Cost-effectiveness of four immunomodulatory therapies for relapsing-remitting multiple sclerosis: a Markov model based on data a Balkan country in socioeconomic transition

Analiza troškova/kliničkog efekta četiri imunomodulatorne terapije relapsno-remitirajuće multiple skleroze: Markovljev model baziran na podacima iz države na Balkanu koja je u socioekonomskoj tranziciji

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Abstract

Background/Aim. A cost-effectiveness analyses of immunomodulatory treatments for relapsing-remitting multiple sclerosis (RRMS) in developed countries have shown that any benefit from these drugs is achieved at very high cost. The aim of our study was to compare the cost-effectiveness of five treatment strategies in patients diagnosed with RRMS (symptom management alone and in combination with subcutaneous glatiramer acetate, intramuscular interferon β-1a, subcutaneous interferon β-1a, or intramuscular interferon β-1b) in a Balkan country in socio-economic transition. Methods. The Markov model was developed based on the literature about effectiveness and on local Serbian cost calculations. The duration of a cycle in the model was set to a month. The baseline time horizon was 480 months (40 years). The societal perspective was used for costs and outcomes, and they were discounted for 3% annually. Monte Carlo simulations were done. Results. Significant gain with immunomodulatory therapy was achieved only in relapse-free years, while the time spent in health states EDSS 0.0–5.5 was longer with symptomatic therapy. Moderate gain in relapse-free years does not translate to gain in QALYs, probably due to adverse effects of immunomodulatory therapy. Key words: multiple sclerosis; cost and analysis; immunologic factors; treatment outcome; Yugoslavia.

Apstrakt

Uvod/Cilj. Analize troškova/efekata imunomodulatorne terapije za relapsnu-remitirajuću multiplu sklerozu u zemljama u razvoju pokazale su da se svaki pozitivan efekat ove terapije postiže samo uz vrlo visoke troškove. Cilj naše studije bio je da se uporedi odnos troškovi/efekat pet strategija lečenja bolesnika sa dijagnostikovanom relapsno-remitirajućom multiplom sklerozom (samo simptomatsko lečenje i u kombinaciji sa glatiramer-acetatom potkožno, interferonom β-1a intramuskularno, interferonom β-1a potkožno ili sa interferonom β-1b intramuskularno) u državi na Balkanu koja je u socioekonomskoj tranziciji. Metode. Markovljev model razvijen je na osnovu podataka iz literaturi o efektivnosti i na osnovu troškova lečenja u Srbiji. Trajanje jednog ciklusa u modelu bilo je jedan mesec. Vremenski horizont iznosio je 40 godina. Za troškove i ishode korišćena je perspektiva društva i oni su diskontovani po stopi od 3% godišnje. Urađena je Monte Carlo mikrosimulacija modela sa 1 000 virtualnih bolesnika. Rezultati. Značajan dobitak sa imunomodulatornom terapijom registrovan je samo u godinama bez relapsa, dok je vreme provedeno u stanjima EDSS 0.0–5.5 bilo duže samo sa simptomatskom terapijom, a dobitak u godinama života i godinama života prilagođenim za kvalitet bio je samo marginalan. Jedna dobijena godina života prilagođena za kvalitet košta više od milijardu srpskih dinara, što čini svaku od imunomodulatornih terapija farmakoekonomski nesisplativom. Zaključak. Naša studija ukazuje da imunomodulatorna terapija relapsno-remitirajuće multiple skleroze u zemljama u socioekonomskoj tranziciji nije farmakoekonomski isplativa, bez obzira na vrstu terapije. Umešteni dobitak u godinama bez relapsa ne pretrvava se u dobitak u godinama života prilagođenim za kvalitet, verovatno zbog neželjenih dejstava imunomodulatorne terapije.

Key words: multiple sclerosis; cost and analysis; immunologic factors; treatment outcome; Yugoslavia.
Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system with significant prevalence. Multiple sclerosis affects approximately 2.5 million individuals worldwide, with an incidence of approximately 7 new cases per 100,000 people per year, and a lifetime risk of 1 in 400. The prevalence of MS in Serbia, one of the Balkan countries, is 41.5 cases per 100,000 inhabitants. Due to high costs of MS treatment and care (annual drug costs/patient are estimated to range from 60 pounds to 10,200 pounds in the UK), this disease is one of the major causes of rapidly increasing pressure to limited health budgets of Balkan countries in socio-economic transition. More than 10% of all drug costs in Serbian hospitals are caused by immunomodulatory drugs for MS.

There are three main types of MS: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive/relapsing MS (PPMS or PRMS). At disease onset, approximately 80% of MS patients have RRMS, and the remaining 20% have PPMS or PRMS. The majority of RRMS patients progress to SPMS after 10 years. Two new classes of immunomodulatory drugs (subcutaneous glatiramer acetate and β-interferons) have been approved as first-line treatments for RRMS in Serbia a few years ago, after their effectiveness and cost-effectiveness were shown in a number of studies. These drugs reduced frequency of relapses for approximately 30% in the majority of the studies. However, all published cost-effectiveness evaluations of immunomodulatory therapies for RRMS have been conducted from perspectives outside of health budgets of Balkan countries in socio-economic transition. The societal perspective was used for costs and outcomes, and they were discounted for 3% annually. All costs were expressed in 2008 Serbian dinars (RSD). The data on probabilities of progression, utilities, initial patient distribution and effectiveness (quality-adjusted life years gained, life years gained; etc.) of the five treatment options were obtained from the study of Bell et al., who, for the purpose of their analysis, reviewed published clinical trials, meta-analyses and systematic reviews on the topic. The data on costs were taken from the files of the patients in each of the health states, randomly selected from the patient population treated in the Clinical Center in Kragujevac, Serbia, during the first half of the year 2008. The prices of health services were taken from the Institute for Health Insurance (RIHI) Tariff Book, and the prices of drugs from the List of drugs issued by RIHI. The costs of lost wages were calculated on the basis of the value of average monthly net salary in Serbia during the first six months of 2008. The parameters and values used in the base-case Markov model are shown in Table 1.

There were the following outcomes from the model: life-years gained; quality-adjusted life years (QALYs) gained; average number of years spent in EDSS 0.0–5.5; average number of years spent relapse free; total costs, costs of drug therapy, costs of MS-patients’ care [e.g., physical therapy, check-ups, tests, etc.], and lost wages costs. The incremental cost-effectiveness ratios comparing symptom management alone with symptom management combined with each of the 4 immunomodulatory therapies were also calculated. Model parameters were varied in sensitivity analyses for ± 50%.

The model was built with the help of TreeAge software. The Monte Carlo Simulations of the model were performed, using microsimulation trials with 1,000 hypothetical patients. For each immunomodulatory therapy the mean cost and mean effect of a treatment were calculated, as well as its
tains diagnosed with RRMS in Serbia. The strategies were symptom management alone and symptom management in combination with one of the following: with subcutaneous glatiramer acetate (SC GA), subcutaneous interferon β-1a (SC IFNβ-1a), intramuscular interferon β-1a (IM IFNβ-1a), or subcutaneous interferon β-1b (SC IFNβ-1b). Seven health states were established in the model in terms of the Kurtzke Expanded Disability Status Scale (EDSS), like in the study of Bell et al.: EDSS 0.0–2.5 (no or few limitations in mobility), EDSS 3.0–5.5 (moderate limitations in mobility), EDSS 6.0–7.5 (walking aid or wheelchair necessary), EDSS 8.0–9.5 (confined to bed), death (natural causes or EDSS 10), relapse EDSS 0.0–2.5 (relapse with a change in disability within EDSS 0.0–2.5) and relapse EDSS 3.0–5.5 (relapse with a change in disability within EDSS 3.0–5.5). All health states may transit in the next cycle to itself or to death; the EDSS 0.0–2.5 may transit to EDSS 3.0–5.5 or the relapse states; relapse EDSS 0.0–2.5 may transit to relapse EDSS 3.0–5.5, EDSS 0.0–2.5 or EDSS 3.0–5.5; relapse EDSS 3.0–5.5 may transit to EDSS 3.0–5.5 or EDSS 6.0–7.5; EDSS 3.0–5.5 may transit to relapse EDSS 3.0–5.5 or to EDSS 6.0–7.5; finally, EDSS 6.0–7.5 may transit to EDSS 8.0–9.5.

The duration of one cycle in the model was set to one month. The baseline time horizon was 480 months (40 years). The societal perspective was used for costs and outcomes, and they were discounted for 3% annually. All costs were expressed in 2008 Serbian dinars (RSD). The data on probabilities of progression, utilities, initial patient distribution and effectiveness (quality-adjusted life years gained, life years gained; etc.) of the five treatment options were obtained from the study of Bell et al., who, for the purpose of their analysis, reviewed published clinical trials, meta-analyses and systematic reviews on the topic. The data on costs were taken from the files of the patients in each of the health states, randomly selected from the patient population treated in the Clinical Center in Kragujevac, Serbia, during the first half of the year 2008. The prices of health services were taken from the Institute for Health Insurance (RIHI) Tariff Book, and the prices of drugs from the List of drugs issued by RIHI. The costs of lost wages were calculated on the basis of the value of average monthly net salary in Serbia during the first six months of 2008. The parameters and values used in the base-case Markov model are shown in Table 1.

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incremental cost/effectiveness in regard to symptomatic therapy. The willingness to pay was set up at 5,000,000.00 RSD.

**Results**

When cost/effectiveness calculation method was used in the model, comparing total costs with QALY gained, life-years gained, years spent in EDSS 0.0–5.5 or with years spent relapse free, Monte Carlo simulation had the output shown in Table 2. While the total costs of all four immunomodulatory therapies are 2–3 times higher than total costs of symptomatic therapy, the difference in effectiveness is very low (e.g. 0.6 QALYs or 0.4 LYs), making one additional QALY gained extremely expensive (more than 1 billion RSD).
for glatiramer and more than 4 billion RSD for interferons beta). Although glatiramer has better cost/effectiveness ratio in MS when compared with interferons beta, it is not cost/effective alternative to symptomatic therapy of MS.

The average costs of drug therapy were compared with average number of QALYs gained, average number of life-years gained, average number of years spent in EDSS 0.0–5.5 or with average number of years spent relapse free, by Monte Carlo simulation. The results relate to whole time horizon of the study (480 months), and are shown in Table 3.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Drug costs and QALYs (mean ± SD)</th>
<th>Drug costs and life years gained (mean ± SD)</th>
<th>Drug costs and years EDSS 0–5.5 gained (mean ± SD)</th>
<th>Drug costs and relapse free years gained (mean ± SD)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Costs</td>
<td>QALYs</td>
<td>Costs</td>
<td>ICER</td>
</tr>
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</table>

Results of Monte Carlo simulation when costs of drug therapy were used as outcome. Incremental cost-effectiveness ratios (ICERs) were calculated with symptomatic therapy as baseline. The costs are expressed in millions of Serbian dinars (MRSID).

While the drug acquisition costs of all four immunomodulatory therapies are 10–30 times higher than drug acquisition costs of symptomatic therapy, the difference in effectiveness is very low (e.g. 0.5 QALYs or 0.2 LYs), making one additional QALY gained extremely expensive (more than 2 billion RSD for glatiramer and more than 6 billion RSD for interferons beta). Although glatiramer has better drug acquisition cost/effectiveness ratio in multiple sclerosis when compared with interferons beta, it is not drug acquisition cost/effective alternative to symptomatic therapy of multiple sclerosis.

The average costs of MS-patients’ care were compared with average number of QALYs gained, average number of life-years gained, average number of years spent in EDSS 0.0–5.5 or with average number of years spent relapse free, by Monte Carlo simulation. The results relate to the whole time horizon of the study (480 months), and are shown in Table 4. When the patient-care costs of all four immunomodulatory therapies are compared with patient-care costs of symptomatic therapy, they are still higher; in the same time, the difference in effectiveness is very low (e.g. 0.5 QALYs or 0.4 LYs), making one additional QALY gained still expensive (more than 11 million RSD for glatiramer and more than 300 million RSD for interferons beta). However, the costs of one additional LY gained (35,000 RSD for glatiramer and more than 0.4 million RSD for interferons) and one additional relapse-free year gained (0.35 million RSD for glatiramer and more than 0.4 million RSD for interferons) are reasonable. This result shows that principal source of unbeneficial cost/effectiveness ratio of immunomodulatory therapy in MS patients are high drug acquisition costs.

The average lost wages costs were compared with average number of QALYs gained, average number of life-years gained, average number of years spent in EDSS 0.0–5.5 or with average number of years spent relapse free, by Monte Carlo simulation. The results relate to the whole time horizon of the study (480 months), and are shown in Table 5. The lost wages total costs of all four immunomodulatory therapies are lower for up to 5% than lost wages costs of symptomatic therapy, while the gain in effectiveness with immunomodulatory therapy is still present, albeit low (e.g. 0.5 QALYs or 0.4 LYs); the results show beneficial effect of immunomodulatory therapy on working ability of the patients. The cost-effectiveness ratios of all four immunomodulatory therapies are similar (see Table 5).

Results of Monte Carlo simulation when costs of MS-patients’ care were used as outcome. Incremental cost-effectiveness ratios (ICERs) were calculated with symptomatic therapy as baseline. The costs are expressed in millions of Serbian dinars (MRSID).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Care costs and QALYs (mean ± SD)</th>
<th>Care costs and life years gained (mean ± SD)</th>
<th>Care costs and years EDSS 0–5.5 gained (mean ± SD)</th>
<th>Care costs and relapse free years gained (mean ± SD)</th>
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<td>Costs</td>
<td>ICER</td>
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EDSS – Expanded Disability Status Scale; QALYs – Quality-adjusted life years

Table 3

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<tr>
<th>Treatment</th>
<th>Costs (mean ± SD)</th>
<th>QALYs (mean ± SD)</th>
<th>Costs (mean ± SD)</th>
<th>LYs (mean ± SD)</th>
<th>ICER (mean ± SD)</th>
<th>Costs (mean ± SD)</th>
<th>YEdss (mean ± SD)</th>
<th>RFYs (mean ± SD)</th>
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<td>SC GA</td>
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EDSS – Expanded Disability Status Scale; QALYs – Quality-adjusted life years

Table 4

The distribution of incremental cost-effectiveness ratios (ICERs) calculated by Monte Carlo simulation for total costs per Quality adjusted life year (QALY) is shown at Figure 1 for all four immunomodulatory therapies. For all four immunomodulatory therapies ICERs for the majority of virtual patients lay on the left of willingness-to-pay line, making these options cost/ineffective.

The multiple univariate sensitivity analysis was made using Tornado diagram. All parameters used in the model were varied simultaneously, changing their values for ±50%. Even with the most influential variable (discount rate) net monetary benefit remained positive, within the range 30 - 47 millions of Serbian dinars. Besides the discount rate, other

| Table 5 |
|-----------------|-----------------|-----------------|-----------------|
| Treatment      | Lost wages costs and QALYs (mean ± SD) | Lost wages costs and life years gained (mean ± SD) | Lost wages costs and years EDSS 0.0-5.5 gained (mean ± SD) | Lost wages costs and relapse free years gained (mean ± SD) |
| Symptom management | 7.2±3.8 9.0±4.1 - | 7.5±3.9 16.1±7.2 - | 7.4±3.8 9.0±6.3 - | 7.4±3.8 11.2±6.4 - |
| SC GA | 7.0±3.6 9.5±4.3 -0.29±2.20 7.3±3.7 16.5±7.3 -0.03±1.08 7.2±3.6 9.2±6.6 0.005±1.30 7.2±3.6 12.6±6.8 1.6±53.7 |
| SC IFNβ-1a | 7.0±3.6 9.5±4.3 -0.30±2.11 7.3±3.7 16.5±7.3 -0.03±1.08 7.2±3.6 6.9±6.2 -0.59±10.54 7.2±3.6 16.0±7.1 -0.22±2.02 |
| IM IFNβ-1a | 7.0±3.6 9.5±4.3 -0.29±2.20 7.3±3.7 16.5±7.2 -0.03±1.08 7.2±3.6 6.9±6.2 -0.59±10.54 7.2±3.6 16.0±7.1 -0.22±2.02 |
| SC IFNβ-1b | 7.0±3.6 9.5±4.3 -0.30±2.21 7.3±3.7 16.5±7.2 -0.03±1.08 7.2±3.6 6.9±6.2 -0.59±10.54 7.2±3.6 16.0±7.1 -0.22±2.02 |

EDSS – Expanded Disability Status Scale; QALYs – Quality-adjusted life years

Fig. 1 – Distributions of incremental cost-effectiveness ratios (ICERs) calculated by Monte Carlo simulation for total costs per Quality adjusted life year (QALY). a) Subcutaneous glatiramer acetate; b) Subcutaneous interferon β-1a; c) Intramuscular interferon β-1a (IM IFNβ-1a); d) Subcutaneous interferon β-1b.
influential variables were QALYs gained and lost wages in different EDSS states of MS (Figure 2). However, even 50% increase in effectiveness could not offset maleficent effect of high drug acquisition costs on ICER.

Discussion

A cost-effectiveness analysis of three immunomodulatory treatments for newly diagnosed nonprimary progressive MS: interferon beta-1a, interferon beta-1b, and glatiramer acetate was recently performed in the milieu of U.S.A. health system 18. If a treatment lasts for 10 years, interferon beta-1a is the most favorable treatment option, with an incremental cost-effectiveness ratio of $2,200,000/QALY for women and $1,800,000/QALY for men, compared with no treatment 18. The same study has shown that the immunomodulatory therapy does not bring more quality-adjusted life years than no treatment. Some other studies have shown that glatiramer has more favorable cost-effectiveness ratio than interferons 14. A systematic review of cost/effectiveness studies in several European countries has also shown that any benefit from these drugs is achieved at very high cost 19. However, this relatively small benefit is cost/effective only due to the fact that medical treatment constitutes very small part of the total cost of MS in European Union and U.S.A 20.

Within the Serbian health system, the immunomodulatory therapy of RRMS is administered in state-owned hospitals, which do not buy drugs, but are centrally supplied from the Republic Institute for Health Insurance (RIHI) 5. One national Expert Commission appointed by the Managing Board of the RIHI approves administration of the immunomodulatory drugs to any particular patient. The criteria for introduction of the immunomodulatory drugs are not published, but remain at discretion of the Expert Commission. Monte Carlo simulation of our model shows that a significant gain with immunomodulatory therapy is achieved only in relapse-free years, while the time spent in health states EDSS 0.0–5.5 is longer with symptomatic therapy only, and gains in life years and QALYs were only marginal (Tables 2–5). These are the main reasons for one QALY gain costs more than a billion of Serbian dinars (more than 20 million US dollars), making each of the four immunomodulatory therapies cost-ineffective (Figure 1). Another reason for such result are low prices of health services in Serbia, which are arbitrarily decided on by the RIHI 12, 21; the resultant health state-specific MS-related costs used in the model are very low (Table 1). The results of Monte Carlo simulation are the same as above when costs of MS-patients’ care are compared with health benefits instead of total costs, and even more unfavorable when only drug acquisition costs are compared with the benefits (Tables 3 and 4).

A sensitivity analysis has shown that the results of Monte Carlo simulations of the model are not affected by the usual range of the variables variation (± 50%). As it could be expected, the variations in health benefits of the immunomodulatory therapy have the greatest potential to change this unfavorable cost-effectiveness ratio (Figure 2), but these variations have to be of much greater magnitude, i.e. the immunomodulatory therapy should bring much greater benefit to become cost-effective.

Conclusion

Our study suggests that widely prescribed immunomodulatory therapy of RRMS in Balkan country in socio-economic transition, is not cost-effective, regardless of the type of therapy (subcutaneous glatiramer acetate, subcutaneous interferon β-1a, intramuscular interferon β-1a, or subcutaneous interferon β-1b). Moderate gain in relapse-free years (2 to 5 years) does not translate to gain in QALYs, probably due to adverse effects of immunomodulatory therapy and low prices of health services in Serbia. Further research is necessary to identify subsets of patients with multiple sclerosis in which immunomodulatory therapy will be cost-effective in transitional Balkan countries.

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REFERENCES


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