ORIGINAL ARTICLE

UDC: 616.72-002.77-08:657.478
DOI: 10.2298/VSP1402144K

Cost-effectiveness analysis of tocilizumab in combination with methotrexate for rheumatoid arthritis: A Markov model based on data from Serbia, country in socioeconomic transition

Analiza odnosa troškova i efekata tocilizumaba u kombinaciji sa metotreksatom u lečenju reumatoidnog artritisa: Markovljev model baziran na podacima iz Srbije, države u socio-ekonomskoj tranziciji

Marina Kostić*, Snežana Jovanović†, Marina Tomović*, Marija Popović Milenković*, Slobodan M. Janković*

***Faculty of Medicine, University of Kragujevac, Kragujevac, Serbia; †Department of Rheumatology, Clinical Center Kragujevac, Kragujevac, Serbia**

Abstract

Background/Aim. Recent studies have shown that biological treatments for rheumatoid arthritis can change the course of rheumatoid arthritis and improve functional ability of patients with rheumatoid arthritis. In spite of this fact, use of biological therapy is still limited by high prices of these medicines, especially in countries in socioeconomic transition. The aim of our study was to compare cost-effectiveness of a combination of tocilizumab and methotrexate with methotrexate alone for rheumatoid arthritis in Serbia, a country in socioeconomic transition. **Methods.** For the purpose of our study we designed a Markov model using data on therapy efficacy from the available literature, and data on the costs of health states calculated from records of actual patients treated in the Clinical Center Kragujevac, Serbia. The duration of one cycle in our model was set at one month, and the time horizon was 480 months (40 years). The study was done from the social perspective, and all the costs and outcomes were discounted for 3% per year. **Results.** Treating rheumatoid arthritis with disease-modifying antirheumatic drugs (DMARDs) alone was more cost-effective in comparison with a combination of biologic treatment with tocilizumab and DMARDs. The total costs for treating a patient with DMARDs for one year were on average 261,945.42 RSD, or 2,497.70 Euro and the total costs for treatment with tocilizimab plus DMARDs were on average 1,959,217.44 RSD, or 18,659.20 Euro. However, these results are susceptible to changes in costs and treatment effects of tocilizumab in patients with more severe forms of rheumatoid arthritis. **Conclusion.** Our results show that the use of tocilizumab for rheumatoid arthrits in economic environment of Serbia is not cost-effective. Use of tocilizumab for treating rheumatoid arthritis can become affordable, if costs of its use become lower. In order to start using expensive biologic medicines in patients in transitional countries, special strategy and pricing policy of international pharmaceutical companies are necessary, which would include calculation of prices of biologic medicines on the basis of local pharmacoeconomic studies.

Key words:
arthritis rheumatoid; economics, pharmaceutical; biological therapy; methotrexate; serbia.

Apstrakt

Uvod/Cilj. Nedavne studije ukazale su da biološka terapija za reumatoidni artritis može menjati tok bolesti i popraviti funkcionalnu sposobnost obolelih. Uprkos tome, upotreba bioloških lekova ograničena je visokom cenom ovih lekova, posebno u zemljama koje su u socioekonomskoj tranziciji. Cilj ovog istraživanja bio je da se uporede troškovi i efekat kombinacije tocilizumaba i metotreksata sa metotreksatom u terapiji reumatoidnog artritisa u Srbiji, zemlji u socioekonomskoj tranziciji. **Metode.** Za potrebe ovog istraživanja konstruisan je Markovljev model na osnovu podataka o efikasnosti iz dostupne literature, dok su podaci o troškovima za sva zdravstvena stanja procenjeni iz dostupne dokumentacije obolelih od reumatoidnog artritisa koji se leče u Kliničkom centru Kragujevac, Srbija. Jedan ciklus u modelu trajao je jedan mesec, a ukupan vremenski horizont bio je 480 meseci, odnosno 40 godina. Studija je izvedena sa aspekta društva u celini, a svim troškovima i ishodima je pridodata diskontna stopa od 3%. **Rezultati.** Lečenje reumatoidnog artritisa standardnom, nebiološkom terapijom je u pogledu odnosa troškova i efekata povoljnije u poređenju sa biološkom terapijom tocilizumabom u kombinaciji sa standardnom nebiološkom terapijom. Ukupni troškovi lečenja re-

Correspondence to: Marina Kostić, Faculty of Medicine, University of Kragujevac, Svetozara Markovica Street 69, 34 000 Kragujevac, Serbia. Phone: +381 34 306 800 ext 223, Fax: +381 34 306 800 ext 112. E-mail: marrina 2006kg@yahoo.com

umatoidnog artritisa standardnom nebiološkom terapijom tokom jedne godine lečenja po bolesniku iznose 261 945,42 dinara Republike Srbije, odnosno 2 497,70 eura, a ukupni troškovi lečenja tocilizumabom u kombinaciji sa standardnom nebiološkom terapijom u toku jedne godine po pacijentu iznose 1 959 217,44 dinara Republike Srbije, odnosno 18 659,20 eura. Ipak, ovi rezultati su podložni promenama i uticaju troškova i efekata terapije tocilizumabom kod bolesnika sa težom formom bolesti. **Zaključak.** Rezultati našeg istraživanja pokazuju da primena tocilizumaba u lečenju reumatoidnog artritisa nije farmakoekonomski isplativa. Primena tocilizumaba za lečenje reumatoidnog artritisa može postati isplativija u farmakoekonomskom smislu, ukoliko cena tocilizumaba postane niža. Upotreba skupe biološke terapije kod obolelih od reumatoidnog artritisa u zemljama u socioekonomskoj tranziciji može biti izvesna jedino uz postojanje posebne strategije i cenovne politike internacionalnih farmaceutskih kompanija, što podrazumeva određivanje cene ovih lekova na bazi lokalnih farmakoekonomskih studija.

Ključne reči:
artritis, reumatoidni; farmakoekonomika; biološka terapija; metotreksat; srbija.

Introduction

Rheumatoid arthritis is a chronic disease characterized by systemic inflammation and continous irreversible destruction of joints mediated with immunological mechanisms [1]. Rheumatoid arthritis affects 0.5–1% of general population, with severe destructions of joints encountered in 15% of patients. The prevalence of rheumatoid arthritis is 3–4 times higher in women than in men, with the tendency to rise with aging [2, 3]. Diagnosis of rheumatoid arthritis is based on the criteria established by the American College of Rheumatology (ACR), and 4 of 7 criteria must be present: morning stiffness, arthritis in 3 or more joint areas, arthritis of hand joints (more than 1 joint), symmetrical arthritis, rheumatoid nodules, elevated serum rheumatoid factor and typical radiographic changes (with exception for the two last criteria, the listed changes must persist for at least 6 weeks) [4]. These criteria have been lately recognized as less sensitive and updated by the European League Against Rheumatism (EULAR) during 2010, with special concern for early arthritis [5]. The Health Assessment Questionnaire (HAQ) is a dominant instrument for capturing a state of disability in patient with rheumatoid arthritis. The HAQ estimates functional status of patients in several domains: disability, pain and discomfort, adverse drug reactions and economic issues of treating rheumatoid arthritis. Nowdays, HAQ is the most widely used techinque for evaluating disability in patients with rheumatoid arthritis [6].

The therapeutic approach in rheumatoid arthritis involves two strategies: to prevent the spread of chronic inflammatory process and to ensure protection of affected joints from further deterioration [7]. Treatment of rheumatoid artritis with standard disease modifying anti-rheumatic drugs (DMARDs), and newer biologic therapy, alone or in combination, has proven efficacy. Among DMARDs, methotrexate, sulphasalasine and leflunomide with their immunosupressant actions have shown the greatest impact on the course of rheumatoid arthritis [8]. Methotrexate is considered to be the gold standard for treatment of rheumatoid arthritis because of its good efficacy and moderate adverse reactions. However, the response to methotrexate is sometimes inadequate or unsatisfying, so biologic medicines remain the only solution [7]. The targets of biologic medicines are different cytokines or their receptors, and these medicines (etanercept, adalimumab, infliximab, tocilizumab, rituximab and others) have shown beneficial effect on the course of rheumatoid arthritis [7, 9, 10]. Biologic therapy use differs among Europian countries and depends mostly on available budgets for buying these medicines. High prices of biologic medicines are the main reason for restrictive utilization of these medicines [11]. The majority of European countries uses similar criteria for reimbursing prescription of a biologic medicine like those recommended by the National Institute for Clinical Excellence (NICE) from U.K.: treatment with biologic medicine (mostly with a TNF blocker) is given to a patient whose response to methotrexate is poor and incomplete; if there is no response to the first biologic medicine after 3 to 6 months of treatment, the patient should be switched to another biologic medicine [12–14].

In spite of large evidence on therapeutic effects of biologic medicines on rheumatoid arthritis, the data is limited to economic aspects of this therapy, especially with newer biologic medicines. The question of cost-effectiveness ratio is important issue nowadays, especially in countries in socioeconomic transition, since introduction of new medicines often means a substantial increase in total health care costs. Economic burden of rheumatoid arthritis involves direct and indirect costs, and it depends mostly on prices of a prescribed medication [11].

The aim of this study was to compare cost-effectiveness of two therapeutic strategies in patients with rheumatoid arthritis: treatment with DMARDs alone or in combination with tocilizumab using a Markov model based on data on efficacy from published clinical trials and costs sampled from the economic environment in Serbia.

Methods

The Markov model was designed in order to compare the cost-effectiveness of two therapeutic strategies for patients with rheumatoid arthritis. The startegies were therapy with DMARDs alone and therapy with a combination of DMARDs and tocilizumab. For the purpose of modelling we presented rheumatoid arthritis as 5 primary health states based on the Health Assesment Questionnaire (HAQ), according to Kobelt et al. [15]. These states reflect chronic course and severity of rheumatoid arthritis: HAQ score less than 0.6, HAQ score from 0.6 to 1.1, HAQ score from 1.1 to 1.6,

HAQ score from 1.6 to 2.1 and HAQ scores higher than 2.1. For every node we added death as potential state. After taking into account activity of the disease, each primary HAQ state was subdivided into two new states: one with high and another with low activity. Each state in the model except death was not definitive, and a hypothetic patient could move from one to another state, depending on natural course of the disease and experiences from clinical trials. The initial patient distribution, transitional probabilities, utilities, and effectiveness of the two treatment options were obtained from the available literature [15–17], while the costs of health states were calculated from records of actual patients treated in Clinical Center Kragujevac, Serbia.

The duration of one cycle in our model was one month, and the time horizon was 480 months (40 years). All the costs and outcomes were analyzed from social perspective and discounted for 3% annually. For the purpose of modelling, we conducted a pilot survey to estimate costs of rheumatoid arthritis. We analyzed all the aspects of economic issues of treating rheumatoid arthritis. Using interview techniques we collected data from our patients about direct (costs of medicines, hospitalization, diagnostic procedures, medical exams etc.) and indirect costs (costs of transportation, lost wages etc.) of treating rheumatoid arthritis. All the costs were expressed in 2010 Serbian dinars (RSD) and the data on health services utilization were collected from files of rheumatoid arthritis patients, for each HAQ state and disease activity score separately. The patients were randomly chosen from the population of patients with rheumatoid arthritis treated in the Clinical Center Kragujevac, Serbia, during one year (from June 2009 to June 2010). The prices of health services were obtained from the Republic Institute for Health Insurance (RIHI) Tariff Book and prices of medicines were those from the list of medicines financed by the RIHI, issued in 2010 [18]. The process of modelling requires a definition of willingness to pay, i.e. how much a society is willing to pay for one quality-adjusted life year (QALY) gained with certain treatment of the disease. For societies in socioeconomic transition there is a recommendation from the World Bank that the value of willingness to pay should be equal to two to three multiples of gross national income *per* capita. In case of Serbia, gross national income *per* capita (GDP/capita) was 563,400 dinars (RSD) in 2009 [19]. We also used the value of average monthly net income in Serbia during 2009 to calculate the costs of lost wages.

The model was constructed using TreeAge pro® software, version 2006 [20]. We performed Monte Carlo simulations using microsimulation trial, where cohorts of virtual patients, which consist of 1,000 virtual patients, passed through all hypothetical scenarios. The model of Monte Carlo simulation randomly chooses patients from the cohort, and every patient from the cohort runs through different scenarios and results are the summaries as incremental cost-effectiveness ratio [21–23]. For each therapeutic option we calculated the mean costs and the mean effects, and expressed them also as incremental cost-effectiveness ratio. We followed the following outcomes: gains in utility for each therapy option, expressed as QALYs gained, and total and mean costs incurred by each therapeutic option. Incremental cost effectiveness ratio for tocilizumab *vs* DMARDs therapy as baseline was also calculated. Two-way sensitivity analysis (± 50% of baseline values of a variable) was performed in order to check for robustness of the model results, and its outcome is shown as a Tornado diagram.

Results

Treating rheumatoid arthritis with DMARDs alone was more cost-effective than a combination of biologic treatment with tocilizumab and DMARDs. The total costs for treating a patient with DMARDs for one year (2009–2010) were on average 261,945.42 RSD, or 2,497.70 Euro (on August 12, 2010) and total costs for treatment with tocilizimab plus DMARDs were on average 1,959,217.44 RSD, or 18659,20 Euro (on August 12, 2010) (Figure 1).

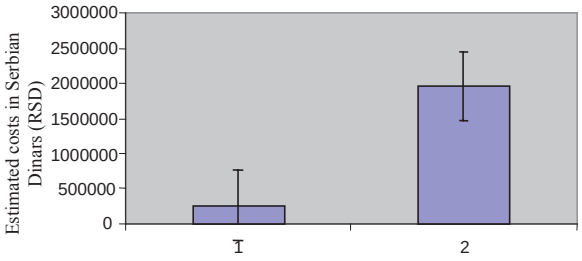

Fig. 1 – Total costs for one year-treatment (2009–2010) *per* patient for DMDARs and a combination of tocilizumab and metotrexate (prices on August 12, 2010).

Using the cost-effectiveness calculation method we compared total costs per QALY gained for both examined therapeutic options. The results of this method indicate that standard non-biological therapy requires much less investment than therapy with a combination of tocilizumab and methotrexate for higher gain in QALY. Treatment with standard non-biological therapy for gain of one QALY requires investment of 1,446,640.78 RSD, which is more cost-effective than treatment with tocilizumab and methotrexate together which costs 6,171,321.57 RSD *per* QALY gained. The results of cost-effectiveness analysis are shown in Table 1.

The distribution of incremental cost-effectiveness ratios (ICERs) calculated by Monte Carlo simulations (using a cohort of 1,000 virtual patients) for total costs *per* QALY is shown in Figure 2. For therapeutic option combination of tocilizumab and metotrexate the calculated ICERs (with only methotrexate as baseline comparator) for the majority of virtual patients fall on the left side of willingness-to-pay line, which indicates that this kind of biological therapy for rheumatoid arthritis in Serbian socioeconomic enviroment is not cost-effective.

In order to check robustness of our conclusion, we made two-way sensitive analysis using a Tornado diagram. In this analysis, all the parameters were varied simultaneously in the range ± 50%. The most influential variables

Table 1

Cost effectiveness analysis of the two therapeutic strategies: disease modifying anti-rheumatic drugs (DMARDs) only and tocilizumab in combination with methotrexate

Therapeutic option	Costs (RSD)	The difference in costs (RSD)	Effectiveness expressed in quality adjusted life years (QALY)	The difference in effectiveness (QALY)	Cost-effectiveness ratio (RSD/QALY)	Incremental cost effectiveness ratio (ICER)
DMDARs	7.788.768,97		5.38		1.446.640,78	
Tocilizumab + methotrexate	20.731.954,15	12.943.185,18	3.36	-2.02	6.171.321,38	(Dominated)

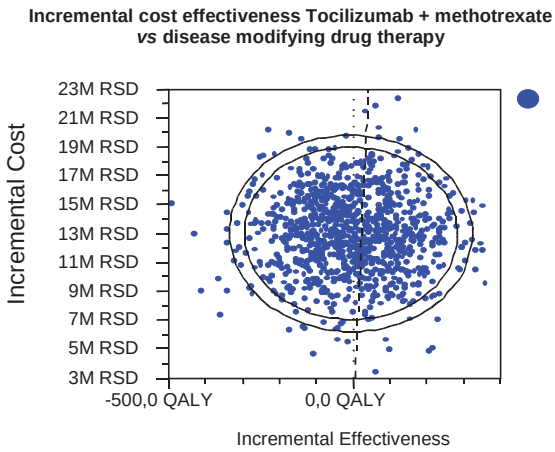

Fig. 2 – Distributions of the incremental cost-effectiveness ratio (ICER) calculated by Monte Carlo simulation for the total costs *per* quality-adjusted life years (QALY) for tocilizumab and metotrexate comparing with the standard nonbiological therapy

were those which describe state with HAQ score higher than 2.1: the costs for non-biological therapy for HAQ states higher than 2.1, discount rate for the costs, the costs for biological therapy for HAQ state higher than 2.1 with low activity of the disease, utility score for HAQ state higher than 2.1 with high activity of the disease and discount rate for effects of the treatment. With changes in these variables, the value of the net monetary benefit becomes negative, within the range from -7.3 to -2.8 milions of Serbian dinars, which means that our conclusion is susceptible to changes in costs and treatment effects of tocilizumab in patients with more severe forms of rheumatoid arthritis.

Discussion

Efficacy of tocilizumab has already been tested in a recent randomized controlled clinical trial, and because it achieved a significant benefit on the course of rheumatoid arthritis, it was approved for treatment of rheumatoid arthrits in Europian Union [24, 25]. Nevertheless, pharmacoeconomic studies on tocilizumab in rheumatoid arthritis have not been conducted to this date, and certainly not based on socioeconomic enviroment of Balkan countries in transition from controlled economy to free market.

The use of biological therapy for rheumatoid arthritis is not common within the Serbian health system, and is limited mostly by high prices of these medications and restrictive treatment guidelines. Similiar experience has been gained by physicians and patients in most countries of Balkan region [11].

The results of our model suggest that therapy with a combination of tocilizumab and methotrexate in comparison with methotrexate alone is not cost-effective. A gain in QALYs is lower and costs are higher with tocilizumab and methotrexate together than with methotrexate alone. Apart from relatively moderate clinical effect of tocilizumab, an important reason for such an outcome was a large disproportion between prices of medicines, which are almost the same in Serbia and in developed European countries, and prices of health care services, which are 10–100 times lower in Serbia than in developed countries. Therefore, beneficial effects of tocilizumab on decrease in health care utilization do not translate to significant savings in costs. The prices of health care services in Serbia are controlled by the RIHI, which publishes them periodically in its internal publications, which are not accessible to general public. To show how unrealistic these prices are, we mention the prices of one hospital day for basic care, which range from 10 to 20 euro, depending on the branch of medicine. Actually, we have two systems operating in the same time: free market rules for medicines, and controlled economy rules for health care services. Such duality inevitably creates paradoxical results of health economics studies situated in Balkan countries in socioeconomic transition.

The sensitivity analysis shows that this conclusion could be changed if the effectiveness of tocilizumab is increased in more severe forms of rheumatoid arthritis (which is unlikely to happen, since the degree of efficacy was well-established) or if the price of tocilizumab goes down and the prices of health care services go up. The second option (decrease in the price of medicine) could happen if the producer of tocilizumab finds interest to increase the volume of its sales in transitional and other poor countries and maintain profit selling more of the less expensive medicine. For the time being, this is also the only option how patients with severe forms of rheumatoid arthritis in transitional Balkan countries could reach this effective but very expensive medicine.

In order to start using expensive biologic medicines in patients in transitional countries, special strategy and pricing policies of international pharmaceutical companies are necessary. The prices of biologic medicines should be calculated on the basis of local pharmacoeconomic studies (like this

one), up to the point where the prices make the studies outcomes cost-effective. This would provide for the acceptance of such medicines by the local health insurance funds and sufficient financing to make registration of the medicine in such a country profitable for the pharmaceutical companies [26].

Conclusion

Due to the progressive nature and chronic course of rheumatoid arthritis, it is important to estimate cost-effectiveness of new medicines for rheumatoid arthritis by pharmacoeconomic modelling. Cost-effectiveness ratio of tocilizumab could be acceptable if the price of tocilizumab reaches a lower value. Further research is necessary to indentify a subset of patients with rheumatoid arthritis in which tocilizumab could be cost-effective therapy.

Acknowledgments

This study was partially funded by the grant No 175007 from the Serbian Ministry of Education, Science and Technological Development.

R E F E R E N C E S

1. *Firestein GS*. Evolving concepts of rheumatoid arthritis. Nature 2003; 423(6937): 356–61.
2. *Firestein GS*. Rheumatoid arthritis. In: *Ruddy S, Harris ED, Sledge CB, Budd RC, Sergent JS,* editors. Kelley's Textbook of rheumatology. 6th ed. Philadelphia: W.B. Saunders Company; 2001. p 921−67.
3. *Bush M, Emery P*. The aetiology and pathogenesis of rheumatoid arhtritis. Hospital Pharmacist 2002; 9: 5−11.
4. *Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS,* et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31(3): 315−24.
5. American College of Rheumatology. The 2010 ACR-EULAR classification criteria for rheumatoid arthritis [Internet]. Available from: http://www.rheumatology.org/practice/clinical/classification/ra/ra_2010.asp [updated 2011 January 24].
6. *Bruce B, Fries JF*. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol 2003; 30(1): 167−78.
7. *Schett G, Stach C, Zwerina J, Voll R, Manger B*. How antirheumatic drugs protect joints from damage in rheumatoid arthritis. Arthritis Rheum 2008; 58(10): 2936−48.
8. *van Vollenhoven RF*. Treatment of rheumatoid arthritis: state of art 2009. Nat Rev Rheumatol 2009; 5: 531−41.
9. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41(9): 1552−63.
10. *Fan PT, Leong KH*. The use of biological agents in the treatment of rheumatoid arthritis. Ann Acad Med Singapore 2007; 36(2): 128−34.
11. *Kobelt G, Kasteng F*. Access to innvative treatments in rheumatoid arthritis in Europe. A report prepared for the Europian Federation of Pharmaceutical Industry Associations (EFPIA). Stockholm: Lunds University; 2009.
12. National Institute for Health and Clinical Excellence. Nice clinical guideline 79. The reumatoid arthritis. The menagment of rheumatoid arthritis in adults 2009. Available from: www.nice.org.uk/CG79 [cited 2010. October 21].
13. National Institute for Health and Clinical Excellence. Nice clinical guideline 130. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis 2010. Available from: www.nice.org.uk/TA130 [cited 2010. October 21].
14. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 195. Adalimumab, eternecept, infliximab, rituximab and abatacept for the treatment for rheumatoid arthritis after the failure of a TNF inhibitor 2010. Available from: www.nice.org.uk/guidance/TA195 [cited 2010. October 21].
15. *Kobelt G, Lindgren P, Singh A, Klareskog L*. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis 2005; 64(8): 1174−9.
16. *St. Clair EW, Pisetsky DS, Haynes BF*. Rheumatoid arthritis. Philadelphia: Lippincott Williams & Wilkins; 2004.
17. *Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E*, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008; 371(9617): 987−97.
18. Tariff book of health care services in health facilities of Republic of Serbia. Belgrade: Republic Institute for Health Insurance; 2008.
19. The World Bank. Data and Statistics. Available from: hptt://web.worldbank.org./wbsite/external/datastatistics/0. [updated 2010 September 12].
20. Tree Age Pro. Healthcare software. Tree Age Software Inc [release 2005,1998-2005]. Available from: www.softscout.com/software/healthcare-and-Human Services/Diagnosis
21. *Janković S*. Modelling in Pharmacoeconomy In: *Prostran M, Stanulović M, Marisavljević D, Đurić D,* editors Pharmaceutical Medicine. Beograd: Hemofarm AD Vršac; 2009. p. 526−33. (Serbian)
22. *Drummond MF, Barbieri M, Wong JB*. Analytic choices in economic models of treatments for rheumatoid arthritis: What makes a difference? Med Decis Making 2005; 25(5): 520−33.
23. Markov Modeling. In *Rascati K*, editor. Essentials of Pharmacoecmics. Philadelphia: Lipincott Williams&Wilkins; 2009. p. 155−75.
24. *Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J*. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. Ann Rheum Dis 2009; 68(10): 1580−4.
25. National Institute for Health and Clinical Excellence. NICE technology appraisal guidance 198. Tocilizumab for the treatment of rheumatoid arthritis. Available from: http://guidance.nice.org.uk/TA198/Guidance/pdf/English [cited 2011 August 23].
26. The Prices of Medication in Serbia, from July/2010. ("RS Official Gazette", No 45/2011). (Serbian)

Received on October 7, 2011.
Revised on July 17, 2012.
Accepted on December 19, 2012.