

№3 ^{Том3}
2015

Фармакоэкономика
теория и практика

ФФВ

Pharmacoeconomics
theory and practice

№3 ^{Volume3}
2015

- ОПРЕДЕЛЕНИЕ ПОРОГА «ГОТОВНОСТИ ПЛАТИТЬ» ПРИ ОДОБРЕНИИ МЕДИЦИНСКИХ ТЕХНОЛОГИЙ В УСЛОВИЯХ РОССИЙСКОГО ЗДРАВООХРАНЕНИЯ, РАССЧИТАННОГО НА ОСНОВЕ ПАРИТЕТА ПОКУПАТЕЛЬНОЙ СПОСОБНОСТИ
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

THE COST-EFFECTIVENESS OF ABATACEPT COMPARED TO ADALIMUMAB FOR ADULT PATIENTS WITH RHEUMATOID ARTHRITIS IN THE RUSSIAN FEDERATION

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Abstract: Recent market entry of disease-modifying anti-rheumatic drugs (DMARDs) for patients with rheumatoid arthritis (RA) who had an inadequate response to methotrexate in Russia has secured patient access to highly effective treatment options. Access to effective treatment options are of particular importance for highly prevalent conditions with early function impairment such as RA. Innovative medicines, such as DMARDs, are however typically characterized by high treatment costs and require pharmacoeconomic assessment as part of the decision making process regarding federal reimbursement. In the present study, adaptation of an Italian health economic model was performed with the aim to compare cost-efficacy of subcutaneous abatacept versus adalimumab from the Russian Federation national health care system perspective. Clinical efficacy data as well as patient characteristics were based on the AMPLE trial patient population, which was a direct head-to-head comparison of subcutaneous abatacept and adalimumab in RA. The time horizon was set at 2 years, which corresponds with the length of the AMPLE study. Direct medical costs included pharmaceutical costs based on the registered maximum selling prices, cost of adverse event treatment, outpatient and inpatient treatment, and diagnostic and laboratory monitoring costs (Rubles, 2015).

Results showed that the total 2-year costs of treating 100 patients were 143,750,205.87 rubles for abatacept compared with 165,749,479.26 rubles for adalimumab, at a total cost-savings of treating an entire cohort with abatacept equal to 21,999,273.38 rubles or 219,992.73 rubles per patient. The cost-effectiveness ratios across all disease activity measures (ACR 20, 50, 70, 90; DAS-28; HAQ-DI; CDAI; SDAI) demonstrated that abatacept compared to adalimumab had a lower cost per health outcome. Therefore, from a pharmacoeconomic point of view, subcutaneous abatacept is most likely a preferable alternative compared with adalimumab for the treatment of RA patients in the Russian Federation.

Key words: abatacept, adalimumab, rheumatoid arthritis, cost-effectiveness analysis, disease-modifying anti-rheumatic drugs, pharmacoeconomics, pharmacoeconomic model

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases of unknown aetiology, which is associated with inflammation of joint connective tissue [2, 3]. RA prevalence rate varies from 0.5 % to 3 % worldwide [3, 16]. The chronic progression of rheumatoid arthritis results in joint destruction, impaired joint function and increasing disability in mostly 70 % of all disease cases [1,

4, 5]. Therefore, the high prevalence and severe consequences of this disease leading to permanent loss of capacity for work and early disability mean that RA presents an essential problem for society as a whole.

Anti-inflammatory drug methotrexate (MTX) is considered to be the first-line therapy for most patients with RA [5]. If methotrexate is not sufficiently effective, the biological disease-modifying antirheumatic drugs (DMARD's) are additionally administered as a second-line therapy [5].

Recent market entry of disease-modifying anti-rheumatic drugs (DMARDs) for patients with RA who had an inadequate response to MTX in Russia has secured patient access to highly effective treatment options. The difference between the biologic DMARDs and all other drug classes used in rheumatoid arthritis (corticosteroids, nonsteroidal anti-inflammatory agents) is a specific directed action on target cells participating in the development of major pathogenetic pathways of rheumatoid arthritis [5]. The biologic DMARDs include drugs with different mechanisms of action: tumour necrosis factor alpha inhibitors (infliximab, adalimumab, etanercept, and certolizumab pegol); an interleukin-6 receptor blocker (tocilizumab); a T-lymphocyte co-stimulation inhibitor (abatacept); and an inhibitor of the CD20 antigen located on the surface of B-lymphocytes (rituximab) [2, 4, 5, 11]. All biologic DMARDs have a proven clinical efficacy, which was demonstrated in patients with rheumatoid arthritis in randomized placebo-controlled clinical studies [17, 18].

Use of innovative DMARDs is associated with considerable costs from the health care system prospective. In 2012, the total sales of DMARDs in the Russian Federation amounted to 9.54 billion rubles [1]. Therefore, the diversity of the drugs of this class, their high cost under conditions of restricted health care budget, entail the need for a scientific approach to decision-making process regarding rheumatoid arthritis therapy. Results obtained by means of pharmacoeconomic analysis can become a scientific rationale for decision makers [7]. International pharmacoeconomic models may also be considered in decision-making process however, they should be adapted for the Russian health care system.

The current study represents adaptation of the pharmacoeconomic model developed by Mapi Consultancy (www.mapi-consultancy.com). This model had been used in Italy for pharmacoeconomic assessment of abatacept subcutaneous (SC) versus adalimumab in patients with rheumatoid arthritis and inadequate response to MTX. The model was based on a variant of cost-effectiveness analysis, which permits comparison of alternative therapies based on a cost per unit of efficacy-related health benefits. For the analysis data from the Phase III multicentre randomized double-blind clinical trial AMPLE that directly compared subcutaneous abatacept (Orencia®) versus adalimumab (Humira®) was used [12].

Modeling results obtained with Italian data demonstrated that abatacept

SC was a preferable treatment option, as compared with adalimumab in RA patients with an inadequate response to MTX from the Italian health care system perspective [19].

Therefore, the objective of this study was to perform an adaptation of the international pharmacoeconomic model for assessment of abatacept SC versus adalimumab in combination with MTX in patients with RA and based on cost-effectiveness analysis determine preferable treatment option from the Russian health care system perspective.

Materials and methods

Model description

The study included the following patient population: adults with RA for < 5 years that met the American College of Rheumatology (ACR) 1987 classification criteria, with active disease and an inadequate response to MTX, and had not received previous biologic DMARD therapy [12].

The model has a decision tree structure, its schematic representation is provided on Figure 1:

According to the structure of the model, treatment with abatacept SC and adalimumab in RA patients with inadequate response to MA is characterized by respective cost-effectiveness ratios (CER), which permit comparison of the total costs of treating all patients relative to each of the various efficacy outcomes of interest.

The efficacy analysis of abatacept SC versus adalimumab in combination with MTX was carried out based on the results of the AMPLE clinical trial with 2 years follow up [12]. This study employed the following efficacy criteria:

- the percentage of responders according to ACR20, ACR50, ACR70, ACR90, and HAQ-DI criteria (Health assessment questionnaire disability index);
- the percentage of patients in remission according to the DAS-28 score (Disease activity score for 28 joint counts) and the activity indexes CDAI (Clinical disease activity index) and SDAI (Simplified disease activity index) .

A time horizon of 2 years was applied as based on the AMPLE trial results [12].

The following medical costs were determined in the course of the study in relation to the health care system budget:

- pharmacological treatment with DMARDs;
- concomitant pharmacological therapy;
- out-patient visits;
- in-patient medical services;
- diagnostic costs (X-ray imaging and laboratory blood tests);
- treatment of adverse events (AE) and serious adverse events (SAE), including treatment of local injection site reactions, malignancies, and autoimmune disorders.

To make up for missing clinical data indispensable for the model's

adaptation, a questionnaire for leading rheumatology specialists was compiled. An expert opinion was thus obtained, which was used to determine duration and dosage of concomitant therapy; number of required out-patient visits; duration of hospitalization; number of X-ray imaging procedures and laboratory blood tests in the two compared treatment groups. The expert opinion also served to determine specific therapy of the adverse events with no published standards of care or clinical guidelines.

The rates of AE and SAE were taken from the AMPLE trial. All malignancies and autoimmune diseases that patients developed in the course of the clinical study were assumed to be treatment-related and were included in the results for costs. For patients with chronic adverse events (chronic obstructive pulmonary disease, malignancies, and autoimmune diseases), the assumptions for frequency of hospitalization and ambulatory visits per year were based on expert opinion.

The treatment duration, dosing regimen, and frequency of dosing for the compared drugs were taken from the protocol for the AMPLE clinical study, which is in agreement with the current product label information. Abatacept SC was administered at a dose of 125 mg given subcutaneously once a week, adalimumab was given as a 40 mg subcutaneous injection once in two weeks. Both treatment options were combined with a stable weekly MTX dose, which corresponded to the average MTX dose administered in the AMPLE study. It should be mentioned that presented analysis included proportion of missed drug injections based on the AMPLE study results. The cost of pharmacological therapy with adalimumab and abatacept SC was calculated using equation 1:

$$\text{Cost (t)} = D \times (N(t) - M(t)) \times P \tag{1}$$

- Cost (t) – cost of therapy, rubles;
- D – drug dose per injection, mg;
- N(t) – number of injections over a certain period of time (t);
- M(t) – number of injections missed over a certain period of time (t);
- P – drug cost per milligram, rubles.

The cost of concomitant medication was calculated according to equation 2:

$$\text{Cost (t)} = D \times N(t) \times P \tag{2}$$

- Cost (t) – cost of therapy, rubles;
- D – single drug dose, mg;
- N(t) – number of single drug doses taken over a certain period of time (t);
- P – drug cost per milligram, rubles.

Both studied DMARDs are included in the Essential Drug List (EDL), and

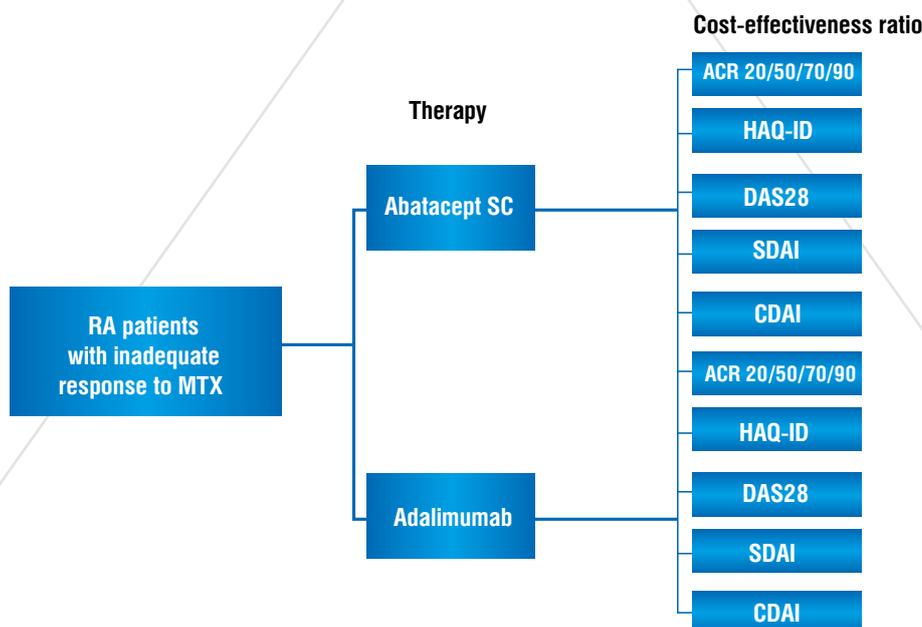


Figure 1. Decision tree structure



their registered ceiling sales prices for pharmaceuticals included into EDL list with VAT were used for the cost calculation [8, 9]. The price for abatacept SC package (Orencia®, four 125 mg syringes) was 61,172 rubles, and the price of one adalimumab package (Humira®, two 40 mg syringes) was 74,800 rubles. The Moscow tariffs of the Federal Compulsory Medical Insurance Fund were used to calculate the cost of medical services and laboratory tests.

The cost-efficacy ratios to compare the two treatment options were calculated with the help of equation 3:

$$CER = \frac{Cost}{Ef} \quad (3)$$

CER – cost-efficacy ratio;
Cost – cost of treatment, rubles;
Ef – treatment efficacy [6].

This model also included a one-way sensitivity analysis with the aim to determine the most influential parameters on the difference in costs and their respective impact. All parameters presented as a proportion were varied based on the 95 % confidence interval (CI) where reported, and otherwise a beta distribution with a standard deviation equal to the mean was used. Continuous variables were varied based on the 95 % CI where available, or else, in the absence of the latter, a triangular distribution with a standard deviation of 30 % of the mean was used. Parameters that represent a fixed point, such as time horizon, dosage and duration of DMARDs therapy, drug prices, cohort size, and patient weight, were not varied as they are not subject to parameter uncertainty.

Efficacy analysis

The following efficacy criteria to compare abatacept SC and adalimumab according to the results of the AMPLE clinical study were selected for the analysis in adapted model (Table 1).

Table 1 Efficacy criteria for comparison of adalimumab and abatacept SC in patients with RA over 2-year period [AMPLE]

Efficacy criteria	Abatacept SC	Adalimumab
ACR20	59,70 %	60,10 %
ACR50	44,70 %	46,60 %
ACR70	31,10 %	29,30 %
ACR90	14,50 %	8,20 %
HAQ-DI	54,10 %	48,80 %
DAS28	50,60 %	53,30 %
CDAI	32,00 %	30,30 %
SDAI	31,20 %	32,50 %

According to the results of the AMPLE clinical study presented in Table 1 the proportion of patients who achieved ACR 20 and ACR50 response was higher in the adalimumab group as compared with abatacept-treated patients, difference of 0.4 % and 1.9 %, respectively. For ACR70 and ACR90 criteria, abatacept SC demonstrated an advantage over adalimumab in efficacy (the differences being 1.8 % and 6.3 %, respectively). Similar results were obtained for the HAQ-QI functional criterion, with a difference of 5.3 % in favour of abatacept SC. For the outcome remission, the results are mixed, with adalimumab favoured based on the DAS28 and SDAI scale and abatacept favoured based on the CDAI scale. When measuring remission based on the DAS28 and SDAI scales, a total of 2.7% and 1.3% fewer proportions of patients treated with abatacept achieved remission compared to adalimumab. Conversely, an additional 1.7% of patients achieved remission based on the CDAI scale when treated with abatacept compared to adalimumab [12].

Cost analysis

The cost analysis was performed for a cohort of 100 patients. This analysis only took into account direct medical costs.

Cost of pharmacological therapy

The drug therapy costs for a cohort of 100 patients over two years time horizon were found to be 136,414,225 rubles for abatacept SC and 159,324,000 rubles for adalimumab. Therefore, a cost-saving of treating an entire a cohort of 100 patients will be 2,909,775 rubles in favor of abatacept SC.

Cost of concomitant therapy

Subsequently, the cost of concomitant medication was taken into account; the following drugs were considered: methotrexate, sulfasalazine, hydroxychloroquine, ciclosporin, methylprednisolone, and meloxicam. The proportions of patients who took these drugs were determined using AMPLE clinical study data. The costs of concomitant medication over two-year treatment were 1,888,031 rubles for abatacept group and 1,749,408 rubles for adalimumab. Therefore, the cost of concomitant therapy was higher in the abatacept group than in adalimumab-treated patients, and the difference in cost was 138,623 rubles for the entire cohort.

Cost of medical services

The costs of medical services were calculated separately and included the cost of out-patient care (ambulatory visits) and in-patient medical services (hospitalization), as well as diagnostic costs (laboratory blood tests and radiographic imaging).

It should be noted that the number of ambulatory visits and the length of hospitalization for rheumatoid arthritis patients treated with abatacept SC or adalimumab were obtained based on the expert opinion. Patients with RA in both study groups required 6 out-patient visits during the first year and 4 visits during the second year of treatment. Therefore, the cost of out-patient treatment was amounted to 256,470 rubles for both groups. The mean duration of hospitalization over the two-year treatment period was 16 days for patients treated with adalimumab. The proportion of patients on adalimumab requiring hospitalization due to rheumatoid arthritis was based on AMPLE clinical study data, and was equal to 5.5%. At the same time according to the expert opinion, hospitalization was not required in the abatacept group, which resulted in a cost saving (Figure 2). The cost of in-patient care was 283,012 rubles over two-year treatment in a cohort of 100 patients receiving adalimumab.

The number of X-ray imaging procedures required for monitoring in patients with RA was set to 2 over two-year treatment period for both alternative treatment options. The cost of X-ray imaging during two-year treatment was found to be 90,610 rubles for the cohort of 100 patients. A patient receiving abatacept SC has 20 blood tests (complete blood counts, blood chemistry, and immunological tests) while an adalimumab-treated patient has 24 blood tests according to the expert opinion over 2 years. The cost of laboratory tests was 2,205,006 rubles for the abatacept group and 2,646,007 rubles for the adalimumab group, calculated for 100 patients treated for 2 years.

The total cost of medical services in a cohort of 100 patients with RA treated over 2 years was 2,552,086 rubles for abatacept SC and 3,276,099 rubles for adalimumab (Figure 2).

Table 2 Costs for correction of AES in the cohort of 100 patients with RA within 2 years old when receiving adalimumab and abatacept treatment

Adverse events	Abatacept (rubles)	Adalimumab (rubles)
Adverse events occurring ≥ 5 %	567,661	484,540
Serious adverse events (excluding malignancies)	29,570	208,707
Local injection site reactions	154	1,383
Malignancies (classified as serious adverse events)	2,214,691	657,332
Autoimmune disorders	83,788	48,010
Total:	2,895,864	1,399,972

As Table 2 demonstrates, the highest spending was associated with malignancies treatment requiring administration of the expensive medicines. In the AMPLE trial over two-year period 7 patients (2.2 %) developed malignancies in abatacept group (squamous cell carcinoma of the skin, diffuse large B-cell lymphoma, acute myeloid leukaemia, squamous cell carcinoma of lung, prostate cancer, and uterine cancer) and 7 patients (2.1 %) – in the adalimumab group (basal cell carcinoma, transitional cell carcinoma, breast cancer, malignant melanoma, small cell lung cancer).

The total cost analysis for the treatment of adverse events demonstrated that in total 2,895,864 rubles was required for the abatacept SC group and 1,399,972 rubles for the adalimumab group (cohort of 100 patients receiving

two-year treatment). The higher cost of treatment of adverse events in the abatacept group was related to the most expensive malignancies developed in that group, specifically B-cell lymphoma (occurrence rate: 0.3 %), leukaemia (0.03 %), and prostate cancer (0.03 %).

Therefore, we obtained the total cost of two-year treatment for a cohort of 100 patients with RA: 143,750,206 rubles and 165,749,479 rubles for adalimumab and abatacept SC, respectively (Table 3).

Table 3 Total 2-year costs of treatment in a cohort of 100 patients with RA

Costs	Abatacept (rubles)	Adalimumab (rubles)
Biologic DMARDs therapy	136 414 225	159 324 000
Concomitant therapy	1 888 031	1 749 408
Concomitant therapy	2 552 086	3 276 099
Treatment of AE and SAE	2 895 864	1 399 972

As shown in Figure 3, the main driver of the total costs for both drugs is the drug price accounting for more than 95 % of the total costs. At the same time, the combined cost of concomitant therapy, medical services, and monitoring, as well as treatment of adverse events, constitutes for less than 5% of the total cost of treatment.

Therefore, the cost analysis demonstrated that subcutaneous abatacept was associated with the lower cost of two-year treatment for 100 patients with rheumatoid arthritis; the cost saving, as compared with adalimumab, was 21,999,273 rubles per 100 patients or 219,993 rubles per patient for two-year treatment.

Cost-effectiveness analysis

Upon efficacy assessment and cost calculation for 100 patients with rheumatoid arthritis receiving two-year treatment with abatacept or adalimumab, we performed a cost-effectiveness analysis, the results are presented in Table 4 and Figure 4.

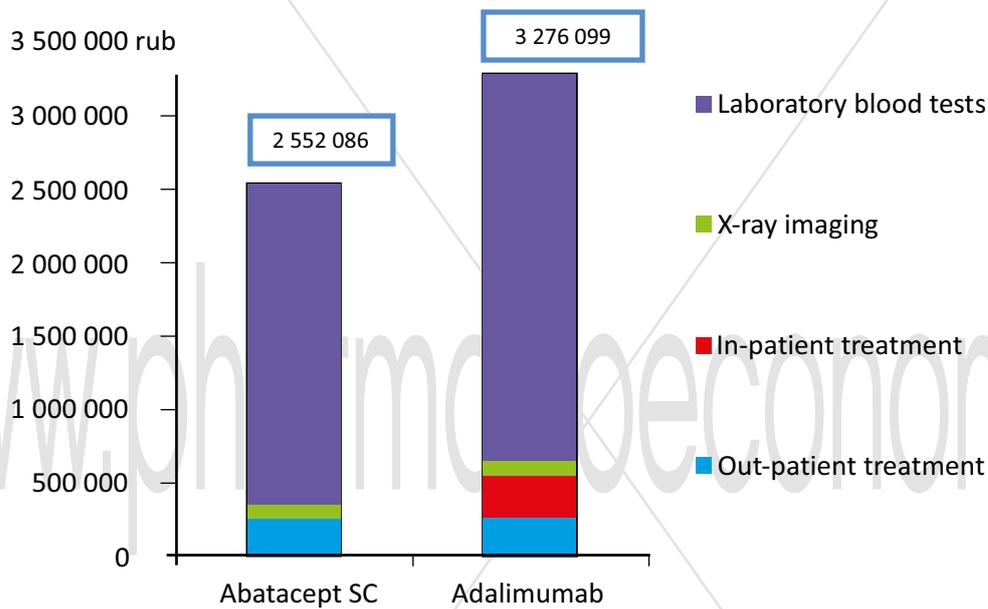


Figure 2. Cost of medical services in a cohort of 100 patients with RA over two-year period

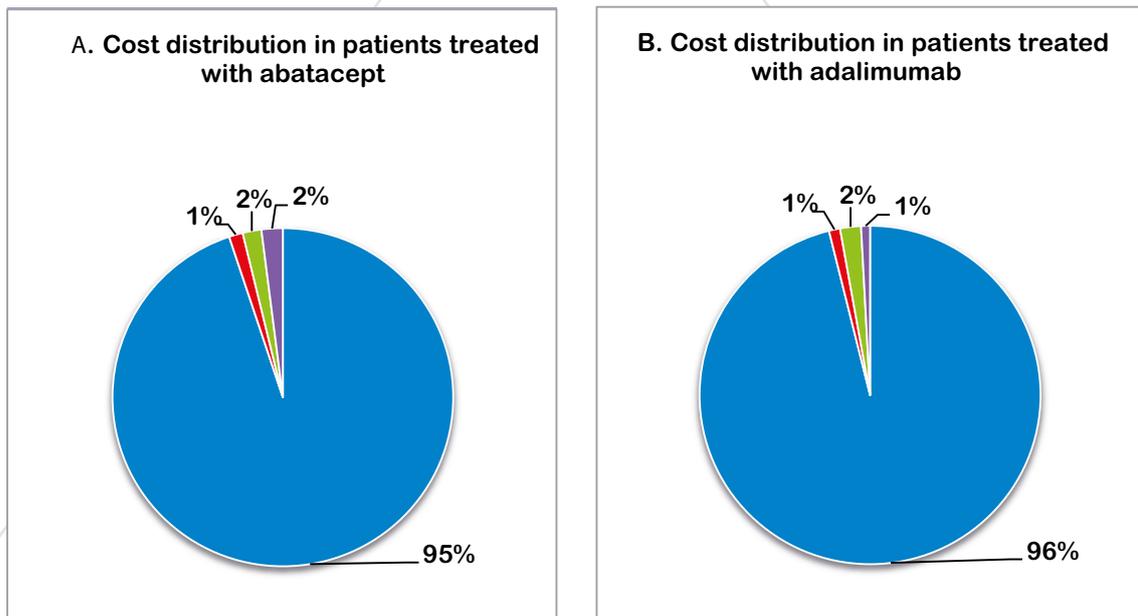


Figure 3. Cost distribution in patients treated with two biologic DMARDs



Table 4 Cost-effectiveness ratios (CER) for subcutaneous abatacept and adalimumab in patients with RA

Efficacy criteria	Cost-effectiveness ratio Abatacept	Cost-effectiveness ratio Adalimumab
ACR20	2 407 876	2 757 895
ACR50	3 215 888	3 556 856
ACR70	4 622 193	5 656 979
ACR90	9 913 807	20 213 351
HAQ-DI	2 657 120	3 396 506
DAS28	2 840 913	3 109 746
CDAI	4 492 194	5 470 280
SDAI	4 607 378	5 099 984

It was demonstrated that the highest cost-effectiveness ratio corresponded to ACR 90, which means a 90 % improvement in patient's condition. At the same time, the lowest cost-effectiveness ratio corresponded to ACR 20 (meaning a 20 % improvement).

This analysis revealed that abatacept SC as compared to adalimumab was associated with a lower cost per health outcome for all reported clinical efficacy criteria.

Sensitivity analysis

One-way sensitivity analysis determined the most influential parameters on the difference in costs and their respective impact. The results are presented in the form of a tornado diagram showing the 10 most influential factors on the difference in costs (Figure 5).

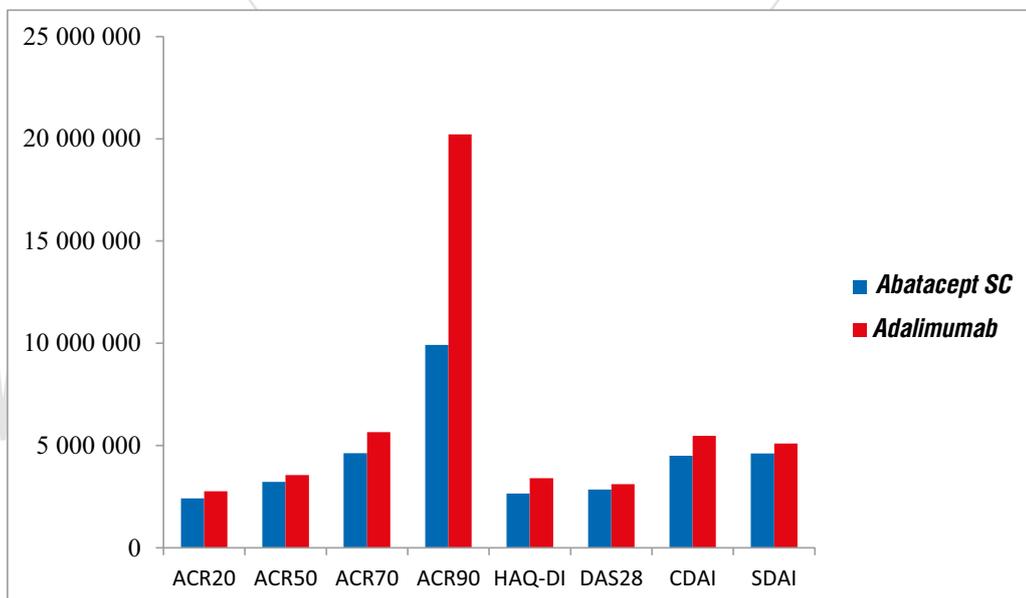


Figure 4. Cost-effectiveness ratios obtained for abatacept and adalimumab groups

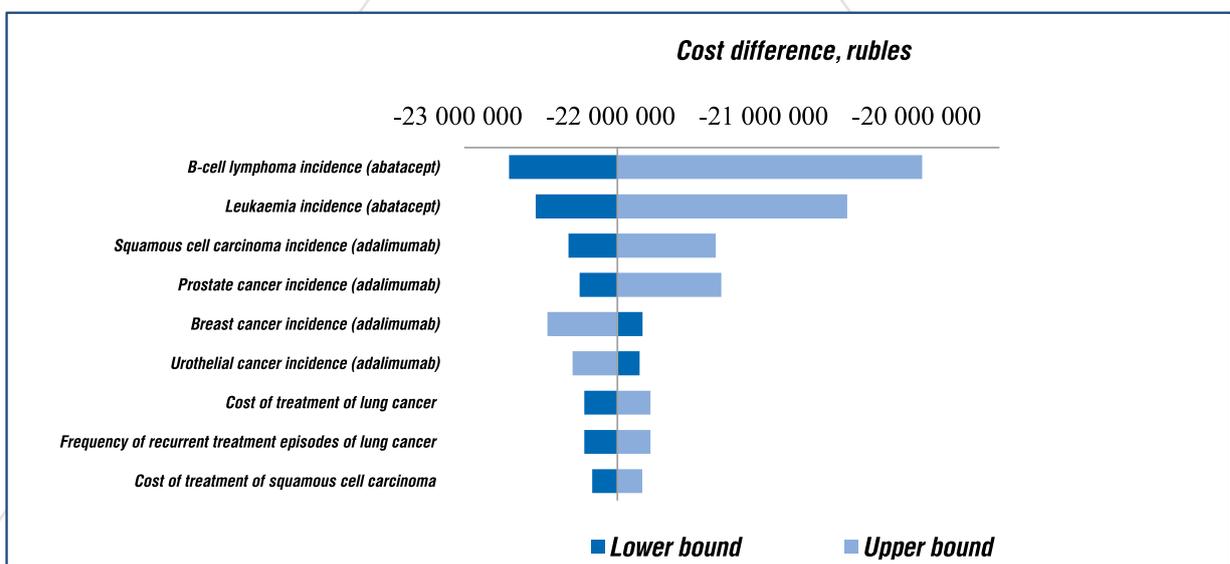


Figure 5. Tornado diagram.

As demonstrated by Figure 5, the parameters with the largest impact on the difference in costs include the most costly malignancies (B-cell lymphoma, leukaemia, squamous cell skin carcinoma, prostate cancer, breast cancer, etc.). It should be taken into consideration, that even with a higher incidence of the aforementioned malignancies in the abatacept group, this group was still characterized by a total cost saving as compared with adalimumab group. At the same time, a lower incidence rate of aforementioned malignancies in adalimumab group entailed a clear need for more budget spending, as compared with subcutaneous abatacept group.

Conclusion

A pharmacoeconomic model adapted to the Russian health care system was utilized to perform a cost-effectiveness analysis and evaluate the use of abatacept SC and adalimumab in rheumatoid arthritis patients with an inadequate response to methotrexate therapy. The medical cost calculation demonstrated that subcutaneous abatacept, as compared with adalimumab, was associated with a cost saving of 21,999,273 rubles for 100 patients over 2-year time period, or 219,993 rubles per patient. The cost-effectiveness ratios across all disease activity measures (ACR 20, 50, 70, 90; DAS-28; HAQ-DI; CDAI; SDAI) demonstrated that abatacept compared to adalimumab had a lower cost per health outcome. Therefore, from a pharmacoeconomic point of view, subcutaneous abatacept is most likely a preferable alternative compared with adalimumab for the treatment of RA patients in the Russian Federation.

Acknowledgment: We would like to acknowledge N.V. Chichasova, MD, Prof., the Sechenov First Moscow State Medical University, department of rheumatology for the expert opinion and contribution into adaptation of the pharmacoeconomic model.

Conflict of interest: The study was conducted with financial support of Bristol-Myers Squibb.

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