THESES

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Economic consideration of the implementation of biotechnological therapies in chronic diseases

Ph.D. Dissertation

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I. Research background and relevance of the topic

Biopharmaceutical drugs have been available for more than 20 years. The agents revolutionised the treatment of chronic diseases in several areas of medicine; however, these have an increased effect on the societies due to their high costs, thus the benefits also bring challenges and concerns about their value for money. Therefore there is an increased importance about health economic analysis where we analyse the unit expenses and also the unit health gain. Biologics represent only about 2-5 percent 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. On one hand, there is a clinical demand for wider use of biologics, and thus preference for the increasing use of these drugs. On the other hand, there are also certain limitations in terms of resource restrictions on financing (affordability),
meaning 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. The Central Eastern European (CEE) countries 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. Furthermore, the growth in the number of patients with chronic diseases is accompanied by the growth of the health care expenditures. 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.
Thus the introduction and continuous development of biologicals speeded up health economic research worldwide. The key questions are whether efficacy, cost-effectiveness and budget impact results can be transferred between jurisdictions of Europe and what lessons can a country like Hungary with limited capacity for health economic analyses learn from these. There is limited data on the above mentioned topics in Hungary and in the CEE region and the proportion of patients treated with biological vary significantly between the countries. Therefore with this dissertation inter alia I would like to provide country specific data and analysis to expand the relevant literature. Here should be mentioned that in order to plan interventions, data-supported facts derived from well-established, reproducible, reliable analysis are necessary.

Therefore, the purpose of this dissertation was to provide more knowledge and insight on this topic in the CEE region, focusing mainly on Hungary, by exploring evidences using methods from the field of health economics and health technology assessment. Although
this dissertation was mainly focused on Hungary, its relevance is not exclusive to the Hungarian context: the topic is also relevant for other countries facing similar challenges with the introduction of biological treatments, 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) and a book chapter. 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. Chapter 4 presents 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.
II. Methods

In this section I present the applied methods within each chapter of the thesis. Chapter 4 of the thesis presents a book chapter and an article about the efficacy and safety of biologicals in Psoriatic Arthritis (PsA) and in Ankylosing Spondylitis (AS). We conducted a quantitative review on efficacy and safety of the biologicals based on a systematic literature review for randomised controlled trials (RCT). In this chapter a direct meta-analysis and mixed treatment comparison was performed. In the direct comparison: the relative risk, rate difference, numbers needed to treat and appropriate 95% CI were derived for each study according to the number of events reported in the original studies. Under the mixed treatment comparison we examined the relative effectiveness of each individual treatment using a mixed treatment comparisons model in a Bayesian framework.
Chapter 5 presents an article related to the cost-of-illness (COI) of patients with moderate to severe Psoriasis in Hungary. We conducted a non-interventional, cross-sectional questionnaire survey in 2 university dermatology clinics in Hungary. Patients included in the research completed a set of questions in which demographic data, employment status, disease duration, self-assessed disease activity on a visual analogue scale (VAS) and Psoriasis related treatments were surveyed. Psoriasis related outpatient care utilisations, hospitalisations and transportation to attend medical care in the previous 12 months were also recorded. Informal care was assessed for the past month. Absence from work and reduced work productivity were captured by the Work Productivity and Activity Impairment questionnaire. 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) and patients on biological systemic treatment (BST). We measured both the direct medical and non-medical costs, and also indirect costs with
Human Capital Approach (HCA) and with Friction Cost Approach (FCA).

Based on the same study as in Chapter 5, Chapter 6 presents an article which analysed the relationship between utility (measured by the EQ-5D) and disease specific quality of life and clinical scales (Dermatology Life Quality Index (DLQI) and Psoriasis Area and Severity Index (PASI)) in Psoriasis. Spearman’s rank correlation was used to test association between the above mentioned 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 measure’s ability to detect differences between groups with known attributes.

Chapter 7 presents the estimated budget impact of the introduction of biosimilar infliximab in rheumatoid arthritis (RA) over a three year time period in six selected countries, Bulgaria, the Czech Republic, Hungary, Poland, Romania and Slovakia. A prevalence based country-specific budget impact model was developed for RA. Two extreme scenarios were used: Biosimilar
scenario 1 (BSc1): Changing originator infliximab with biosimilar infliximab was disallowed. Only patients starting a new biological therapy were allowed to use biosimilar infliximab. Biosimilar scenario 2 (BSc2): Changing of originator infliximab with biosimilar infliximab was allowed after 6 months from treatment start, and originator infliximab is changed by biosimilar infliximab in 80% of patients. Also patients starting a new biological therapy were allowed to receive biosimilar infliximab as first line therapy. Finally, 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.
III. Results

My dissertation is among the first papers to provide data on chronic diseases involving patients with biological treatment. This dissertation therefore seeks to deal with a synthetised knowledge about the implementation of biotechnological therapies, using methods related to health economics.

The following section states the main hypothesis, objectives and results of the dissertation, along with the relevant policy implications and limitations.

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
Some biologicals have been approved by the European Medicine Agency (EMA) for the treatment of adults with
severe, active AS and PsA. Furthermore, in September 2013, the first biosimilar therapy, namely infliximab-biosimilar 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 infliximab-biosimilar treatment to the other biological drugs indicated in AS.

Results
In the first book chapter we dealt with a quantitative review on efficacy and safety of the drugs in PsA based on 7 RCTs. Our quantitative review delivered both direct and indirect comparisons of the efficacy and safety of four biologics for PsA from double-blind, placebo-controlled trials. However, one biological (adalimumab) was significantly less effective on achieving PsARC\(^1\) response than the others. We conclude that the first part of the hypothesis was partially right, because every biological showed similar efficacy except one (as summarised on Figure 1). Regarding AS we can say that

\(^1\) The PsARC was developed as a PsA-specific composite responder index
this was the first study to include a biosimilar drug in the meta-analysis of biological treatments in AS. The results showed similar efficacy and safety profile of infliximab-biosimilar treatment compared to other biologicals (as shown on Figure 2), proving the second part of the hypothesis.

Figure 1. Statistical analysis and indirect comparison of efficacy of biologicals in clinical studies

<table>
<thead>
<tr>
<th>Comparison</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept-adalimumab</td>
<td>1.22 (0.10-28.56)</td>
</tr>
<tr>
<td>golimumab-adalimumab</td>
<td>1.33 (0.16-12.26)</td>
</tr>
<tr>
<td>infliximab-adalimumab</td>
<td>1.52 (0.16-16.63)</td>
</tr>
<tr>
<td>golimumab- etanercept</td>
<td>1.09 (0.04-16.59)</td>
</tr>
<tr>
<td>infliximab- etanercept</td>
<td>1.24 (0.05-22.67)</td>
</tr>
<tr>
<td>infliximab-golimumab</td>
<td>1.14 (0.10-13.79)</td>
</tr>
</tbody>
</table>
Policy implications
Transferability of efficacy and safety results from researches conducted in one country to another needs further consideration. This is especially relevant for the CEE countries that are characterised by particular economic conditions, health and social care systems. With these data we can provide input for further analysis. Biosimilar infliximab has the same effect as the existing drugs, and it is also cheaper than the existing biologicals in the market, therefore cost saving can be achieved, evidencing the appropriateness to choose this drug.

Limitations
A potential weakness of the meta-analyses arises from the fact that the trials from which data are combined are likely to differ in their design and patient population characteristics.
Figure 2. Statistical analysis and indirect comparison of safety of biologicals in clinical studies (serious adverse event)

Explanation of the figure: Results for week 30 were available and considered for infliximab-biosimilar. 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.
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
My second objective was to assess the COI of patients with moderate to severe Psoriasis in Hungary, based on a cross-sectional survey in Hungarian dermatological centers. We analysed the results from a non-interventional, cross-sectional questionnaire survey in 2 university dermatology clinics in Hungary.

Results
The majority of the patients (N=103, 52%) received 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. 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). Taking into account that the first biological agent was registered for the treatment of Psoriasis in 2004 we would have expected COI studies analysing patients with biological treatment by the end of January 2010, the date when the last systematic literature review was closed. 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 it was in a previous study. Our search identified nine publications (results can be seen in Table 1), seven of which involved Psoriasis patients with biological treatment. We fund that the total costs of treatment with biologicals were higher compared to our results in
Hungary almost all cases. In three studies the costs of hospitalization and out-patient visits were lower in biological treated subgroups, similarly to our findings. In line with our hypothesis, biological treatment increased the direct costs associated with Psoriasis while considerably improved quality of life of patients, so the hypothesis was right. Our study was the first from the CEE region to provide COI data and had the largest sample size of biologic treated patients in Europe.

Policy implications
Our study showed that the economic burden of Psoriasis is considerable in Hungary, however comparing to international data we observe lower costs in Hungary. With this study we provided input for further health economic analyses and a baseline to evaluate the economic effects of Psoriasis treatment in Hungary. These information are useful for medical decision making, developing guidelines and value based reimbursement.
Limitations
The survey was conducted in two university based dermatology centres 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 utilisations, recall bias might be present. Another limitation is due to the cross-sectional design; the current treatment was used as a proxy to measure disease severity and costs.
Table 1. Cost-of-illness studies of Psoriasis, reporting costs of biological treated patients (BST), till December 2013 in comparison with results of the current survey

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

n.r.: not reported; n.a.: not applicable
Hypothesis 3: Generic and disease specific quality of life scales and disease severity scores correlate with utilities.

Objective
According to literature search there was no data based on empirical research from the CEE region regarding biological treated patients in Psoriasis. Our study was the first research in this topic. My third objective was to provide data regarding utility and quality of life of Psoriaris patients, contributing to the international literature. Further objectives were to analyse the utilities between general and disease specific scales and disease severity measurement in Psoriasis and to transform scores, key clinical, demographic and health service utilisation variables into utility measures.

Results
This study provided the first evidence that patients with visible psoriatic lesions have significantly worse health related quality of life (HRQOL) compared to those with non-visible lesions, measured not just only with disease
specific questionnaire DLQI but also with a general questionnaire, EQ-5D. In addition to demographic and clinical variables, our model included health service utilisation variables related to Psoriasis, and explained higher proportion of EQ-5D variance than any previous findings in the literature (see in Table 2). EQ-5D score showed a moderate negative correlation with DLQI, PASI and with patients self-assessed disease severity VAS (0.29 < r < 0.5). Strong significant correlation was found between DLQI, PASI, and self-assessed disease severity VAS. The models are explaining 48.8% of EQ-5D variance (adjusted R2=0.488, ANOVA p<0.001), so the hypothesis was approved.

Table 2. Regression coefficients in the multivariate mapping on EQ-5D

<table>
<thead>
<tr>
<th>EQ-5D score</th>
<th>Unstandardised regression coefficient</th>
<th>Standardised regression coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>1.026</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>-0.090</td>
<td>-0.145</td>
<td>0.014</td>
</tr>
<tr>
<td>BMI</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psoriasis duration</td>
<td>-0.004</td>
<td>-0.169</td>
<td>0.006</td>
</tr>
<tr>
<td>DLQI</td>
<td>-0.080</td>
<td>-0.190</td>
<td>0.023</td>
</tr>
<tr>
<td>EQ-5D score</td>
<td>Unstandardised regression coefficient</td>
<td>Standardised regression coefficient</td>
<td>P</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>----------------------------------------</td>
<td>------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Self-assessed disease severity VAS</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chronic plaque Psoriasis</td>
<td>-0.089</td>
<td>-0.151</td>
<td>0.029</td>
</tr>
<tr>
<td>Palmoplantar Psoriasis</td>
<td>-0.347</td>
<td>-0.269</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Scalp Psoriasis</td>
<td>0.152</td>
<td>0.252</td>
<td>0.001</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>-0.134</td>
<td>-0.212</td>
<td>0.002</td>
</tr>
<tr>
<td>GP visit(s) due to Psoriasis in the last month</td>
<td>-0.160</td>
<td>-0.227</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalisation(s) due to Psoriasis in the last 12 months</td>
<td>-0.104</td>
<td>-0.160</td>
<td>0.013</td>
</tr>
<tr>
<td>Use of home help (professional or informal) in the last month</td>
<td>-0.139</td>
<td>-0.160</td>
<td>0.021</td>
</tr>
</tbody>
</table>

**Policy implications**

This study confirmed previous findings about correlations between questionnaires and quality of life scores. 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. Furthermore, cost-effectiveness analyses require input data both on effectiveness in terms of health gain (considering the quality of the life years gained and utilities) and disease related costs on the social level.

Limitations
To our knowledge, HRQOL median values of our sample were 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 may also be 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.
Hypothesis 4: The introduction of biosimilar infliximab leads to substantial savings in health care budgets.

Objective
The first biosimilar monoclonal antibody (biosimilar infliximab) was registered by the EMA in 2013 for the treatment of several inflammatory conditions including RA and AS. Biosimilar infliximab is first marketed in the CEE countries. My fourth aim was to build a model to perform budget impact analysis of biological therapies in six CEE countries for 3 years within RA.

Results
In 2013, approximately 17,300 RA patients were treated with biological drugs in the six CEE countries. Findings showed 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 changing of original infliximab to biosimilar infliximab had a significant impact on budget savings. In BSc2 the total saving was estimated to be €20.8 M (see in Table 3) over the three years. The cost savings may be reinvested to treat
additional patients with biological drugs. If all budget savings were spent on reimbursing biological therapy of new patients with biosimilar infliximab, an 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.

Policy implications
This was the first study to estimate the budget impact of introducing the first biosimilar (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. Based on the present analysis, the introduction of biosimilar infliximab as an alternative treatment option for RA in CEE was predicted to bring substantial cost savings to the national health care budget. Based on these results, the use of biosimilar infliximab appeared to be economically attractive because it offers the potential to
reduce the total expenditures or to increase the number of patients treated on a fixed budget with biologicals.

Furthermore, biosimilar infliximab has the same effect as the existing drugs with the additional benefit of cost saving, therefore it is appropriate to choose this drug.

Table 3. Results of the scenario analyses

<table>
<thead>
<tr>
<th></th>
<th>Budget impact (euro)</th>
<th>Number of new RA patients on biological treatment if budget savings would be spent on biosimilar infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>year 1</td>
<td>year 2</td>
</tr>
<tr>
<td>Biosimilar Scenario 1</td>
<td>- 945,241</td>
<td>- 4,782,462</td>
</tr>
<tr>
<td>Biosimilar Scenario 2</td>
<td>- 2,394,545</td>
<td>- 6,968,620</td>
</tr>
</tbody>
</table>

Biosimilar scenario 1: interchanging of biosimilar and original biologicals is not allowed
Biosimilar scenario 2: interchanging of biosimilar and original biologicals is allowed at least six months after treatment start
Limitations

Due to the number of limitations of this budget impact analysis the results should be interpreted with caution. First, it should be taken into 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.
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V. Publications of the author related to the thesis

Cumulated IF: 7,652

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Books, book chapters, conference proceedings:

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Journal articles:

Baji, P. et al [2014]: Comparative efficacy and safety of biosimilar infliximab and other biological treatments in ankylosing spondylitis: systematic literature review and meta-analysis. *The*


**Publications in Hungarian**

Books, book chapters, conference proceedings:

