K. Simpson[1], N. Marlow[1], J. Shaw[2], A. V. Rudakova[3]

[1] Medical University of South Carolina, USA
[2] Abbott, USA
[3] Saint Petersburg Chemical and Pharmaceutical Academy

Pharmacoeconomic issues of adalimumab therapy in juvenile idiopathic arthritis

Author for correspondence:
Rudakova Alla, Doctor of pharmacy, Saint Petersburg Chemical and Pharmaceutical Academy
Address: 197376, Saint Petersburg, Prof. Popov str., 14, **tel.:** (812) 234-57-29, **e-mail:** rudakova_a@mail.ru
Accepted: 22.05.2012 г., **submitted for publication:** 04.07.2012 г.

Background. *Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in children and is associated with reduced quality of life and increased health care costs.* ***Objective***. *To evaluate the cost effectiveness of the tumour necrosis factor inhibitor adalimumab (ADA) vs. non-biologic therapy for the treatment of JIA in Russian children and adolescents.* ***Materials and Methods.*** *A Markov model was developed on the basis of the DE038 clinical trial, which compared ADA plus methotrexate (MTX) vs. placebo plus MTX for the treatment of JIA in children aged 4–17 years. Cost-effectiveness analyses were performed from the standpoint of the Russian health care system and society as a whole. Base case analyses followed 11-year-old patients with JIA for a period of 7 years (until the age of 18 years) or over an expected lifetime. Additional analyses followed patients aged 7 years at treatment initiation for a period of 11 years or over a simulated lifetime. The cost of treating severe JIA was assumed to be the same as reported in a published investigation. The cost of ADA therapy was based on the expected cost assuming inclusion in the List of Vital and Essential Medicinal Products. This took into account the Value Added Tax and a 10% trade mark-up. Treatment outcomes were measured in quality-adjusted life years (QALYs).* ***Results and Discussion***. *Over a 7-year time horizon, the incremental cost-utility ratio (ICUR) for ADA vs. conventional non-biologic therapy in the treatment of JIA in 11-year-old patients was 1,571,500 roubles/QALY when using a health care system perspective and 1,515,000 roubles/QALY when using a societal perspective. Over a simulated patient lifetime, the corresponding ICURs were 286,300 roubles/QALY and 275,300 roubles/QALY, respectively. Over an 11-year time horizon, the ICUR for ADA vs. conventional non-biologic therapy in the treatment of JIA in patients aged 7 years at the start of therapy was 852,400 roubles/QALY when using a health system perspective and 802,900 roubles/QALY when using a societal perspective. The corresponding ICURs were 229,700 roubles/QALY and 215,500 roubles/QALY, respectively, when modeling cost effectiveness over a simulated patient lifetime. In each set of analyses, the ICUR for ADA over conventional therapy declined precipitously when taking the long-term consequences of JIA into account.* ***Conclusions***. *Relative to conventional non-biologic therapy, ADA is cost effective when used to treat JIA patients whose disease severity is comparable to that of participants in DE038. ICURs estimated in the base case lifetime analyses did not exceed the per-capita gross domestic product (GDP) for the Russian Federation — i. e., approximately 380,000 roubles in in 2011— which is regarded as the upper threshold for highly cost-effective interventions. These findings support the use of ADA in clinical practice.*
Key words: *juvenile idiopathic arthritis; adalimumab; cost-effectiveness analysis.*

BACKGROUND

Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in children aged less than 16 years [12]. The prevalence of JIA ranges from 17.8 per 100,000 children in Canada to 19.5 per 100,000 children in Finland and 21.7 per 100,000 children in Estonia [1]. Research has shown the economic impact of JIA to be substantial. Children with JIA accrue higher annual average direct medical costs than those without the condition [13]. However, few data exist regarding the long-term cost effectiveness of drugs used to treat JIA. Previous studies of the cost implications of biologic treatment for JIA followed patients for 1 year or less due to the absence of long-term efficacy data [2; 3]. These investigations ignored the long-term consequences of JIA, including the need for prosthetic surgery on large joints, which is seen in approximately 50% of patients [4–6]. Given these concerns, a study was conducted to evaluate the cost effectiveness of the tumour necrosis factor inhibitor adalimumab (ADA) for the treatment of JIA in patients < 18 years of age who reside in the Russian Federation.

MATERIALS AND METHODS

A Markov model was developed to assess the cost effectiveness of ADA relative to conventional disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of JIA. The model was based on the results of the randomized double-blind placebo-controlled trial DE038, which compared ADA plus methotrexate (MTX) vs. placebo plus MTX for the treatment of JIA in children aged 4–17 years [7]. Given that the mean age of patients at the start of DE038 was 11.2 years, the base model followed patients from 11 through 18 years of age. A second part of the model followed patients from the age of 18 years until death.

The primary analysis used a health care system perspective and included only direct health care costs.

A secondary analysis using a societal perspective accounted for both direct and indirect costs. The latter included the value of time lost from work due to the need to provide care for a sick child, which was estimated from the mean number of days of school absence recorded in DE038. It is likely that indirect costs were underestimated since school absenteeism data were not collected at all DE038 study sites. Because of this, the model's societal cost estimates may be viewed as being conservative.

The structure of the model is presented in Figure. The base model included five mutually exclusive health states that were defined using patient data from DE038 [11]. Childhood Health Assessment Questionnaire (CHAQ) scores [14] and active joint counts were used to identify groups of patients with mild (DS2), moderate (DS3), or severe disease activity (DS4) or no overt signs of active disease (remission). The remission group was further subdivided into patients with residual joint movement limitations (DS1) and those with no residual movement limitations (DS0). For the second part of the model, Markov health states were constructed to capture the effects of joint damage during childhood on the need for joint replacement during later years. These included remission, active mild disability, active moderate disability, and active severe disease. It was assumed that patients with moderate-to-severe disability would have hip and knee prosthetic surgery at a frequency corresponding to the rate of prosthetic surgery observed in adult patients with JIA [15].

Treatment effects were measured in quality-adjusted life years (QALYs). QALYs are calculated by multiplying the amount of time lived in a health state by the perceived quality of living in that state, where quality of life is measured on a scale ranging from 1 (full health) to 0 (death). Quality-of-life (i.e., utility) estimates were assigned to the five health states included in the base model using a novel mapping algorithm [11]. CHAQ items were selected and matched by response category to Health Utilities Index Mark 2 (HUI2) items measuring similar attributes. The resulting algorithm was applied to CHAQ responses recorded in DE038 to predict HUI2 utilities [16]. The aggregate utility of a health state was taken to be equal to the mean of the predicted HUI2 utilities for all individuals occupying that state at a given time. Mean predicted utilities and other health out-comes for the five health states are presented Table 1.

Figure. Markov model for the treatment of JIA

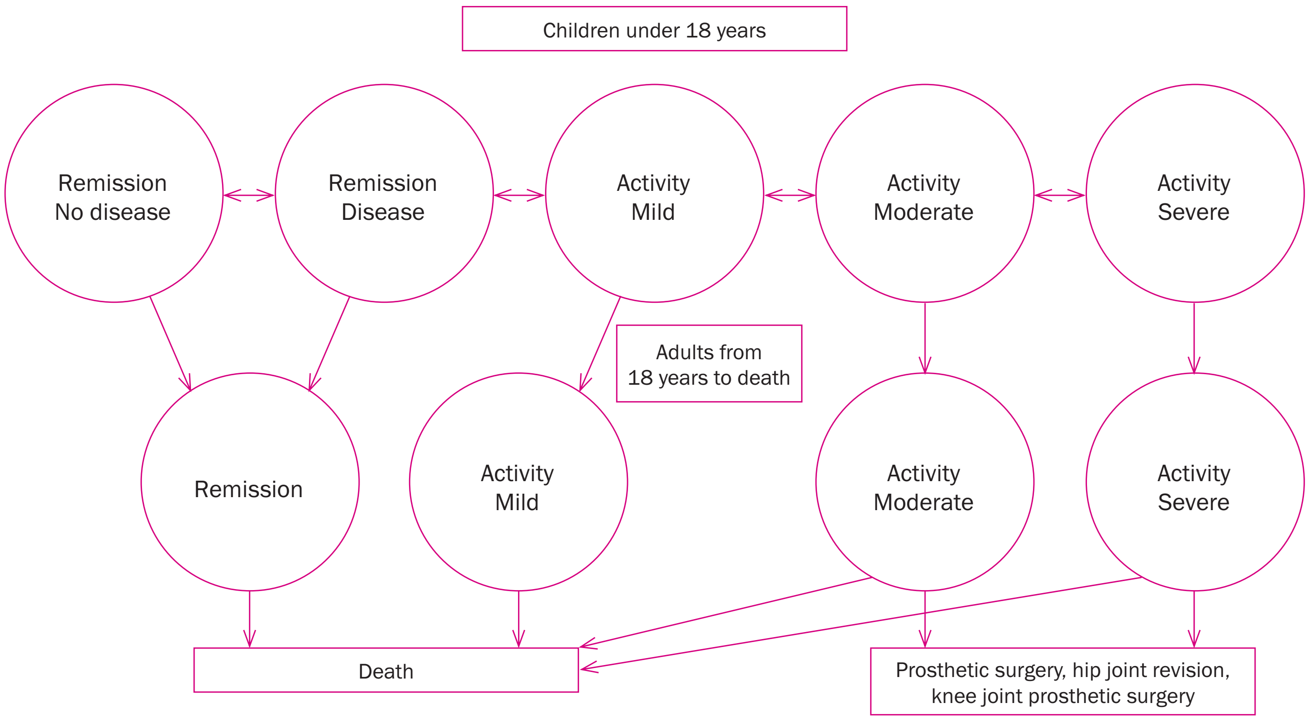

Table 1. Mean predicted utility and other health outcomes by health state [11]

Outcome	DS0	DS1	DS2	DS3	DS4	Range
	***n* = 747**	***n* = 672**	***n* = 1496**	***n* = 769**	***n* = 141**	
Predicted HUI2 utility	0.98	0.96	0.94	0.79	0.56	0.18–1.00
CHAQ score	0.03	0.08	0.03	0.42	1.37	0–2.9
Pain score	4.3	7.6	12.4	34.3	58.5	0–100
Global disease activity score	4.1	8	12.6	35.3	59.2	0–100
Number of LOM joints	0.03	4.00	4.9	9.3	13.9	0–66
Number of active joints	0	0	8	20	32.3	0–168
Weighted joint score	0.01	0.02	6.1	11.7	15.5	0–47

Note. Means were estimated over the average number of person-years spent in each health state in DE038. *Abbreviation*: LOM, limitation on passive motion.

Utilities for the four health states included in the second part of the model were derived from the literature on adult patients with limitations of movement due to rheumatoid arthritis. The values for remission, active mild disability, active moderate disability, and active severe disease were 0.85, 0.83, 0.71, and 0.50, respectively [17].

Time in the model was defined as four months per model cycle based on an assessment of the DE038 trial and follow-up data. The model assumed that patients who failed to achieve remission (i.e., in DS0 or DS1) after 1 year of treatment had a median time on treatment of 3 years, as we observed in DE038. Additionally, mortality rates were assumed to be equal to published rates for the Russian Federation [8].

Health care costs were derived from the findings of Yagudina et al. [3]. Yagudina and colleagues reported the cost of 15 months of JIA treatment (i.e., 14 months of outpatient treatment and 1 month of inpatient treatment), excluding the cost of biologic therapy, to be 1,339,712 roubles. The cost per patient-year of treatment was estimated to be 1,071,770 roubles. Given the high rate of hospitalization observed in Yagudina et al.'s study, it was assumed that this cost would be applicable to patients in health state DS4 (severe JIA). In DE038, patients in health state DS4 missed an average of 57.6 school days per year, whereas patients in health state DS0 or DS1 missed an average of 2.6 days, those in health state DS2 missed an average of 4.1 days, and those in health state DS3 missed an average of 15.6 days per year. For health states DS0, DS1, DS2, and DS3, medical care costs were estimated by multiplying the ratio of the average number of school days missed relative to state DS4 by the patient-year cost for DS4. ADA treatment costs were calculated based of the expected cost of the drug following its inclusion in the List of Vital and Essential Medicinal Products (58,100 roubles for two 40 mg syringes after adjustment for the Value Added Tax and a 10% trade mark-up). The costs attributable to each of the five health states are presented in Table 2.

In the base case, the model predicted costs and outcomes for a cohort of 100 children with a mean age of 11 years. Costs and outcomes were discounted at a rate of 3% per year. Incremental cost-utility ratios (ICURs) were calculated based on discounted cost and QALY estimates. A sensitivity analysis was performed to assess the robustness of the model's predictions to variation in the assumed age at treatment initiation. Specifically, the age of treatment initiation was lowered from 11 to 7 years. Additional sensitivity analyses were performed in which a 5% discount rate was applied to costs and outcomes or costs and outcomes were not discounted.

RESULTS AND DISCUSSION

The results of analyses using a 7-year time horizon (i.e., from 11 to 18 years of age) are presented in Table 3. Relative to PBO + MTX, ADA + MTX was observed to be more costly but also more effective. The incremental cost per QALY gained was 1,571,490 roubles when using a health care system perspective and 1,514,955 roubles when using a societal perspective.

Results for the lifetime analyses are presented in Table 4. Similar to the analyses using a 7-year time horizon, ADA + MTX was found to be more costly but also more effective than PBO + MTX. The incremental cost per QALY gained was 286,267 roubles when using a health care system perspective and 275,315 roubles when using a societal perspective.

Results for sensitivity analyses of the influence of age at treatment initiation are presented in Table 5. When the model was modified to reflect the costs and outcomes observed over 11 years after initiating treatment at 7 years of age, the incremental cost per QALY gained improved from 1,571,490 roubles to 852,382 roubles. This finding can be attributed to the fact that the distribution of patients among health states changed minimally after six years of follow up. Consistent with this observation, published reports have indicated that approximately 50% of JIA patients

Table 2. Mean direct and indirect costs for each health state (per 4-month cycle)

Cost (in roubles)	DS0	DS1	DS2	DS3	DS4
Direct					
• ADA treatment	251 767	251 767	251 767	251 767	251 767
• MTX treatment	602	602	602	602	602
• Treatment without biologic therapy	16 002	16 002	25 678	96 757	357 257
Indirect	584	584	936	3528	13 027

Table 3. Base case results with seven-year time horizon

Parameter	ADA + MTX	Placebo + MTX
Total direct cost, roubles	4 291 785	2 844 102
Total societal cost (including direct and indirect costs), roubles	4 317 800	2 922 198
Total QALYs	5.8943	4.9731
Difference in direct costs, roubles	1 447 683	–
Difference in societal costs, roubles	1 395 602	–
Difference in QALYs	0.9212	–
Medical cost in roubles/QALY gained (health care system perspective)	1 571 490	–
Societal cost in roubles/QALY gained (social perspective)	1 514 955	–

Note. Predicted per-patient costs and outcomes are presented. The model assumed a mean age of 11 years at the start of therapy. Costs and outcomes were discounted by 3%. *Abbreviation*: QALY, quality-adjusted life year.

Table 4. Base case results with lifetime time horizon

Parameter	ADA + MTX	Placebo + MTX
Total direct cost, roubles	4 116 231	2 753 954
Total societal cost (including direct and indirect costs), roubles	4 320 964	2 959 566
Total QALYs	24.80	20.04
Difference in direct costs, roubles	1 362 277	–
Difference in societal costs, roubles	1 361 398	–
Difference in QALYs	4.76	–
Medical cost in roubles/QALY gained (health care system perspective)	286 267	–
Societal cost in roubles/QALY gained (social perspective)	275 315	–

Note. Predicted per-patient costs and outcomes are presented. The model assumed a mean age of 11 years at the start of therapy. Costs and outcomes were discounted by 3%. *Abbreviation*: QALY, quality-adjusted life year.

Table 5. Sensitivity analysis of the influence of initiating treatment at 7 (as opposed to 11) years of age

Parameters	ADA + MTX	Placebo + MTX
11-year time horizon		
Total direct cost, roubles	5 880 878	3 556 745
Total societal cost (including direct and indirect costs), roubles	5 913 161	4 665 869
Total QALYs	8.79	7.24
Difference in direct costs, roubles	1 324 132	–
Difference in societal costs, roubles	1 247 292	–
Difference in QALYs	1.55	–
Medical cost in roubles/QALY gained (health care system perspective)	852 382	–
Societal cost in roubles/QALY gained (social perspective)	802 917	–
Lifetime time horizon		
Total direct cost, roubles	5 910 057	4 672 210
Total societal cost (including direct and indirect costs), roubles	5 942 341	4 781 334
Total QALYs	27.70	22.31
Difference in direct costs, roubles	1 237 848	–
Difference in societal costs, roubles	1 161 007	–
Difference in QALYs	5.39	–
Medical cost in roubles/QALY gained (health care system perspective)	229 744	–
Societal cost in roubles/QALY gained (social perspective)	215 483	–

Note. Predicted per-patient costs and outcomes are presented. The model assumed a mean age of 7 years at the start of therapy with patients being followed for 11 years (i.e., until the age of 18) or until death. Costs and outcomes were discounted by 3%. *Abbreviation*: QALY, quality-adjusted life year.

Table 6. Sensitivity analysis of the influence of discount rate applied to costs and outcomes

Model	7-Year Time Horizon	Lifetime Time Horizon
Health care system perspective, no discounting	1 437 480 roubles/QALY	119 496 roubles/QALY
Health care system perspective, discounted 3%	1 571 490 roubles/QALY	286 267 roubles/QALY
Health care system perspective, discounted 5%	1 663 470 roubles/QALY	428 236 roubles/QALY
Societal perspective, discounted 3%	1 514 955 roubles/QALY	275 315 roubles/QALY

Abbreviation. QALY, quality-adjusted life year.

experience spontaneous remission as they progress toward adulthood [18–19]. The results of the lifetime analyses were more consistent with the base case results using a lifetime time horizon (Table 4).

Table 6 presents the results of sensitivity analyses of the influence of the discount rate applied to costs and outcomes. For comparison, the base case results (i.e., 7-year and lifetime time horizons, health care system and societal perspectives, 3% discount rate) are also presented. Lowering the discount rate to 0% or raising it to 5% had little impact on the results when using a 7-year time horizon. When using a lifetime time horizon, varying the discount rate had a more noticeable effect with the incremental cost per QALY gained changing from a base case of 428,236 roubles to 119,496 roubles if no discounting was applied or 428,236 roubles if costs and outcomes were discounted by 5%.

The World Health Organization suggests that an intervention can be considered to be highly cost-effectiveness if the cost per QALY gained does not exceed a country's per-capita gross domestic product, which was approximately 380,000 roubles for the Russian Federation in 2011. Based on this, regardless of the perspective taken, one could conclude that ADA+MTX is more cost effective than conventional DMARD therapy for treating JIA when costs and outcomes are assessed over a patient's lifetime.

Finally, the model's ability to reproduce results observed in DE038 was examined by comparing the predicted proportion of patients in remission at five years with the actual proportion in the remission health state in the clinical data. At five years, the model predicted a remission rate of 53.1%, which was similar to the five-year remission rate of 55.0% observed in DE038.

CONCLUSIONS

Relative to conventional non-biologic therapy, ADA appears to be cost effective when used to treat JIA patients whose disease severity is comparable to that of participants in DE038. ICURs estimated in the base case lifetime analyses did not exceed the per-capita gross domestic product (GDP) for the Russian Federation — i. e., approximately 380,000 roubles in 2011 — which is regarded as the upper threshold for highly cost-effective interventions. These findings support the use of ADA in clinical practice.

ACKNOWLEDGEMENT

The authors would like to express their deepest gratitude to Dr. Natalya Krupenko, MD, PhD, Assistant Professor of Biochemistry and Molecular Biology, Medical University of South Carolina, for her help in translating some of the references into English.

REFERENSES

1. Feldman D., Bernatsky S., Houde M. The incidence of juvenile rheumatoid arthritis in Quebec: a population data-based study. Pediatr. Rheumatol. Online J. 2009; 7: 20.
2. Costa V., Ungar W.J., Hancock R. The use of biologic response modifiers in polyarticular-course juvenile ideopatic arthritis. Report No. 2010-01. January 11, 2010. http://pede.ccb.sickkids.ca/pde/task.jsp.
3. Yagudina R.I., Zinchuk I.Yu., Kulikov A.Yu. Farmako eko no micheskii analiz primeneniya genno-injenernyh biologicheskih preparatov pri yuvenil'nom revmatoidnom artrite. Farmakoekonomika 2011; 4 (1): 18–23.
4. Duarte-Salazar C., Guzman-Vaquez S., Soto-Molina H. et al. Disability impact on quality of life in Mexican adults with juvenile ideopatic arthritis and juvenile ankylosing spondylitis // Clin. Exp. Rheumatol. 2007; 25 (6):922–7.
5. Osnes-Ringen H., Kvien T.K., Henriksen J.-E. et al. Orthopedic surgery in 255 patients with inflammatory arthropathies: longitudinal effects on pain, physical function and health related quality of life. Ann. Rheu. Dis. 2009; 68 (10): 1596–1601.
6. Weiss J., Ilowite N. Juvenile idiopathic arthritis. Pediatrics Clinics of North America 2005; 52: 413–442.
7. Lovell D.J., Ruperto N., Goodman S. et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N. Eng. J. Med. 2008; 359: 810–20.
8. Life tables for WHO Member States. Russian Federation. 2009. (www.who.int)
9. Prilojeniya k General'nomu tarifnomu soglasheniyu po tarifam na medicinskuyu pomosch' (medicinskie uslugi) i usloviyam oplaty medicinskoi pomoschi, okazyvaemoi v ramkah deistvuyuschei Territorial'noi programmy obyazatel'nogo medicinskogo strahovaniya grajdan Rossiiskoi Federacii v Sankt-Peterburge na 2011 g. (www.spboms.ru)
10. Lundquist J., Kastang F., Kobelt G. The burden of rheumatoid arthritis and access to treatment: Health burden and cost. Eur. J. Health Econ. 2008; 8 (Suppl. 2): S49-S60.
11. Simpson K.N., Shaw J.W. Mapping the Childhood Health Assessment Questionnaire to the Health Utilities Index Mark 2 and Mark 3 in children with juvenile idiopathic arthritis [abstract]. *Quality of Life Research*. In press 2012.
12. Andersson G.B. Juvenile arthritis: who gets it, where and when? A review of current data on incidence and prevalence // Clin Exp Rheumatol. 1999; 17: 367–74.
13. Bernatsky S., Duffy C., Malleson P., Feldman D.E., St. Pierre Y., Clarke A. Economic impact of juvenile idiopathic arthritis//Arthritis and Rheumatism. 2007; 15: 44–48.
14. Lam K., Young N., Marwaha j. et al. Revised version of the Childhood Health Assessment Questionnaire (CHAQ) are more sensitive and suffer less from a ceiling effect. Arthritis & Rheumatism. 2004; 51 (6); 881–889.
15. Packham J.C., Hall M.A. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: Functional outcome // Rheumatology. 2002; 41: 1428–1435.
16. Torrance G.W., Feeny D.H., Furlong W.J., Barr R.D., Zhang Y., Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2 // Medical Care 1996; 34 (7): 702–722.
17. Lundquist J., Kastang F., Kobelt G. The burden of rheumatoid arthritis and access to treatment: hHealth burden and cost // Eur. J. Health Econ. 2008; 8 (Suppl. 2): S49-S60.
18. Duarte-Salazar C., Guzman-Vaquez S., Soto-Molina H. et al. Disability impact on quality of life in Mexican adults with juvenile ideopatic arthritis and juvenile ankylosing spondylitis // Clin. Exp. Rheumatol. 2007; 25 (6): 922–7.
19. Osnes-Ringen H., Kvien T.K., Henriksen J.-E. et al. Orthopedic surgery in 255 patients with inflammatory arthropathies: longitudinal effects on pain, physical function and health related quality of life // Ann. Rheu. Dis. 2009; 68 (10): 1596–1601.