Interest of modelling in rheumatoid arthritis

A. Beresniak[1,2], D.M. Dupont[3], J.-C. Becker[4], S. Merkesdal[5]

[1]Data Mining International, Geneva, Switzerland; [2]Paris-Descartes University, Paris, France; [3]Data Mining America, Montreal, Canada; [4]Becker Clinical Research Consulting, NY, USA; [5]Hannover Medical School, Clinic for Immunology and Rheumatology, Hannover, Germany.

Ariel Beresniak, MD, MPH, PhD
Danielle M. Dupont, Pharm, MSc, PhD
Jean-Claude Becker, MD
Sonja Merkesdal, MD

Please address correspondence to:
Dr Ariel Beresniak,
Data Mining International,
Route de l'Aéroport, 29-31, CP 221,
CH-1215 Geneva, Switzerland.
E-mail:
aberesniak@datamining-international.com

Received and accepted on September 14, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 73): S96-S101.

Key words: modelling, rheumatoid arthritis, QALY

Competing interests: none declared.

ABSTRACT

Such as prospective studies can provide evidence-based information for clinicians and regulatory agencies, modelling studies provide useful information when experimental studies are to complex, too long, or too expensive to carry out. If modelling has been widely used in pharmacokinetics, it is in the field of pharmacoeconomics that numerous models have been published in recent years, including models relevant to the management of rheumatoid arthritis (RA). The most common modelling techniques published in RA are decision trees and Markov models which are used to perform cost-effectiveness and cost-utility analyses using real or simulated populations. This paper reviews the main types of modelling techniques used in pharmacoeconomic studies with the aim of clarifying their interest and limitations for the clinicians. Generating such evidence is highly relevant to assisting clinical recommendations and reimbursement decisions towards enabling the optimal management of RA and reducing its overall clinical and economic burden, for the benefits of patients and health systems.

Introduction

Despite the expected clinical and economic benefits of optimal RA management, establishing the value for money of new therapies has become a requirement from payers, health care authorities and health technology assessment (HTA) agencies around the world. If the final objective of the pharmaceutical industry is to convince the prescriber to prescribe and the payer to pay, the objective of health services is to provide the best treatments to patients, and the objective of reimbursement authorities is to assess the value for money of new *versus* existing treatments. These assessments are needed to assist resource allocation decisions based on evidence relevant to country-specific health systems. The role of HTA agencies is thus to assess the clinical and pharmacoeconomic (PE) evidence relevant to new technologies compared to current treatment standards and to make reimbursement recommendations to "payers" (public or private insurance, hospital, etc.) based on their assessment and comparison of the overall value of different treatment strategies. The vast majority of PE studies are based on modelling techniques because most clinical studies do not include any resource utilisation parameters. Moreover, clinical studies having a limited time horizon, they often do not allow for an appropriate comparison of various and complex treatment strategies over a meaningful timeframe.

Such as prospective studies can provide evidence-based information for clinicians and regulatory agencies, PE modelling studies can thus provide useful information for payers and health policy makers. Relevant to RA, the high costs of biological agents introduced in the late 90s led to the publication in the rheumatology literature of many PE studies of variable scientific quality over the last decade. In addition, because modelling studies use specific terminologies and various techniques, they are often not understandable by non specialists. Clinicians should be able to discriminate in the medical literature what models are based on validated assumptions and clinical practices. This paper reviews the main types of modelling techniques used in PE studies in the field of RA with the aim to clarify their interest and limitations.

Real data *vs.* virtual data

A PE study can be carried out using real data (*in vivo*) or virtual data (*in silico*) using modelling techniques. Real data can be collected prospectively during clinical trials by integrating resource utilisation questionnaires (to calculate costs), appropriate clinical endpoints (to assess effectiveness), or quality of life questionnaires (to describe quality

of life or to derive utility values). The main issue with this approach is that the interventions are imposed by the protocol and not driven by patients' needs. Another limitation is that clinical trials assess single therapeutic regimens over limited time horizons while the management of RA may require the use of several therapeutic strategies successively. This explains the interest of using modelling techniques, which allow the use of mathematical language to construct formulas which link different parameters together, therefore allowing the calculation of the value of one parameter according to the others. However, models can only be valid if their underlying assumptions are valid, in particular, if their designs are consistent with medical practices and if data sources are robust and used appropriately. For example, any model simulating effectiveness and costs for one specific biologic agent over a life time horizon should not be considered as valid because no patient suffering from RA is treated with the same therapeutic regimen over a life time. Moreover, there is no life-long experimental clinical trial in the field of RA that could generate robust data to validate this assumption.

Main types of modelling studies

Decision and event trees

Decision trees are widely used in medicine as simple decision tools. They consist of graphs composed of nodes and branches to represent different clinical decisions, their consequences and conditional probabilities. These simple algorithms allow taking into account any quantitative outcome such as effectiveness, costs and their probabilities. Many decision trees have been published in the field of RA, mainly to assess and compare different disease management pathways or and treatment strategies. Suter (1) used a decision tree to assess the interest of adding magnetic resonance imaging (MRI) in RA management. The American College of Rheumatology (ACR) used a decision tree to address RA classification criteria, which appears to be a more dynamic alternative to using a conventional list of criteria (2). Event trees are very similar to decision trees but each node represents an event, and not a decision. For example a potential complication is an event, but the action to treat with a new agent is a decision. In fact, a number of decision trees include both events and decisions nodes. Because of their simplicity and transparency, decision/event trees are considered very meaningful and understandable by clinicians. However, when the number of branches is very large, or when cycles exist between nodes, decision/event trees can become very complex and unmanagable.

Markov models

Markov models have been described by Andrei Markov (1856-1922), a Russian mathematician specialised in probability theory, with the aim to handle complex decision trees using matrixes and stochastic processes. Although published one century ago, this approach was extensively used in in the 80s-90s with the emergence of PE studies, thanks to the availability of powerful computers and specialised softwares. Markov models are particularly useful when a decision problem involves exposure to risks or events over time, or ongoing exposures or situations where the specific timing of an event is regarded as important or uncertain. A "Markov chain" is a mathematical system representing transitions between states (such as health states) with the possibility of using cycles (such as disease relapses). The number and choice of health states depends on what is important to the problem being studied and what information is available to describe them. Such as standard decision trees, Markov models can be populated by valid data sources from literature, reports or expert opinions. The main assumption is the "lack of memory", which means that one health state only depends on the previous one, and not on the full history of events. As such, simulated cohorts or individuals cannot carry a history of their disease or health. All this knowledge must be embedded in the structure of the model. When conditional probabilities evolve over time, the model is called "Markov process". Markov models are often used to carry out cost-effectiveness and cost-utility analyses (3, 4).

Advanced simulation models

When data variability or uncertainty is expected to be important, "advanced" simulation models can be used to estimate results distributions. Simulation models not only enable the simulation of costs and effectiveness of various strategies over time, but can also simulate various treatment "sequences" found in real life clinical practice, such as first, second and third line treatment strategies, including the successive use of different biological agents in RA (5-9). Given that these therapeutic sequences cannot be reproduced in clinical trial settings due to the complexity and prohibitive costs that such study protocols would entail, advanced simulation modelling provides useful information to assist health care decision making. This approach is based on various uses of random number generators, which simulate data variability in the frame of a distribution function (normal, lognormal, beta, gamma, uniform, etc.). Then advanced simulation models do not calculate fixed results, but the distribution functions of the results. In 2008, Russel *et al*. (5) used a cost-effectiveness advanced simulation model in Canada to compare various biologic treatment sequences including up to three successive agents. Using similar methodological approaches, other cost-effectiveness simulation models were published in European countries by Saraux *et al*. in France (6), Beresniak *et al*. in Spain (8), Cimmino *et al*. in Italy (7) and Puolakka *et al*. in Finland (9).

Multi-criteria models

Under most circumstances, decision-makers have access to a vast quantity of data. So much so that it is generally impracticable to extract from these huge amounts of data the most relevant information needed to enrich knowledge and support decisions. When using multi-criteria models, all observations are typically grouped in one table where the patients are listed line by line, with their corresponding statistical variables provided in the columns. Each variable then corresponds to a descriptive criterion where each subject is perfectly characterised by each of these criteria. These dataset are typically available in

registries or any other kind of longitudinal surveys. Multi-criteria model design typically requires the use of a series of mathematical programming models in order to implicitly reveal defined solutions. Main multi-criteria techniques include the use of Principal Componant Analysis (PCA), a mathematical procedure that uses mathematical projections to convert a set of n variables possibly correlated and representing *n* dimensions into a smaller number of dimensions called "principal components" which are classically represented over 2 or 3 axes. The projections use orthogonal transformations defined in such a way that the first principal component (first axis) has the highest possible variance in order to synthesise most of the initial information. The main objective of PCA is to reduce the size of the dataset. PCA is often presented as a technique of factor analysis for quantitative variables. Multiple Correspondence Analysis (MCA) is another type of factor analysis for quantitative, qualitative and categorical variables and is useful to conduct multi-criteria analyses such as multi-criteria risk assessments. These techniques are very useful to extract meaningful information from a large set of data, which may include PE, clinical or epidemiological criteria. Lakota *et al*. (10) used PCA to analyse 29 parameters in order to associate anti-Ku positive patients with joint/bone features. Another non-published application of multi-criteria modelling in RA has been tested by co-author AB to assess the impact of a new biologic agent on six immunological factors. Very probably because the clinical trial was under-powered, no significant differences were established for each of the six immunological factors. After aggregating the six factors into one composite immunological indicator constructed using multi-criteria modelling, a significant statistical difference was established, allowing the full development of this new agent thanks to more powered confirmatory clinical trials.

Monte-Carlo simulations

Monte Carlo simulation was first used in operational research in the 1940s for modelling atomic processes. This type of modelling is based on the use of random number and probability statistics leading to a large number of iterations (several thousands) to obtain stable estimates of the variability surrounding each outcome. A very high quality random number generator is necessary to avoid potential over-representations of some iterations, which would create bias. The result is a probability distribution of possible outcomes. The name "Monte Carlo" comes from the famous casino on the French Riviera where some gamblers studied how they could maximise their chances of winning by using simulations to check the probability of occurrence for each possible case. Nowadays, Monte Carlo simulations are widely used in medicine to manage data variability. It is the reason why Monte Carlo simulations are used in association with Markov models and simulation models to assess the impact of uncertain variables on the expected results. In this case, Monte-Carlo simulations are also called "probabilistic sensitivity analyses", and are used in a number of cost-effectiveness and cost-utility simulation models in RA (4-9, 11).

Resampling simulations

Resampling is a set of methods used for estimating one statistical parameter (ie mean, median, variance, etc.) by randomly drawing the replacement of a set of subjects (bootstrapping) or by using subsets of available data (jackknifing). In the case where a set of observations can be assumed to be from an independent and identically distributed population, this can be implemented by constructing a number of resamples of the observed dataset (and of equal size to the observed dataset for the bootstrapping technique), each of which is obtained by random sampling with replacement from the original dataset. Then numerous iterations (between 1,000 and 100,000 according to computer performances) generate a number from slightly different samples derived from the original samples, allowing statistics on the iterations. Despite that they use similar random number generators, the fundamental difference between Monte Carlo simulations and resampling is that in Monte-Carlo simulations, data could be totally hypothetical, while in resampling, the simulation must be based upon some real data. Even if not used often in RA, resampling techniques would allow to handle and compare small populations when classical statistical tests are unable to establish any differentiation. These techniques would be very useful to assess new therapeutic strategies in the frame of personalised medicine or pharmacogenetics, or when studies based on large number of observations are not easily managed. As a limitation, resampling techniques assume that the master sample is a good representation of the target population, which imposes a careful selection of the subjects composing the original sample.

Econometric modelling

Econometric models investigate the statistical relationship between variables based on historical data. As many registries collect rigorous clinical data over time, they provide unique datasets for potential use of econometric techniques. Even if developed in applied mathematics and economics, econometric modelling has been widely applied in health care to study the impact of one variable on the others (explanatory variables) based on historical data collected over time. For example, econometric time-series models can be developed to project clinical or economic outcomes in the long term for forecasting purposes. However, any modelling process assuming a long period of time is inevitably speculative to some extent and the results obtained depend heavily on the assumptions made in setting up the econometric model. Mitchell *et al*. (12) used an econometric model to study the importance of socio-demographic factors and comorbidity in earnings losses of patients with symmetric polyarthritis in the US. These authors concluded that earnings of women and men with symmetric polyarthritis were respectively only 27% and 48% of earnings of individuals without arthritis. Econometric regression analyses indicated that about one-third of this earnings gap was explained by the presence of symmetric polyarthritis. The remaining two-thirds

were explained by differences in age, education, and comorbidity between individuals with symmetric polyarthritis and those without arthritis.

Bayesian modelling

For a long time, the concept of probability used in Bayesian approaches was opposed to the one defined in Frequentist terms, which considers that it is impossible to assign a probability to an event that is not repeatable such as "Mrs Smith will be in remission on December 31st 2015". Conversely, the Bayesian approach considers that it is possible to assess grades or degrees at which it is reasonable to believe that the proposals are true. Bayesian models allow the possibility of updating the results from inferences based on recently acquired information (experts' opinions or publications), by integrating them in an *a priori* probability law, In addition, Bayesian statistics permit to work on small size samples without using assumptions on the distribution of the random phenomenon being studied, and in full transparency with the available *a priori* information. This approach is beginning to appear in new health technology assessments, namely in meta-analyses and indirect treatment comparisons methods. N'Guyen *et al*. (13) used a Bayesian approach connected with a Markov model to assess the cost-utility of Tumour Necrosis Factor Inhibitors in RA to better manage uncertain data. Another application has been recently published by Stahl *et al*. (14) who used a Bayesian model to analyse the genetic architecture of chronic diseases such as RA.

Cluster analyses modelling

The term *cluster analysis* includes a number of different techniques for grouping objects of similar kind into respective categories. A common question facing clinicians is how to organise observed patients' data into meaningful structures in order to perform logical, consistent and efficient decisions. One of the advantages of cluster analyses is that they can be used to discover structures in databases without providing any obvious interpretation of the subgroup partitioning. Clustering techniques use various grouping algorithms where observations are 'similar' within a group and 'dissimilar' in different groups. Technically, the statistical "distance" between two observations is a real number representing the dissimilarity between two observations, which allows the identification of subgroups with similar characteristics. The calculation of the distance depends on the nature of the variables considered. The "centroid" of a cluster is a point whose parameter values are the means of the parameter values from all the points composing the cluster. Different clustering techniques exist and can lead to different groups. It is a reason why a complete clustering approach classically tests three techniques to assess if the results are technique dependent or not. Main techniques include "Two-way joining", k-means clustering, and "EM clustring" (Expectation Maximisation). Clustering modelling was used to define rheumatoid arthritis states according to selected important items for conducting further valuation studies (15).

Neural network modelling

Artificial neural networks, also called neural networks, consist of mathematical models inspired by the structure and the functioning of biological neural network of the central nervous system. Neural networks process input data to provide a result in a way analogous to biological networks, based on a connecting approach where artificial neural networks theory is a part of artificial intelligence. Neural networks are organised in different layers of nodes (neurons). Links between neurons are weighted and used in data computation during the learning process of the network. Different types of structure have been defined for neural networks, including the feed-forward structure, which is the most common one. The number of layers and the number of neurons in each layer must be determined by the user according to his/her objectives. Each neuron behaves like an automat; by way of links entering it, one neuron computes a weighted sum of different values moving on these links and transforming the result according a specified function defined by the user. The main advantages of neural networks are their flexibility, their ability to «learn» and to improve their accuracy over time. Neural networks have already been widely used in health care (16), for example to determine if patient visit adherence could be predicted by a set of known variables for patients suffering from chronic diseases (17). Zha *et al*. (18) have developed a neural network to predict from diagnostic information the efficacy of RA treatment. Another team from China, Zhou *et al*. (19) proposed to use a neural network approach for grading RA.

Which outcome for modelling?

The QALY controversy

Integrating outcomes in a mathematical formula to construct a model suggests knowing the structural properties of each candidate indicator in order to avoid misleading results. Indicators can be quantitative or qualitative (logical Yes/No, or categorial). Quantitative indicators can be ordinal, Neumanian (or interval) or cardinal. Ordinal indicators follow an order (3 is greater than 2, and 2 is greater than 1) without necessarily using regular degrees. Neumanian indicators have regular degrees but can have different 0 origin (such as temperature scales expressed in Celsius or in Fahrenheit). Cardinal indicators have regular degrees and consistent 0 origin, which allows their use in all classical calculations. There are a number of clinical outcomes in RA and the selection of one specific clinical outcome to be integrated in a model will directly impact the modelling results. It is for example well known that HAQ (Health Assessment Questionnaire) or DAS (Disease Activity Scores) scale degrees are not all equals. It is therefore not methodologically appropriate to use DAS or HAQ value as a quantitative outcome ("cardinal") because they only have an "ordinal" property. Despite the fact that DAS is an ordinal and not a cardinal scale, some authors (5-8) proposed to use the proportions of DAS thresholds (remissions or Low Disease Activity) in cost-effectiveness analyses (CEA). Another way to improve scale properties has been proposed by economists in order to trans-

form ordinal Quality of Life scales into Neumanian scale, more suitable for modelling purpose. They define a utility measure, which is a preference value about Quality of Life status calibrated between 0 for death and 1 for perfect health. This utility value is then considered as a Neumanian scale but is rarely used alone, as it is often combined with a survival measure to create a synthetic indicator, the Quality-Adjusted Life-Year (QALY) used for conducting cost-utility analyses (CUA). In the 80s, some economists proposed the use of the QALY indicator as universal outcome in order to perform cross-diseases comparisons. This is the reason why cost-utility models have been officially favoured by some regulatory authorities from Commonwealth nations in charge of health technology assessments such as the CADTH in Canada, the NICE in the UK or the PBAC in Australia. These agencies consider cost per QALY studies as their reference case for priority arbitration across diseases and for comparing the value of different treatment strategies using arbitrarily set thresholds. For example the NICE in the UK considers that an innovative drug would be "cost-effective" if a cost-utility modelling would establish a cost/QALY of £30,000 or less.

For years now, the methodological criticisms of the QALY have fuelled an international debate in the scientific international community between their supporters and detractors. The most reported and well published criticism of the QALY measure is that their value depends directly on the technique and on the subjects chosen to derive utility scores. This often leads to inconsistent results (20). Because utility scores may vary widely depending on the method used, this explains how model results can diverge dramatically and can lead to different reimbursement decisions (21). Then the QALY outcome measure is not deemed sufficiently accurate or reliable to be used by decision makers as a basis for comparison of the estimated value of different health technologies. Acknowledging these issues, some countries such as USA and Germany do not recommend the use of cost/QALY models for health care decision making. Because of this international methodological controversy (22) and the possibility of generating highly contradictory results from the same observed data, it is expected that more countries may ban cost/QALY models in the future in favour of real cost-effectiveness studies in order to inform reimbursement decisions (21, 23).

Lastly, a number of authors have labelled CUA indistinctively as CEA in the medical literature, which contributes to creating more confusion than scientific clarity. This incorrect practice (24-26) may be perceived as lack of transparency for most published CUA.

Conclusion

The introduction of new and expensive therapeutic strategies for RA has led to having to conduct complex assessments. It also raised important concerns for reimbursement policies. These factors have stimulated a new domain of research relevant to modelling studies in RA. Moreover, it would be impractical and prohibitively costly to conduct vast clinical and health economic studies to address all potential treatment scenarios using multiple agents. It is the reason why modelling studies provide new powerful tools which can assess and compare the overall clinical and economic value of different treatment strategies in RA. Mathematical models can provide unlimited conceptual frameworks for conducting multiple simulations, in addition to effectively managing the uncertainty. Generating such evidence is highly relevant to assisting medical practices recommendations and reimbursement decisions towards enabling the optimal management of RA, and reducing its overall clinical and economic burden, for the benefits of both patients and health systems.

References

1. SUTER LG, FRAENKEL L, BRAITHWAITE RS: Cost-effectiveness of adding magnetic resonance imaging to rheumatoid arthritis management. *Arch Intern Med* 2011; 171: 657-67.
2. LUNT M, SYMMONS DP, SILMAN AJ: An evaluation of the decision tree format of the american college of rheumatology 1987 classification criteria for rheumatoid arthritis: Performance over five years in a primary care-based prospective study. *Arthritis Rheum* 2005; 52: 2277-83.
3. HALLINEN TA, SOINI EJ, EKLUND K, PUOLAKKA K: Cost-utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. *Rheumatology* (Oxford) 2010; 49: 767-77.
4. SCHIPPER LG, KIEVIT W, DEN BROEDER AA *et al*.: Treatment strategies aiming at remission in early rheumatoid arthritis patients: Starting with methotrexate monotherapy is cost-effective. *Rheumatology* (Oxford) 2011; 50: 1320-30.
5. RUSSELL A, BERESNIAK A, BESSETTE L *et al*.: Cost-effectiveness modeling of abatacept versus other biologic agents in dmards and anti-tnf inadequate responders for the management of moderate to severe rheumatoid arthritis. *Clin Rheumatol* 2009; 28: 403-12
6. SARAUX A, GOSSEC L, GOUPILLE P *et al*.: Cost-effectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in france. *Rheumatology* (Oxford) 2010; 49: 733-40.
7. CIMMINO MA, LEARDINI G, SALAFFI F *et al*.: Assessing the cost-effectiveness of biologic agents for the management of moderate-to-severe rheumatoid arthritis in anti-TNF inadequate responders in italy: A modelling approach. *Clin Exp Rheumatol* 2011; 29: 633-41
8. BERESNIAK A, ARIZA-ARIZA R, GARCIA-LLORENTE JF, RAMIREZ-ARELLANO A, DUPONT D: Modelling cost-effectiveness of biologic treatments based on disease activity scores for the management of rheumatoid arthritis in Spain. *Int J Inflam* 2011; 2011: 727634.
9. PUOLAKKA K, BLÅFIELD H, KAUPPI M *et al*.: Cost-effectiveness modelling of sequential biologic strategies for the treatment of moderate to severe rheumatoid arthritis in finland. *Open Rheumatol J* 2012; 6: 38-43.
10. LAKOTA K, THALLINGER GG, SODIN-SEMRL S *et al*.: International cohort study of 73 anti-ku-positive patients: Association of p70/p80 anti-ku antibodies with joint/bone features and differentiation of disease populations by using principal-components analysis. *Arthritis Res Ther* 2012; 14: R2.
11. MICHAUD K, MESSER J, CHOI HK, WOLFE F: Direct medical costs and their predictors in patients with rheumatoid arthritis: A three-year study of 7,527 patients. *Arthritis Rheum* 2003; 48: 2750-62.
12. MITCHELL JM, BURKHAUSER RV, PINCUS T: The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. *Arthritis Rheum* 1988; 31: 348-57.
13. NGUYEN CM, BOUNTHAVONG M, MENDES MA *et al*.: Cost utility of tumour necrosis factor-α inhibitors for rheumatoid arthritis: An application of bayesian methods for evidence synthesis in a markov model. *Pharmacoeconomics* 2012; 30: 575-93.
14. STAHL EA, WEGMANN D, TRYNKA G *et al*.: Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis. *Nat Genet* 2012; 44: 483-9.
15. MCTAGGART-COWAN HM, BRAZIER JE, TSUCHIYA A: Clustering rash results: A novel method for developing rheumatoid arthri-

tis states for use in valuation studies. *Value Health* 2010; 13: 787-95.
16. SORDO M: Introduction to neural networks in health care. *Open Clinical* 2002; Harvard: 1-17.
17. NOLTING J: Developing a neural network model for health care. *AMIA Annu Symp Proc* 2006: 1049.
18. ZHA QL, HE YT, YAN XP *et al*.: Predictive role of diagnostic information in treatment efficacy of rheumatoid arthritis based on neural network model analysis. *Zhong Xi Yi Jie He Xue Bao* 2007; 5: 32-8.
19. ZHOU Z, MAO Z, DENG Z: Neural network approach to medical grading of rheumatoid arthritis. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi* 1999; 16: 479-82.
20. MC GREGOR M, CARO JJ: Qalys: Are they helpful to decision makers? *Pharmacoeconomics* 2006; 24: 947-52.
21. BERESNIAK A, RUSSELL AS, HARAOUI B, BESSETTE L, BOMBARDIER C, DURU G: Advantages and limitations of utility assessment methods in rheumatoid arthritis. *J Rheumatol* 2007; 34: 2193-200.
22. RAMSEY S: Is there an international backlash against cost-utility analysis? *ISPOR Connections* 2010; 16: 3.
23. DURU G, AURAY JP, BERESNIAK A, LAMURE M, PAINE A, NICOLOYANNIS N: Limitations of the methods used for calculating quality-adjusted life-year values. *Pharmacoeconomics* 2002; 20: 463-73.
24. SOINI EJ, HALLINEN TA, PUOLAKKA K, VIHERVAARA V, KAUPPI MJ: Cost-effectiveness of adalimumab, etanercept, and tocilizumab as first-line treatments for moderate-to-severe rheumatoid arthritis. *J Med Econ* 2012; 15: 340-51.
25. KOBELT G, LEKANDER I, LANG A, RAFFEINER B, BOTSIOS C, GEBOREK P: Cost-effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment. *Int J Technol Assess Health Care* 2011; 27: 193-200.
26. TOSH JC, WAILOO AJ, SCOTT DL, DEIGHTON CM: Cost-effectiveness of combination non-biologic disease-modifying antirheumatic drug strategies in patients with early rheumatoid arthritis. *J Rheumatol* 2011; 38: 1593-600.