Pharmacoeconomic aspects of oral nonsteroidal anti-inflammatory drugs in rheumatoid arthritis focusing on the selective COX-2 inhibitor celecoxib

Ph.D. thesis outlines

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1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with high influence on patient's quality of life (QoL), mainly because the chronic pain and limited mobility. Although disease modifying antirheumatic drugs (DMARDs) gain increasing importance in the treatment of RA, there are still many patients who need nonsteroidal anti-inflammatory drug (NSAID) medication. The selective Cyclooxygenase (COX)-2 inhibitors – despite of their favourable gastrointestinal (GI) side effect profile – are not adequate for every patient, mainly due their cardio-vascular (CV) side effects and significant price premium.

Ageing, changes in disease structure, the prevalence and the economic burden of chronic diseases increase the demand for health care services. The subvention of this demand is challenging even for well developed countries. The conflict of medically possible and economically affordable highlights the importance of explicit and transparent decision methods, as well as the equity and justice in the course of resource allocation.

Pharmacoeconomic analyses facilitate the expression of these aspects via the preparation of decision making.

2. Objectives

The purpose of this research was to analyse the pharmacoeconomic aspects of oral NSAIDs in RA, focusing on the selective COX-2 inhibitor celecoxib. The following studies were conducted:

1. The full economic evaluation of the selective COX-2 inhibitor celecoxib in RA aimed:

a. to calculate the incremental cost effectiveness ratio (ICER) of celecoxib compared to relevant comparators in average GI risk RA patients,

b. to assess the influence of uncertain parameters on decision with one-way deterministic sensitivity analyses.

2. The non interventional clinical study in a group of RA patients aimed:

a. to compare the QoL, utility and disease activity of patients on biological treatments for at least six months with patients on conventional antirheumatic treatments,

b. to determine the strength of correlation between disease activity, QoL and utility measures,

c. to identify a possible difference between the NSAID active agents group concerning QoL in the RA population.

3. The drug utilization study aimed:

a. to assess patterns of NSAID use in the sample of RA patients requiring chronic NSAID treatment, with consideration of GI, CV risk profile and pharmacoeconomic aspects,

b. to compare the patterns of oral NSAID use in the sample of RA patients requiring chronic NSAID treatment to the Hungarian population's total NSAID consumption (excluding the topical forms),

c. to compare the results of the total Hungarian population's NSAID consumption to Czech, Latvian, Lithuanian, Polish and Slovakian NSAID consumption data.

3. Methods

3.1. A decision tree model was built for one year to indentify celecoxib's ICER compared to traditional NSAIDs and NSAID+PPI (proton pump inhibitor) combination in RA-patients with average GI risk. The

efficacy of different NSAID strategies in therapeutically relevant doses were assumed to be the same, consequently, difference in health gain was derived only from the different side effect profile. Three GI outcomes were identified among arthritis patients: 1. no GI side effect outcome; 2. dyspepsia (within dyspepsia: possibility of peptic ulcer with or without hospitalisation); 3. serious GI side effects (such as bleeding with the possibility of death); probabilities were based on a systemic literature search. We identified two CV outcomes: 1. no CV disease and 2. MI (myocardial infarction), with the possibility of death. According to the third party payer's perspective, the following cost categories were distinguished: drug costs of the three therapeutic strategies; the cost of post CV and/or GI drug therapy; inpatient costs related to side effect hospitalisation; direct medical cost not related to the NSAID choice. Sensitivity was tested with one way deterministic sensitivity analyses. All variables were changed within a $\pm$5 % interval.

3.2. In 2009, a cross-sectional, non interventional study was conducted in the Polyclinic of the Hospitaller

Brothers of St. John of God. Disease activity score (DAS)-28, generic- (EuroQol five Dimension (EQ-5D) Visual Analogue Scale (VAS)) and disease specific QoL (Rheumatoid Arthritis Quality of Life (RAQoL)), and utility with direct- (Time Trade-off (TTO)) and indirect (EQ-5D index) methods were measured. Pearson-correlation was used to define the strength of correlation between DAS-28 and the different QoL/utility measures. We also assessed the GI and CV risk status and the patterns of chronic NSAID use of the patients. Statistical analyses were performed with SPSS 15.0 and STATA 10.1.

3.3. Data of NSAID use in RA patients group was gathered from the non-interventional clinical study. The patterns of NSAID use of the total population between 2000 and 2007 in six Central-Eastern European countries were evaluated according to the WHO Anatomical Therapeutical Chemical/Defined Daily Dose (ATC/DDD) methodology. IMS Health database was used; the crude data represented the consumption of M01A and N02B ATC groups in DOTs. Our main outcome measure was DDD/1000 inhabitants/day. We

implemented three different levels of evaluation in our utilization study: total NSAID level, subgroups of NSAIDs (conventional NSAID group; 'stronger COX-2 inhibitors' like nimesulide and meloxicam; selective COX-2 inhibitors (coxibs)) and the level of different drugs. The average consumption for the six countries was weighted by their population.

4. Results

4.1.a. According to our model, the ICER of NSAID vs. NSAID+PPI was 4 776 145 HUF/QALY (Quality adjusted life years), while the ICER of NSAID vs. Celecoxib was 20 609 334 HUF/QALY. Consequently, NSAID+PPI seem to be cost-effective at an implicit threshold of 2-3x GDP/capita. NSAID+PPI provide extra health gain for lower cost compared to celecoxib thus it is the dominant strategy.

4.1.b. According to the sensitivity analysis of NSAID vs. NSAID+PPI, utility value of RA without GI side effects and the utility of dyspepsia had the highest influence on ICER. In their extreme values, they may result that the cost effectiveness of NSAID+PPI cannot be justified.

Further sensitive parameters were focusing on the probability of no GI side effects in the NSAID and NSAID+PPI strategy and the utility of peptic ulcer. The domination of celecoxib by NSAID+PPI (which was considered as a cost-effective, consequently standard therapy) was robust during the sensitivity analysis.

4.2.a. Patients receiving biological treatments for at least six months (n=85) had higher utility (EQ-5D index difference: 0.11, p=0.012, TTO difference: 0.039, ns.), lower disease activity (DAS-28 difference: 0.61, p=0.003) compared to patients on conventional antirheumatic therapy (n=168) after adjusting data by age, gender and disease duration. However, disease specific QoL was slightly worse (RAQoL difference: 1,15, ns.) in the biological treatment subgroup.

4.2.b. Moderate correlation ($0,2<r<0,7$) at p=0.01 significance level was observed in all cases between DAS-28 and different QoL/utility measures.

4.2.c. No clinically significant differences could be identified between NSAID drug groups concerning QoL measures.

4.3.a. Of the 253 RA patients, 143 were on continuous NSAID therapy. RA Patients with previous/current GI side effects (n=36) were much likely to use safer NSAIDs compared to patients with low GI risk (n=107): Meloxicam 52.8% vs. 33.6%; celecoxib: 5.6% vs. 0.9%; etoricoxib: 11.1% vs. 5.6%, respectively. This trend was inverse in the case of diclofenac (5.6% vs. 26.2%), which is considered to have worse GI side effect profile compared to coxibs/'stronger COX-2 inhibitors'. The previous occurrence of GI events were significantly higher (p=0.02) in patients currently treated with safer NSAIDs. None of the 8 post MI RA patients were on coxib therapy. Only three patients (2.1%) were on celecoxib therapy, two of them with prior GI events.

4.3.b. The observed RA patient sample were much likely to use safer NSAIDs (nimesulide: 9.8% vs. 6.1%; meloxicam: 38.5% vs. 9%; coxibs: 9.1% vs. 0.3%) compared to the total population. The trend was inverse in the conventional NSAIDs (diclofenac: 21% vs. 39.4%; ibuprofen: 1.4% vs. 13%, respectively) group.

4.3.c. From 2002 to 2007, the total NSAID consumption was between 30 and 70 DDD/1000 inhabitants/day in the

observed countries; while the average total growth was 25% from 2002 to 2007. The conventional NSAID group represents the majority of the total NSAID consumption in all countries, with an average total growth of 10.4% from 2002 to 2007. Nimesulide and meloxicam achieved a magnitude smaller consumption, however, this group of drugs showed the greatest growth with 325% from 2002 to 2007 (2004-2005: 50.1%). Although selective COX-2 inhibitors show considerable increase till 2004, their consumption is less than 1/100 of total NSAID's. The withdrawal of rofecoxib in 2004 influenced and reduced the consumption of coxibs till 2005, from an average level of 0.41 to 0.15 DDD/1000 inhabitants/day. Consumption of coxibs in Central-Eastern Europe was much smaller than in the most developed countries.

5. Conclusions

5.1. According to our model, celecoxib is not likely to be cost-effective in average GI risk RA patients, compared to conventional NSAIDs, while the combination therapy dominates celecoxib. At a threshold of 2-3x GDP/capita, NSAID+PPI appears to be a cost-effective alternative

(ICER: 4.77 M HUF/QALY) in Hungary compared to traditional NSAIDs. Consequently, PPI co-prescription should be considered to a broader group of patients. Celecoxib is likely to be a rational choice in case of ineffectiveness/intolerance of the combination therapy, or in limited group of patients with very high GI risk (possibly with PPI co-prescription). However, the cost-effectiveness of this strategy should be supported by a separate analysis. Our results are different if comparing to other technology assessments, probably because of the different health care system, inpatient and drug costs, model perspective and structure. These results also highlight the importance of thorough adaptation process of available international HTA models.

5.2.a. Both TTO and EQ-5D indicates that the biological treatment subgroup of RA has better general QoL and higher utility. The initial DAS-28 score (when starting biological treatments) suggests that patients in the biological subgroup represent a more severe initial health status than patients treated with non-biological treatments. The better QoL of the conventional antirheumatic subgroup compared to a previous

multicenter study in 2004 even highlights the beneficial effects of biological drugs on patient's QoL.

5.2.b. We could confirm previous correlation results of different patient reported outcomes published in the literature. However, according to our knowledge, correlation of other instruments and TTO was not previously assessed in Hungarian RA patients. Our results showed a moderate correlation in this case.

5.2.c. No evidence could support that patients on different NSAID drug groups would experience clinically significant difference in their QoL.

5.3.a. Our results indicate that GI and CV risk factors are taken into consideration in the NSAID choice by specialists, as for patients with higher GI risk, safer NSAIDs are much likely to be prescribed; while there were no RA patient on coxibs with post MI. Our results showed the so called 'indication bias'. According to this, drugs considered to be the most effective/safest (coxibs) are more likely to be prescribed to patients considered to be in high GI risk. Consequently, non parallel non randomised observational studies might show worse effectiveness among these drugs, compared with

therapies considered to be less GI safe, but used in healthier patients (with less GI risk). Our results indicated the rational use of celecoxib in limited group of patients with special risk factors. These findings suggest that pharmacoeconomic aspects were also taken into consideration in the everyday clinical practice, and are consistent with the results of our cost-utility analysis.

5.3.b. The considerable difference between the NSAID consumption in the RA study population and the total Hungarian population could be explained with different patient characteristics and daily therapeutic drug costs. Daily therapeutic costs are the lowest in the traditional NSAIDs (mainly COX-1 inhibitors); however, COX-2 inhibitors GI side effect profile is better. The total population's consumption data represents both acute and chronic events, while the sample of RA patients consists mainly of chronic users of NSAID's. GI side effects appear to be dose and therapy duration related, consequently, supposing an average GI risk and shorter disease duration in the total population, traditional NSAIDs seem to be the rational choice. In contrast, because of the chronic use, GI risk is higher in the RA

study population, which indicates the increased use of coxibs and stronger COX-2 inhibitors.

5.3.c. NSAID consumption data shows, that there are no considerable differences between the observed countries regarding total NSAID consumption, NSAID drug groups and NSAID drugs. The conventional NSAID group represents the majority of the total NSAID consumption; the most widely used drugs were diclofenac and ibuprofen. The greatest increase was achieved by nimesulide and meloxicam, which provides GI benefits at rationale price. Consequently, among the non-COX-2 selective NSAIDs, drugs considered to be GI safer are widely used. The scarcity of resources in the observed Central and Eastern European countries and the scepticism around COX-2 inhibitors since the withdrawal of rofecoxib can explain the underuse of selective COX-2 inhibitors compared to the developed countries. Our data indicates that international trends of NSAID consumption are valid in Hungary.

Results of local health technology assessments can contribute to improve the allocative efficiency of public

resources in Hungary, which highlights the significance of our cost utility analysis. Non interventional studies are useful to assess rational use of different drugs, while international drug utilization studies depict actual market trends comprehensively, consequently improve the efficiency of drug use.

6. Publications by the Ph.D. candidate

6.1. Peer-reviewed scientific publications related to the thesis

1. Inotai A, Bodrogi J. (2007) Költség-kontroll technikák a magyar gyógyszer-finanszírozásban [Cost control techniques in Hungarian medicine reimbursement] Acta Pharm Hung, 77: 190-196.
2. Inotai A, Vincze Z. (2008) NSAID szerek költség-értékelése rheumatoid arthritisben az érvényben lévő terápiás protokoll alapján [Cost study of NSAID use in rheumatoid arthritis based on recent therapeutic protocols] Acta Pharm Hung, 78: 79-86.
3. Inotai A, Mészáros Á. (2008) A celecoxib költség-hatékonysági vizsgálata rheumatoid arthritisben. IME Az egészségügyi vezetők szaklapja, 10: 48-50.
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6. Inotai A, Hankó B, Mészáros Á. (2010) Trends in the non-steroidal anti-inflammatory drug market in six Central-Eastern European countries based on retail information. Pharmacoepidemiol Drug Saf, 19: 183-190. **IF: 2,527**
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felhasználásának vizsgálata a Budai Irgalmasrendi Kórház II. Reumatológia osztályának rheumatoid arthritises betegei között [The assessment of oral NSAID use in patients with rheumatoid arthritis in Hungary-a cross sectional non interventional study] Acta Pharm Hung, 80: 47-54.

6.2. Scientific books and chapters

1. Kaló Z, Inotai A, Nagyjánosi L.(szerk.) (2009) Egészség-gazdaságtani fogalomtár I. Egészségügyi technológiák gazdasági elemzése. Professional Publishing Hungary Kft, Medical Tribune Divízió. ISBN: 978-963-87660-8-3

6.3. Scientific abstracts related to the thesis

1. Mészáros Á, Inotai A. (2008) A rheumatoid arthritis nem-szteroid gyulladás-gátlókkal történő kezelésének költséghatékonysági szempontjai. Gyógyszerészet, (Suppl): 26-27.
2. Inotai A, Mészáros Á. (2008) Cost-effectiveness of celecoxib compared to conventional NSAIDs and NSAID+PPI combination therapy in the treatment of rheumatoid arthritis. Value Health, 11: A549. **(IF: 3,009)**
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4. Inotai A, Mészáros Á. (2009) Hat Közép-Európai ország NSAID felhasználásának gyógyszer-utilizációs vizsgálata nagykereskedelmi kiszállítások alapján. Gyógyszerészet, 11(Suppl 1): S121-S122.

5. Kaló Z, Pékli M, Inotai A. (2009) Quality assurance of fourth hurdle in Hungary – a methodological approach. Value Health, 12(7): A239. **(IF: 3,032)**
6. Rojkovich B, Inotai A, Mészáros Á, Jászay E, Imre K, Mészáros Gy. (2010) Patient and physicians global assessment on disease activity of rheumatoid arthritis. Magy Reumatol, 51: 190-191.

6.4. Peer-reviewed scientific publications not related to the thesis

1. Inotai A, Kaló Z. (2010) Az egészségügyi ágazat, mint közszolgáltatás kutatási, fejlesztési és innovációs stratégiája és az ágazat innovációs folyamatainak vizsgálata. Egészségügyi Gazdasági Szemle, 48: 33-38.

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