely a legjobban mutatja, hogy az Ön egészségi állapota mennyire jó vagy rossz.

VII. Egészséggel kapcsolatos várakozások

A következő részben az Ön saját egészségével kapcsolatos várakozásaira kérdezünk

Az embereknek gyakran van valamilyen várakozásuk a jövőbeli egészségükkel kapcsolatban.
A következő kérdésekben jelölje X-szel, Ön milyennek gondolja a saját egészségi állapotát **60, 70, 80 és 90** éves korában.

Ha Ön idősebb, lépjen a következő kérdésre.

Jelölje X-szel az Ön elgondolásainak legmegfelelőbb választ!

Úgy gondolom, 60 éves koromban:

Nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a járással.
Nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a tisztálkodással és öltözködéssel.
Nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a szokásos tevékenységek elvégzésével.
Nem	némi	nagyon erős	
☐	☐	☐	fájdalmam / rossz közérzetem lesz.
Nem	mérsékelten	nagyon	
☐	☐	☐	szorongok / lehangolt leszek.

Úgy gondolom, 70 éves koromban:

Nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a járással.
nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a tisztálkodással és öltözködéssel.
nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a szokásos tevékenységek elvégzésével.
nem	némi	nagyon erős	
☐	☐	☐	fájdalmam / rossz közérzetem lesz.
nem	mérsékelten	nagyon	
☐	☐	☐	szorongok / lehangolt leszek.

Úgy gondolom, <u>80 éves</u> koromban:

nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a járással.
nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a tisztálkodással és öltözködéssel.
nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a szokásos tevékenységek elvégzésével.
nem	némi	nagyon erős	
☐	☐	☐	fájdalmam / rossz közérzetem lesz.
nem	mérsékelten	nagyon	
☐	☐	☐	szorongok / lehangolt leszek.

Úgy gondolom, <u>90 éves</u> koromban:

nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a járással.
nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a tisztálkodással és öltözködéssel.
nem	némi	nagyon sok	
☐	☐	☐	problémám lesz a szokásos tevékenységek elvégzésével.
nem	némi	nagyon erős	
☐	☐	☐	fájdalmam / rossz közérzetem lesz.
nem	mérsékelten	nagyon	
☐	☐	☐	szorongok / lehangolt leszek.

Véleménye szerint Ön hány éves koráig fog élni?

☐ éves koromig.

Az Ön egészségi állapotával kapcsolatos várakozásai a közeljövőben.

Az alább szereplő kérdéscsoportok mindegyikébe tegyen keresztet azon válasz melletti négyzetbe, amely az Ön véleménye szerint **HAT HÓNAP MÚLVA LEGJOBBAN JELLEMZI** az Ön egészségi állapotát

Mozgékonyság

Nincs problémám a járással □
Némi problémám van a járással □
Ágyhoz vagyok kötve □

Önellátás

Nincs problémám önmagam ellátásával □
Némi problémám van a tisztálkodással és az öltözködéssel □
Képtelen vagyok önállóan tisztálkodni vagy öltözködni □

Szokásos tevékenységek (pl. munka, tanulás, házimunka, családi vagy szabadidős tevékenységek)

Nincs problémám a szokásos tevékenységeim elvégzésével □
Némi problémám van szokásos tevékenységeim elvégzésével □
Képtelen vagyok elvégezni szokásos tevékenységeimet □

Fájdalom/Rossz közérzet

Nincs fájdalmam vagy rossz közérzetem □
Mérsékelt fájdalmam vagy kissé rossz közérzetem van □
Nagyon erős fájdalmam vagy rossz közérzetem van □

Szorongás/Lehangoltság

Nem szorongok vagy nem vagyok lehangolt □
Mérsékelten szorongok vagy lehangolt vagyok □
Nagyon szorongok vagy nagyon lehangolt vagyok □

BŐRGYÓGYÁSZATI ÉLETMINŐSÉG INDEX

DLQI

Pontszám: ☐

A kérdőívvel azt mérjük, hogy bőrével kapcsolatos problémája mennyire befolyásolta az Ön életét AZ ELMÚLT HÉT SORÁN. Kérjük, egy négyzetet jelöljön ☑ be a válasznál!

1. Az elmúlt hét során mennyire volt **viszketős**, **sebes**, **fájdalmas** vagy **égetően fájdalmas** a bőre?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐

2. Az elmúlt hét során mennyire volt **feszélyezett**, vagy volt **zavarban** a bőre miatt?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐

3. Az elmúlt hét során mennyire akadályozta bőre, hogy elmenjen **vásárolni**, rendben tartsa **otthonát** vagy **kertjét**?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

4. Az elmúlt hét során mennyire befolyásolta bőre, hogy milyen **ruhát** visel?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

5. Az elmúlt hét során mennyire befolyásolta bőre **társasági életét** vagy **szabadidős** tevékenységét?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

6. Az elmúlt hét során mennyire nehezítette meg bőre a **sportolást**?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

7. Az elmúlt hét során meggátolta bőre abban, hogy **dolgozzon** vagy **tanuljon**?
- Igen ☐
- Nem ☐ Nem vonatkozik Önre ☐

Ha válasza "Nem": az elmúlt hét során mennyire jelentett problémát bőre a **munkában** vagy a **tanulásban**?
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐

8. Az elmúlt hét során mennyire okozott bőre problémákat **partnerével**, bármelyik **közeli barátjával** vagy **rokonaival** kapcsolatosan?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

9. Az elmúlt hét során mennyire okozott bőre bármilyen **szexuális nehézséget**?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

10. Az elmúlt hét során mennyire okozott problémát bőre **kezelése**: például bepiszkította lakását, vagy sok időt vett igénybe?
- Nagyon ☐
- Meglehetősen ☐
- Kissé ☐
- Egyáltalán nem ☐ Nem vonatkozik Önre ☐

Kérjük ellenőrizze, hogy MINDEN kérdésre válaszolt-e! Köszönjük.

Kedves Hölgyem/Uram!

Köszönjük, hogy a kérdőív kitöltésével segítette munkánkat!

B. Kezelőorvos rész

Kérjük, jelölje a beteget rendszeresen gondozó intézet típusát!

A beteg rendszeres gondozás alatt áll az osztályunkon ☐

A beteg először jár osztályunkon ☐

A beteg rendszeresen gondozza más bőrgyógyász: ☐

A beteget a háziorvosa gondozza: ☐

A beteg nem áll rendszeres gondozás alatt, betegsége eddig nem volt ismert: ☐

A beteg nem áll rendszeres gondozás alatt, de betegsége ismert: ☐

A beteg rendszeresen gondozás alatt áll reumatológiai centrumban ☐

Ha a beteget az Ön osztályán gondozzák, kérjük, adja meg a gondozás kezdetének időpontját (évszám): ☐☐☐☐

Orvos véleménye a pikkelysömör betegség aktivitásáról

Kérjük, jelölje egy függőleges vonallal az alábbi egyenesen, mennyire ítéli aktívnak jelenleg a bőrtünetek aktivitását?

|——————————————————————|

egyáltalán nem aktív nagyon aktív

A pikkelysömör jelenlegi megjelenése, <u>több válasz is lehetséges</u>:

Krónikus, plakk típusú ☐

Guttált psoriasis ☐

Pustulosus psoriasis ☐

Erythroderma ☐

Arcbőr és inverz tünetek ☐

Fejbőr tünetek ☐

Tenyéri/talpi tünetek ☐

Körömérintettség ☐

Arthritis psoriatica ☐

Tünetmentes ☐

Kapott-e a beteg az <u>elmúlt 12 hónapban</u> pikkelysömör miatt olyan szisztémás kezelést, amit jelenleg (a vizitre érkezve) nem szed?

Nem kapott szisztémás kezelést ☐

<u>Ha igen</u>	Mettől? (évszám, hónap)	Meddig? (évszám, hónap)
methotrexat (Methotrexat)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
retinoidok (Neotigason)	☐☐☐☐,☐☐	☐☐☐☐,
☐☐		
cyclosporin (Sandimmun)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
fényterápia	☐☐☐☐,☐☐	☐☐☐☐,☐☐
etanercept (Enbrel)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
infliximab (Remicade)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
adalimumab (Humira)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
ustekinumab (Stelara)	☐☐☐☐,☐☐	☐☐☐☐,☐☐

Kapott-e a beteg korábban, az elmúlt 12 hónapot megelőzően biológiai terápiát?

<u>Ha igen</u>	Mettől? (évszám, hónap)	Meddig? (évszám, hónap)
etanercept (Enbrel)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
infliximab (Remicade)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
adalimumab (Humira)	☐☐☐☐,☐☐	☐☐☐☐,☐☐
ustekinumab (Stelara)	☐☐☐☐,☐☐	☐☐☐☐,☐☐

Kap-e *<u>jelenleg</u>* (a vizitre érkezve) a beteg pikkelysömör miatt szisztémás kezelést?

Nem kap szisztémás kezelést ☐

<u>Ha igen</u>		Mióta? (évszám, hónap)	Dózis
methotrexat (Methotrexat)	☐	☐☐☐☐,☐☐	_____
retinoidok (Neotigason)	☐	☐☐☐☐,☐☐	
_____			
cyclosporin (Sandimmun)	☐	☐☐☐☐,☐☐	_____
fényterápia	☐	☐☐☐☐,☐☐	_____
etanercept (Enbrel)	☐	☐☐☐☐,☐☐	_____
infliximab (Remicade)	☐	☐☐☐☐,☐☐	_____
adalimumab (Humira)	☐	☐☐☐☐,☐☐	_____
ustekinumab (Stelara)	☐	☐☐☐☐,☐☐	_____

A viziten, a kérdőív kitöltésekor, indikált-e a kezelőorvos új biológiai kezelést?

nem ☐ első biológiai kezelést indikál ☐ kezelés váltást indikál ☐

Kérem, adja meg az induló kezelést:		Dózis
etanercept (Enbrel)	☐	_____
infliximab (Remicade)	☐	_____
adalimumab (Humira)	☐	_____
ustekinumab (Stelara)	☐	_____

Kérjük töltse ki a PASI táblázatot!

	Fej	Felső végtag	Törzs	Alsó végtag	
1. Erythema					
2. Infiltráció					
3. Desquamáció					
4. Összaktivitás (1.+2.+3.)					
5. Terület					
6. Összaktivitás x Terület					
	x0,1	x0,2	x0,3	x0,4	PASI
7. Összesen					

Aktivitási értékek: 0 = tünetmentes, 1 = enyhe, 2 = mérsékelt, 3 = kifejezett, 4 = súlyos,

Kiterjedtségi értékek: 1 = <10%, 2 = 10-29%, 3 = 30-49%, 4 = 50-69%, 5 = 70-89%

Kedves kolléga, köszönjük hogy kitöltötte a kérdőívet!

11 PUBLICATIONS OF THE AUTHOR IN THIS TOPIC

Cumulated IF: 7,652

Publications in English

Books, book chapters, conference proceedings:

Baji, P., Balogh, O. ,Brodszky, V. [2013]: Clinical efficacy and safety of biological medications of rheumatoid arthritis In: Márta Péntek: Systematic review and analysis of evidences on effectiveness and cost-effectiveness of infliximab and comparator biologicals for Rheumatoid Arthritis. 8-46

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Balogh, O. et al [2014]: Cost-of-illness in patients with moderate to severe psoriasis: a cross-sectional survey in Hungarian dermatological centres. *Eur J Health Econ,* Suppl 1, S101-109.10.1007/s10198-014-0599-z

Heredi, E. et al [2014]: Exploring the relationship between EQ-5D, DLQI and PASI, and mapping EQ-5D utilities: a cross-sectional study in psoriasis from Hungary. *Eur J Health Econ,* Suppl 1, S111-119.10.1007/s10198-014-0600-x

Publications in Hungarian

Books, book chapters, conference proceedings:

Balogh, O. et al [2013]: Psoriasisban szenvedő betegek életminőségének keresztmetszeti felmérése, nagy esetszámú magyarországi mintán. Magyar Dermatológiai Társulat 86. Nagygyűlése, Budapest, 2013. december 12.

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