Doctoral Program in Management and Business Administration

THESES

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Economic consideration of the implementation of biotechnological therapies in chronic diseases

Ph.D. Dissertation

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Budapest, 2014

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CONTENT

List of Tables

List of Figures

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.

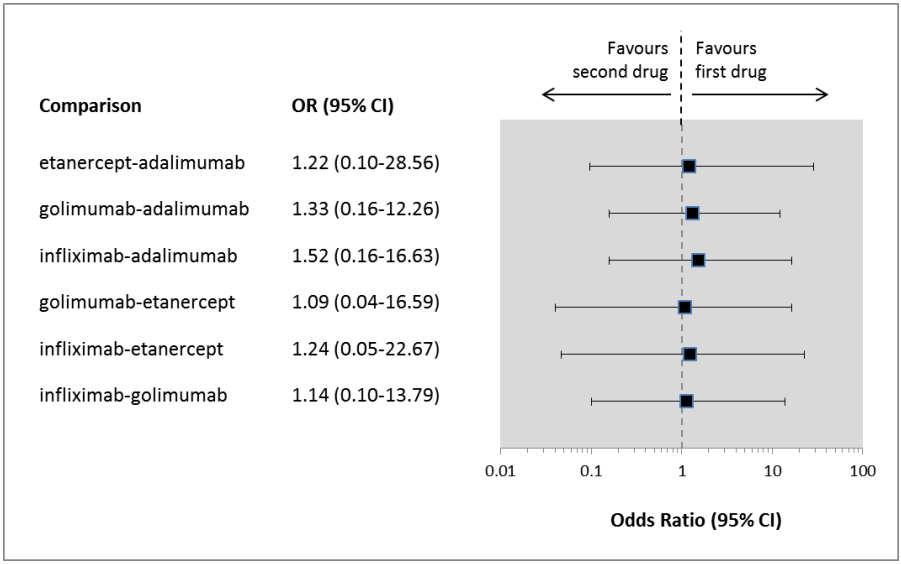
Results

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



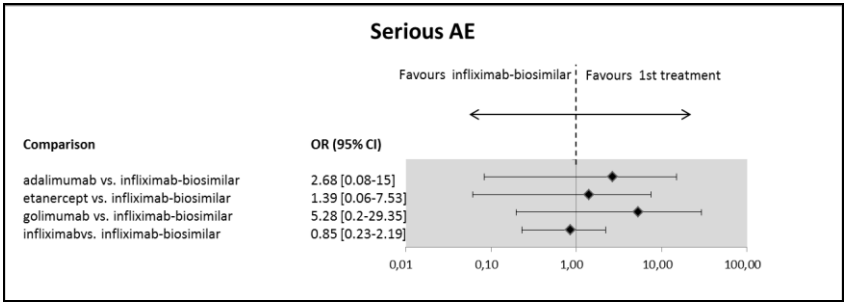
Policy implications

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

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
Fonia et al. 2010, United Kingdom	retrospective chart review	severe Psoriasis, 2 tertiary dermatology centers	76/76	€4,742 / €13,505	n.r.	n.a.
Driessen et 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	1,924/69	€3,356 / €16,214	n.r.	n.a.

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
		an administrative area				
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

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 ($0.29 < r_s < 0.5$). 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

	EQ-5D score		
	Unstandardised regression coefficient	**Standardised regression coefficient**	**P**
Constant	**1.026**		**<0.001**
Age	-	-	-
Gender (female)	-0.090	-0.145	0.014
BMI	-	-	-
Psoriasis duration	-0.004	-0.169	0.006
DLQI	-0.080	-0.190	0.023

	EQ-5D score		
	Unstandardised regression coefficient	**Standardised regression coefficient**	**P**
Self-assessed disease severity VAS	-	-	-
Chronic plaque Psoriasis	-0.089	-0.151	0.029
Palmoplantar Psoriasis	-0.347	-0.269	<0.001
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
Hospitalisation(s) due to Psoriasis in the last 12 months	-0.104	-0.160	0.013
Use of home help (professional or informal) in the last month	-0.139	-0.160	0.021

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

	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
BiosimilarScenario 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

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.

IV. Main references

Ades, A. E. et al [2006]: Bayesian methods for evidence synthesis in cost-effectiveness analysis. *Pharmacoeconomics,* 24**,** 1-19

Anis, A. H., Rahman, T. ,Schechter, M. T. [1998]: Using pharmacoeconomic analysis to make drug insurance coverage decisions. *Pharmacoeconomics,* 13**,** 119-126

Arrow, K. J. ,Lind, R. C. [1970]: Uncertainty and the Evaluation of Public Investment Decisions. *American Economic Review,* 60**,** 364-78

Baji, P. et al [2014]: Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. *Eur J Health Econ,* Suppl 1, 10.1007/s10198-014-0595-3.

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

Barbieri, M., Wong, J. B. ,Drummond, M. [2005]: The cost effectiveness of infliximab for severe treatment-resistant rheumatoid arthritis in the UK. *Pharmacoeconomics,* 23**,** 607-18.2367 [pii]

Boncz, I. [2006]: Népegészségügyi programok egészség-gazdaságtani elemzése. Doktori értekezés tézisei. Pécs

Bouckaert, G. ,Halligan, J. [2007]: *Managing performance: international comparisons*, Routledge

Briggs, A. ,Sculpher, M. [1995]: Sensitivity analysis in economic evaluation: a review of published studies. *Health economics,* 4**,** 355-371

Briggs, A. H. [2000]: Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics,* 17**,** 479-500

Brouwer, W. B., Koopmanschap, M. A. ,Rutten, F. F. [1997]: Productivity costs in cost-effectiveness analysis: numerator or denominator: a further discussion. *Health Economics,* 6**,** 511-514

Brouwer, W. B. et al [1999]: The valuation of informal care in economic appraisal. *International Journal*

of Technology Assessment in Health Care, 15**,** 147-160

Busse, R. et al [2002]: Best practice in undertaking and reporting health technology assessments. *International journal of technology assessment in health care,* 18**,** 361-422

Cohen, J. [1992]: A power primer. *Psychol Bull***,** 155-159

Cunningham, S. J. [2001]: An introduction to economic evaluation of health care. *Journal of Orthodontics,* 28**,** 246-250

Cutler, D. M. ,Mcclellan, M. [2001]: Is technological change in medicine worth it? *Health affairs,* 20**,** 11-29

Dakin, H. [2013]: Review of studies mapping from quality of life or clinical measures to EQ-5D: an online database. *Health Qual Life Outcomes,* 11**,** 151.10.1186/1477-7525-11-151

Dauden, E. et al [2012]: Validation of a new tool to assess health-related quality of life in psoriasis: the PSO-LIFE questionnaire. *Health Qual Life Outcomes,* 10**,** 56.10.1186/1477-7525-10-56

Dolan, P. [1997]: Modeling valuations for EuroQol health states. *Med Care,* 35**,** 1095-108

Drummond, M. [1992]: Cost-of-illness studies. *Pharmacoeconomics,* 2**,** 1-4

Drummond, M. F. et al [2005a]: Methods for the Economic Evaluation of Health Care Programmes. New York, Oxford University Press, 3rd Edition.

Drummond, M. ,Sculpher, M. [2005b]: Common methodological flaws in economic evaluations. *Medical care,* 43**,** II-5-II-14

Eddy, D. M. [1992]: Cost-effectiveness analysis: is it up to the task? *JAMA,* 267**,** 3342-3348

Farfan-Portet, M.-I. et al [2014]: Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? *The European Journal of Health Economics,* 15**,** 223

Gabriel, S. E. ,Michaud, K. [2009]: Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther,* 11**,** 229.ar2669 [pii]10.1186/ar2669

Goldman, D. P. et al [2005]: Consequences of health trends and medical innovation for the future elderly. *Health Affairs-Millwood Va Then Bethesda Ma-,* 24**,** W5

Gulácsi, L., Boncz, I. ,Drummond, M. [2004]: Issues for countries considering introducing the ‘fourth hurdle’; The case of Hungary. *International Journal of Technology Assessment in Health Care,* 20**,** 337-341.

Gulácsi, L., Boncz, I. ,Drummond, M. [2005]: cahpter: 14. Az egészség-gazdaságtani és technológiaelemzési vizsgálatok eredményeinek felhasználhatósága hazánkban. *Medicina Ltd Budapest,*

Gulácsi, L. [2007]: The time for cost-effectiveness in the new European Union member states: the development and role of health economics and technology assessment in the mirror of the Hungarian experience. *The European Journal of Health Economics,* 8**,** 83-88

Gulácsi, L. et al [2009]: History of health technology assessment in Hungary. *International journal of technology assessment in health care,* 25**,** 120-126

Gulácsi, L. [2012]: Egészség-gazdaságtani elemzés in: Egészség-gazdaságtan és technológiaelemzés szerk: Gulácsi László, Budapest, Medicina Könyvkiadóiadó.

Gulácsi, L., Orlewska, E. ,Péntek, M. [2012]: Health economics and health technology assessment in Central and Eastern Europe: a dose of reality. *The European Journal of Health Economics,* 13**,** 525-531

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

Hutton, J. et al [2006]: Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies (fourth hurdle systems). *International journal of technology assessment in health care,* 22**,** 10-18

Jones, D. [1992]: Meta-analysis of observational epidemiological studies: a review. *Journal of the royal society of medicine,* 85**,** 165-168

Jonsson, E. ,Banta, D. [1999]: Management of health technologies: an international view. *Bmj,* 319**,** 1293

Kobelt, G. [2002]: *Health economics: an introduction to economic evaluation*, Office of health economics London

Koopmanschap, M. A. et al [1995]: The friction cost method for measuring indirect costs of disease. *J Health Econ,* 14**,** 171-89.0167629694000445 [pii]

Koopmanschap, M. A. ,Rutten, F. F. [1996]: A practical guide for calculating indirect costs of disease. *Pharmacoeconomics,* 10**,** 460-6

Liljas, B. [1998]: How to calculate indirect costs in economic evaluations. *Pharmacoeconomics,* 13**,** 1-7

Lofland, J. H., Pizzi, L. ,Frick, K. D. [2004]: A review of health-related workplace productivity loss instruments. *Pharmacoeconomics,* 22**,** 165-184

Lu, G. ,Ades, A. E. [2004]: Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med,* 23**,** 3105-24

Lu, G., Brazier, J. E. ,Ades, A. E. [2013]: Mapping from disease-specific to generic health-related quality-of-life scales: a common factor model. *Value Health,* 16**,** 177-84.10.1016/j.jval.2012.07.003

Martelli, F. et al [2007]: Health technology assessment agencies: an international overview of

organizational aspects. *International journal of technology assessment in health care,* 23**,** 414-424

Mason, J. M. [1994]: Cost-per-QALY League Tables. *Pharmacoeconomics,* 5**,** 472-481

Mattei, P. L., Corey, K. C. ,Kimball, A. B. [2013]: Psoriasis Area Severity Index (PASI) and the Dermatology Life Quality Index (DLQI): the correlation between disease severity and psychological burden in patients treated with biological therapies. *J Eur Acad Dermatol Venereol*.10.1111/jdv.12106

Mauskopf, J. A. et al [2007]: Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. *Value Health,* 10**,** 336-47

Mihaylova, B. et al [2010]: Review of statistical methods for analysing healthcare resources and costs. *Health Economics,* 20**,** 897-916

Moh [2012]: Ministry of Health - National Health Insurance Fund's prospectus of the monthly payment of financing of curative and preventing care.

Molodecky, N. A. et al [2012]: Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology,* 142**,** 46-54 e42; quiz e30.S0016-5085(11)01378-3 [pii] 10.1053/j.gastro.2011.10.001

OECD [2014]: Health Statistics. http://stats.oecd.org/index.aspx?DataSetCode=HEALTH_STAT 39.

Orlewska, E. ,Gulacsi, L. [2009]: Budget-impact analyses: a critical review of published studies. *Pharmacoeconomics,* 27**,** 807-27

Pawson, R., Tilley N. [2007]: Realistic Evaluation. SAGE Publications, Inc. London ISBN: 9780761950080

Péntek, M. et al [2007]: Costs of rheumatoid arthritis in Hungary. *J Rheumatol,* 34**,** 1437

Péntek, M. et al [2014]: Biologic therapy in inflammatory rheumatic diseases: issues in Central and Eastern European countries. *Eur J Health Econ,* Suppl 1, 10.1007/s10198-014-0592-6.

Reilly, M. C., Zbrozek, A. S. ,Dukes, E. M. [1993]: The validity and reproducibility of a work

productivity and activity impairment instrument. *Pharmacoeconomics,* 4**,** 353-65

Rossi, P. H. ,Lipsey, M. W. [2004]: *Evaluation: A Systematic Approach*, SAGE

Van De Vooren, K. et al [2014]: A critical systematic review of budget impact analyses on drugs in the EU countries. *Applied health economics and health policy,* 12**,** 33-40.10.1007/s40258-013-0064-7

Van Houwelingen, H. C., Arends, L. R. ,Stijnen, T. [2002]: Advanced methods in meta-analysis: multivariate approach and meta-regression. *Statistics in medicine,* 21**,** 589-624

Weinstein, M. C. [1990]: Principles of cost-effective resource allocation in health care organizations. *International Journal of Technology Assessment in Health Care,* 6**,** 93-103

Weinstein, M. et al [1996]: Cost-effectiveness in health and medicine. *New York: Oxford University 55.*

Yach, D. et al [2004]: The global burden of chronic diseases: overcoming impediments to prevention and control. *Jama,* 291**,** 2616-2622

V. Publications of the author related to the thesis

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

Balogh, O. ,Brodszky, V. [2013]: Epidemiology, clinical characteristics and health status assessment 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. 1-12

Balogh, O. [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

Brodszky, V. et al [2013]: Budget Impact Analysis of Biosimilar Infliximab Treatment for Rheumatoid Arthritis in Six Central European Countries. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 16**,** A558

Brodszky, V. et al [2013]: Indirect Comparison of the Effect of Biologics in Patients with Psoriasis; A Meta-Analysis of Randomized, Double Blind Clinical Trials in Bayesian Framework. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 16**,** A501-A502

Brodszky, V. et al [2013]: Budget Impact Analysis of Biosimilar Infliximab Treatment for Rheumatoid Arthritis in Six Central European Countries. *Value in health : the journal of the International*

Society for Pharmacoeconomics and Outcomes Research, 16**,** A558

Brodszky, V. et al [2013]: Evaluating the Efficacy of Biosimilar Infliximab with the ACR50 Response in Patients with Rheumatoid Arthritis; A Meta-Analysis in Bayesian Framework. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* 16**,** A556

Péntek, M. et al [2012]: PMH35 EQ-5D Utilities and Productivity of Adults With Attention-Deficit/Hyperactivity Disorder: Review of the Literature and a Cross-Sectional Survey in Hungary. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* 15**,** A340

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*

European Journal of Health Economics, 15**,** 45-52.10.1007/s10198-014-0593-5

Brodszky, V. et al [2014]: Budget impact analysis of biosimilar infliximab (CT-P13) for the treatment of rheumatoid arthritis in six Central and Eastern European countries. *The European Journal of Health Economics,* 15**,** 65-71.10.1007/s10198-014-0595-3

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.

Gulácsi, L. et al [2013]: A biológiai terápiák költség-hasznossága psoriasisban; szisztematikus folyóiratkeresés és elemzés. Magyar Dermatológiai Társulat 86. Nagygyűlése, Budapest, 2013. december 12.

Balogh, O. ,Hevér, N. [2011]: Határokon átívelő egészségügy – Trendek és kihívások az Európai Unióban. *KözGazdaság* VI.