№2 Том5 2017

Фармакоэкономика
теория и практика

Pharmacoeconomics
theory and practice

№2 Volume5 2017

- МЕТОДОЛОГИЧЕСКИЕ АСПЕКТЫ ПРОВЕДЕНИЯ ФАРМАКОЭКОНОМИЧЕСКОГО ИССЛЕДОВАНИЯ ТЕРАПИИ СПАСТИЧЕСКИХ ФОРМ ДЕТСКОГО ЦЕРЕБРАЛЬНОГО ПАРАЛИЧА
- МОДЕЛИРОВАНИЕ ВЫЖИВАЕМОСТИ В ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЯХ: МОДЕЛЬ МАРКОВА И МОДЕЛЬ РАЗДЕЛЁННОЙ ВЫЖИВАЕМОСТИ
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

www.pharmacoeconom.com

ASSESSMENT OF CLINICAL AND ECONOMIC EFFECTIVENESS OF APREMILAST IN THE TREATMENT OF PSORIATIC ARTHRITIS

Kulikov A.Yu., Makarova E.I.

State Budgetary Educational Institution of Higher Professional Education "I.M. Sechenov First Moscow State Medical University" of the Ministry of Heath of the Russian Federation, Moscow

Abstract

Psoriatic arthritis (PsA) can develop at any age and often affects the working-age population. In the course of the disease, physical activity of patients decreases, which leads to a drop in performance and absence from work due to treatment. If untreated, this can lead to disability and loss of function of the locomotive system structures. Strategy to combat PsA requires focus on the most effective prevention and control of both the progression of psoriasis, and arthritis associated therewith. It is equally important to minimize the risks associated with major organ toxicity and the development of side effects. In this context, the emergence of drugs for the treatment of psoriasis belonging to a new class of signaling pathways inhibitors seems to be highly relevant both from scientific and practical points of view.

In general, biological products, which are antibodies that selectively bind to receptors or proteins on the extracellular membrane, block one biological marker (e.g., TNF-a, IL-17) participating in the immunopathogenesis of psoriasis, thus interrupting further inflammatory cascade of pathological processes leading to the formation of psoriatic efflorescence. Apremilast, which belongs to a new group of drugs - selective inhibitors of signaling pathways - has a fundamentally different mechanism of action. With targeted effect, the drug modulates intracellular signaling, eventually corresponding to the control of the expression of genes mediating key pro- and anti-inflammatory factors (e.g., release of cytokines) in myeloid, lymphoid and other cells involved in the "orchestration" of epidermis inflammation and hyperproliferation. The drug is administered orally, which eliminates additional costs for administering an injection, as is the case with biological drugs.

The emergence of a new drug for the treatment of psoriatic arthritis, lack of proper control over the course of the disease, as well as limited healthcare system resources resulted in the pharmacoeconomic assessment of the priority drugs Apremilast compared to ustekinumab, adalimumab and infliximab using cost, cost-effectiveness and budget influence analysis methods. The cost analysis results showed that Apremilast treatment costs for the entire study period - 2 years - are on average 27% lower than the cost of treatment with ustekinumab, adalimumab and infliximab. Otezla treatment is characterized by a lower cost per unit of effectiveness - QALY, when considering the cost for the entire time horizon, as compared to Humira, Stelara and Remicade. Furthermore, the use of Apremilast leads to cost savings if administered for either 2 years or 1 year, in comparison with the alternative regimens.

Keywords: *Otezla, Apremilast, psoriatic arthritis, inhibitor of phosphodiesterase 4, signaling pathways inhibitor, cost analysis, cost-effectiveness analysis, budget influence analysis, pharmacoeconomics, direct costs.*

Introduction

Psoriatic arthritis is a chronic, progressive systemic disease that is associated with psoriasis (Ps). The disease is characterized by not only inflammation of the skin, but also of musculoskeletal system tissues leading to the development of erosive arthritis, intraarticular osteolysis and spondyloarthritis [1]. PsA symptoms are often disguised as the symptoms of other rheumatic diseases such as rheumatoid arthritis, osteoarthritis and gout; that is why PsA diagnosis can be a complicated process. In this regard, the exact prevalence of the disease is unknown, and the evaluation thereof is seriously hampered. According to the statistical data of the Ministry of Health of Russia, the number of people suffering from psoriasis is 340 thousand people, and from psoriatic arthritis - 18,545 people (about 5%) [29]. Pain, swelling, inflammation, and soreness of the joints, as well as inflammation of tendons and ligaments associated with Ps leads to a significant decrease in the physical activities and quality of life of the patient. Modern ways of influencing the course of the disease, in accordance with Russian and international guidelines [9,10,14], include drug groups such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCI), disease-modifying anti-inflammatory drugs (DMARDs) - methotrexate, leflunomide, etc., as well as genetically engineered biologic drugs (biologics) - monoclonal antibodies to interleukins (IL) 12/23, as well as tumor necrosis factor alpha (TNF-α).

Typically, systemic therapy is required for patients with medium severe and severe skin lesions, psoriatic arthritis, as well as a significant decrease in the quality of life. The use of methotrexate, cyclosporine and synthetic retinoids in some cases is associated with severe organ toxicity, side effects and requires careful clinical and laboratory monitoring throughout the treatment. [36] The use of modern biological products in some cases is restrained by the therapeutic effect escape phenomenon due to their immunogenicity, development of adverse events (serious infections, tumors, lympho-proliferative disorders), parenteral route of administration, as well as the high cost of the course of therapy [37].

Apremilast, which belongs to a new group of drugs - *selective inhibitors of signaling pathways* - has a fundamentally different mechanism of action minimizing the development of side effects. Intracellular control of signaling pathways is carried out by heterogeneous families of enzymes - phosphodiesterases and janus kinases. It is selective blocking of these enzymes that is the basis of the mechanism of action of this group of drugs, which are also referred to as *"small molecules"* because of their actions within the cell itself. As a result, intracellular signals do not go through the dendritic cells, T-cells, macrophages, and monocytes that are of key importance in terms of psoriasis pathogenesis, and ultimately expression of genes responsible for the release of cytokines is uppressed [39].

PDE4 via its effect on transcription level through the cAMP helps maintain immune balance, including in the skin and synovial structures, by modulating the production of pro- and anti-inflammatory mediators. Influencing the intracellular activity of PDE4 via medication, one can adjust the cytokine response by the immune system. This is the basis for the effect of *Apremilast* intended to combat active psoriatic arthritis in adult patient population. [39] In 2015, the European Medicines Agency approved the drug for the treatment of PsA alone or in combination with DMAIDs, in case of inadequate response or intolerance to the therapy with DMARDs and biologics, which was immediately reflected in the international recommendations of EULAR and GRAPPA [14, 38].

Kulikov A. Yu tel.: +7(968) 879-88-02, e-mail: 7677041@mail.ru

The development of tactics for the treatment of patients with psoriatic arthritis is currently one of the most pressing and complex challenges of modern healthcare. Strategy to combat PsA requires focus on the most effective prevention and control of both the progression of psoriasis, and arthritis associated therewith. The expansion of the range of pharmaceuticals, as well as limited healthcare system resources resulted in this study.

Within the study, pharmacoeconomic evaluation of the application of the following drugs for the treatment of psoriatic arthritis was conducted: ustekinumab (Stelara), infliximab (Remicade), adalimumab (Humira), and apremilast (Otezla). The choice of reference drugs was based on the following selection criteria: the presence of drugs in clinical guidelines and Ps and PsA standards of treatment, the inclusion in the Essential Drug List and Federal Reimbursement, as well as the presence of the leading position in the distribution of market volumes among the biologics. The fact of not meeting at least one of these criteria was the basis for the exclusion of etanercept, as well as generic drugs from the analysis.

The aim of the work was the pharmacoeconomic evaluation of preferential drug apremilast used in the treatment of psoriatic arthritis, by comparing the ratio of cost and performance, safety and quality of life in the treatment with ustekinumab, adalimumab and infliximab.

The following problems were consistently solved to achieve the desired goal:

1. Determination of modern approaches to the treatment of patients with PsA.
2. Conducting information search for pharmacoeconomic, as well as randomized clinical trials results on the effectiveness of modern methods of PsA treatment;
3. Calculating the cost of PsA treatment with apremilast, ustekinumab, adalimumab, and infliximab.
4. Analysis of costs, cost-efficiency and budget influence to compare switching regimens listed above.

Study horizon

Study horizon was 2 years. The time horizon has been considered with a view to analyzing the costs in future years as the dosing regimens for the first and subsequent years differ due to dose titration in the first few weeks of the drug administration (from 14 days to 2 months depending on the drug), as well as in order to take into account the chronic nature of the disease. Given the long duration of the study, the discounting was carried out. The discount rate was 3.5% per year [15].

Target population

On the basis of the PsA treatment principles described above, as well as the available statistical data [29,30] and IMS Health data base, we can show the potential place of Otezla in the treatment of patients suffering from psoriatic arthritis, as follows (Figure 1):

Thus, the target population of patients taking Apremilast was determined according to the IMU [27], international and Russian recommendations [2,9,10,16], as well as clinical trials [6,20,24]. The patients were represented by persons older than 18 years of age with a confirmed PsA diagnosis (over 6 years), lack of progress in the treatment of disease-modifying anti-inflammatory drugs or other biological drugs as a result of intolerance or poor response to treatment.

Analysis of Efficacy

In the first stage of pharmacoeconomic study, in accordance with the above objective, information retrieval of publications relevant to this study was performed. Search engine query was formulated to take into account the basic keywords: 'psoriatic arthritis', 'clinical trial', 'apremilast or otezla', 'infliximab or remicade', 'adalimumab or humira', 'ustekinumab or stelara', 'biosimilar or biological agent' etc. Also in order to review the publications, information search was performed with the 'Russian Medicine' database of the Central Scientific Medical Library of I.M. Sechenov First MSMU, Scientific Electronic Library elibrary.ru, free search resources such as Yandex, Google, etc. Information search included the following key words: 'psoriatic arthritis,' 'biologics', 'biological agents', 'apremilast, 'Otezla' 'efficiency,' 'clinical trial', 'ustekinumab', 'stelara', 'infliximab', ' remicade', 'adalimumab', 'Humira'.

The search meeting these criteria found 2,000 publications. Next, duplicate publications and studies not related to the problem of the PsA treatment using biologics were excluded; publications of preliminary results were not included in the further analysis. For inclusion in the analysis, the studies were to include data on the number of exacerbations, changes in the Psoriasis Area and Severity Index (PASI), Psoriatic Arthritis Response Criteria (PsARC), the frequency of side effects, as well as the quality of life in the 'Results' section. The strength of recommendations was determined according to the scale of assessment of the strength of recommendations from clinical studies and assessment of evidence levels of the clinical studies. The first studies selected were the ones with A or B strength of recommendations: evidence summarized in a systematic review, meta-analysis, and evidence from prospective randomized clinical trials, respectively. In the absence of these, studies with a lower strength of recommendations were considered. The results were summarized in a special table for analysis and subjected to peer review. Due to the fact that internationally apremilast has been used since recently, the public full text direct and indirect comparative studies with selected alternative regimens have not been found, in connection with this meta-analysis (MA) data [6], presented at the XVIII Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research

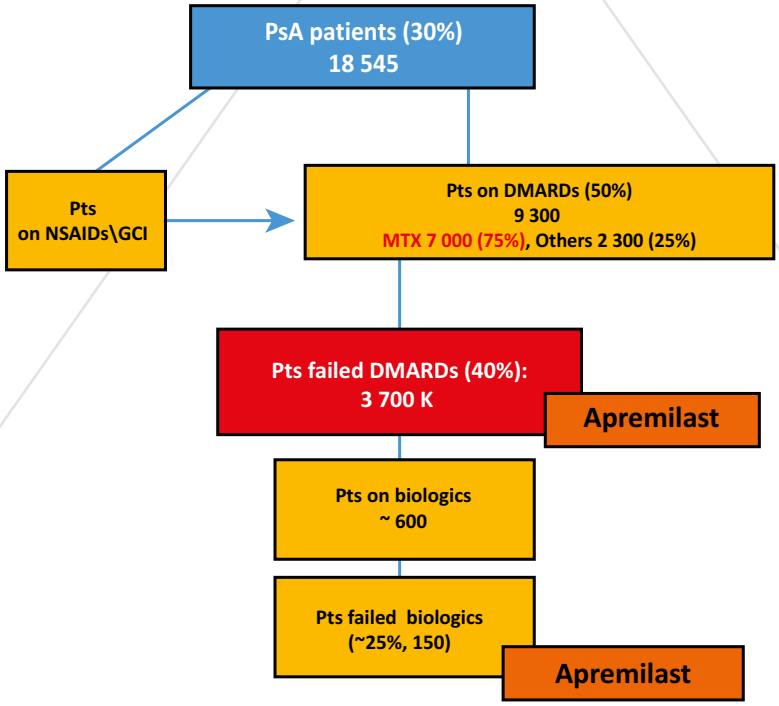

Figure 1. Apremilast place in the treatment of PsA

(ISPOR), were used [11,18]. MA contains data about changes in the PASI scores, as well as the Psoriatic Arthritis Response Criteria PsACR, change in the quality of life score HAQ, which allows us to calculate QALY values for each of the drugs using a special method [3].

Thus, for an objective assessment of response to treatment both in terms of arthritis and psoriasis, based on meta-analysis [6,11,18] QALY has been chosen as an efficiency criterion as it is a flexible parameter that combines both quantitative and a qualitative assessment of the quality of life, and is also of great importance both for the patient and for the healthcare system [24]. However, for the calculation thereof we need to estimate the value of utility under the EQ-5D or SF-36 questionnaire. Therefore, EQ-5D utility values were obtained using the procedure described in studies by Rodgers et al. [3-5], by the formula:

$$Utility = 0.897 - 0.298 \times HAQ - 0.004 \times PASI \quad (1)$$

Where HAQ - quality of life according to the questionnaire, taking into account symptoms, typical of arthritis;

PASI - Psoriasis Area and Severity Index.

Meta-analysis data [6,11,18] on the share of patients who have achieved PASI 75 (due to the fact that this index is considered to be a response to the psoriasis treatment [3,4]), as well as data on HAQ changes were used for the calculation:

Table 1. Meta-analysis data on the clinical efficacy of the drug

INN	PASI 75	PsARC	HAQ change
Apremilast	0,18	0,49	0,22
Ustekinumab	0,32	0,53	0,35
Adalimumab	0,52	0,65	0,35
Infliximab	0,78	0,8	0,75

Using baseline PASI and HAQ described in the studies by Rodgers et al. [3,4] as well as the data listed in Table 1 HAQ and PASI were calculated and substituted in formula 1. Despite the fact that PsACR and ACR were not directly used, response to arthritis treatment was considered in the quality of life according to the HAQ questionnaire [6,26].

Thus, throughout the time horizon amounting to 2 years, the following results were obtained for the comparable treatment alternatives:

Table 2. Efficacy evaluation results according to QALY (with discount)

Treatment regimens	QALY	
	1st and subsequent year	for the entire period (2 years)
Apremilast	0,657	1,277
Ustekinumab	0,696	1,299
Adalimumab	0,696	1,299
Infliximab	0,815	1,522

Based on the efficacy analysis, it can be concluded that the use of apremilast within one year of treatment is characterized by comparable QALY compared to ustekinumab, infliximab and adalimumab.

Cost analysis

Next, cost analysis was performed. At the first stage of cost analysis, monotherapy cost analysis for all compared drugs was carried out, it was further used to calculate the cost of course of pharmacotherapy of the switching regimen.

The cost of monotherapy with the drugs included in the EDL list has been calculated according to the prices of the EDL register as of December 1, 2016 [8]. The price of apremilast planned for registration was provided by Celgene (921 USD at the exchange rate in RUB). The dosage regimen for each drug was determined according to the instructions for medical use of the appropriate drug. The results obtained are shown in Table 3.

Furthermore, it should be noted that the use of infliximab requires additional drugs not included in the drug package - water for injection and sodium chloride solution. Their cost is also calculated on the basis of registered prices of the EDL list according to the average value per 1 mL (the price package section also contains the price of 1 mL). Further, on the basis of the results for the ASD cost and the dosage regimen, the cost of pharmacotherapy courses was calculated for comparable alternatives in the first year of treatment, as well as for 2 years of simulation. The cost of additional drugs was included in the price of the pharmacotherapy course with infliximab.

Table 4. Apremilast dose titration

Day	1	2	3	4	5	6	etc.
Morning	10 mg	10 mg	10 mg	20 mg	20 mg	30 mg	30 mg
Evening	-	10 mg	20 mg	20 mg	30 mg	30 mg	30 mg

Table 3. Data on calculating the average cost (RUB) of the average single dose (ASD) of the compared treatment regimens

Commercial Name	INN	Pharmaceutical form and presentation		Dosing	Package price	ASD cost	Cost of the course, 1st year
		Dosage	Quantity per package				
tablets, film-coated							
Otezla	Apremilast	10,20,30 mg	27	30 mg b.i.d., after dose titration according to the scheme*	RUB 27 867	RUB 1 991	RUB 752 420
		30 mg	56		RUB 57 799	RUB 2 064	
solution for subcutaneous injection, single-dose syringes							
Stelara	Ustekinumab	45 mg/0.5 mL	1	45 mg at weeks 0, 4, and then every 12 weeks	RUB 191,200	RUB 191,200	RUB 1,147,200
Humira	Adalimumab	40 mg/0.8 mL	2	80 mg at week 0, then starting from week 1 - 40 mg every other week	RUB 68,000	RUB 68,000	RUB 952,000
lyophilisate infusion for solution, vials							
Remicade	Infliximab	100 mg	1	5 mg/kg body weight under the scheme on weeks 0, 2 and 6, then every 8 weeks	RUB 43,524	RUB 174,098	RUB 1,393,888
additional drugs for the preparation of infliximab solution							
Water for injection		10 mL	-	10 mL to dissolve the lyophilisate	RUB 0.71	RUB 28	RUB 114
Sodium chloride solution 0.9%		250 mL	-	bring the total volume of the prepared dose to 250 mL	RUB 0.11	RUB 110	RUB 440

* - For apremilast dose titration according to the instructions for use, the following scheme was used:

As can be seen in Table 3, all drugs except apremilast are characterized by injectable route of administration, which entails additional costs for the healthcare services. To calculate the cost of using the subcutaneous dosage forms, it has been assumed that patients use the services of the healthcare professionals throughout the administration of the drugs. Costs of subcutaneous administration were determined according to the Federal Compulsory Medical Insurance Fund Rates in Moscow (as of December 2016) in the amount of RUB 39 per injection [13]. The cost of a single intravenous administration was RUB 694. [7].

The costs of follow-up during ambulatory-outpatient treatment were calculated according to the Federal Compulsory Medical Insurance Fund Rates in Moscow (as of December 2016) [13] on the basis of the current standard of care for the patients with psoriatic arthritis (Russian Ministry of Health Executive Order No. 687n dated November 7, 2012). We took into account only the medical services for the treatment of diseases specified in the standard; and medical services for the diagnosis of the disease were not considered because patients had already been diagnosed with PsA. Thus, the follow-up cost for 1 year was RUB 13,339 for each drug. The cost of medical services was found to be equal in view of the fact that the data on comparison of follow-up services for all the studied drugs was not found in the open information sources. It should be noted that the apremilast application does not require additional follow-up, unlike in case of the reference drugs, however, based on the standards of healthcare, the assumption was made in favor of Humira, Remicade and Stelara.

At the next step, the cost of adverse events (AEs) compensation was calculated. The type and incidence of adverse events due to the lack of data in the MA [6,11,18] have been determined by clinical studies evaluating the effectiveness of a drug and - placebo [19-22]. Also, due to the lack of necessary information, clinical trials with the side effects follow-up of 24 weeks for each of the compared products have been used. The assumption that this frequency corresponds to the frequency in 52 weeks was made in favor of the reference drugs. To compare a 2-year horizon, the extrapolation of values in accordance with a predetermined period of time was performed. However, it should be noted that the number and the frequency of side effects may vary depending on the clinical trial period. For example, the observation of patients taking ustekinumab or adalimumab for 108 weeks reported the occurrence of skin cancer (basal cell carcinoma and other non-melanoma skin cancer) [31,32], which was not observed within shorter study periods. The SE rate for ustekinumab after 60 days was higher than in 24 weeks [32]. Also, the SE rate in the instructions for medical use of Humira, Stelara, and Remicade [33,34,35] is much higher than that in the described studies. Also, the incidence of nosocomial infections was not taken into account due to the lack of information on infections making it difficult to define the tariffs and calculate cost.

When calculating the frequency of side effects for the infliximab, it was assumed that one patient had at least one case of adverse event as data on the number of cases -was not available.

Prices of healthcare services have been calculated on the basis of the relevant standards, clinical guidelines, manuals, tariffs of finished case of treatment or expert opinion, using the Federal Compulsory Medical Insurance Fund Rates in Moscow (as of December 2016) [13]. Due to the fact that apremilast is administered orally, it has significantly fewer side effects. However, frequent adverse effects such as headache, loss of appetite, etc. do not entail serious consequences for the patient, pass within a short time and do not require significant costs.

At the final stage of cost analysis, the total direct medical costs of PsA treatment during 1 and 2 years for each of the compared regimens were calculated. Cost results are presented in Table 5.

As can be seen from the table, apremilast has the lowest total cost per 1 patient for the first year of treatment and 2 years of treatment compared to the ustekinumab, adalimumab and infliximab drugs, due to the lower costs of the course of pharmacotherapy, as well as the lack of the drug administration costs and lower costs of adverse effect compensation.

Cost-effectiveness analysis

In the course of conducting the pharmacoeconomic study, the cost-effectiveness analysis was carried out to calculate the treatment for one patient suffering from PsA. The QALY index was used as an efficiency criterion, it was calculated on the basis of the method described above. The results are presented in Figure 2.

As can be seen from the data obtained, apremilast is characterized by the lowest cost per effectiveness unit - QALY in the first year of treatment, compared to ustekinumab, adalimumab and infliximab. In addition, the cost-effectiveness rate in the following year and throughout the time of treatment for Otezla is lower than that for Humira, Stelara and Remicade.

Budget impact analysis

The next stage of the study was the analysis of budget impact to assess the economic impact on the budget of the healthcare system in case of selection of different treatment regimens. As part of this analysis, assessment of annual pharmacotherapy costs was performed for all regimens at the same time, as well as the assessment of total costs taking into account the entire time horizon (2 years). In addition, to determine the influence on the budget, we implied the possibility to select the number of patients. The number of patients amounted to 1,000 people. We have considered hypothetical situation on the basis of the fact that now the shares of Humira, Remicade and Stelara are distributed uniformly (approximately 33.3%). When simulating the transition of patients to determine the maximum budget savings, it has been assumed that all the patients change to apremilast treatment. Results and patient switching structure are shown in Figure 3.

This calculation allows us to estimate the budget savings in the procurement of various biologics taking into account the changes in the share ratio of the alternatives studied between the current and simulated situations.

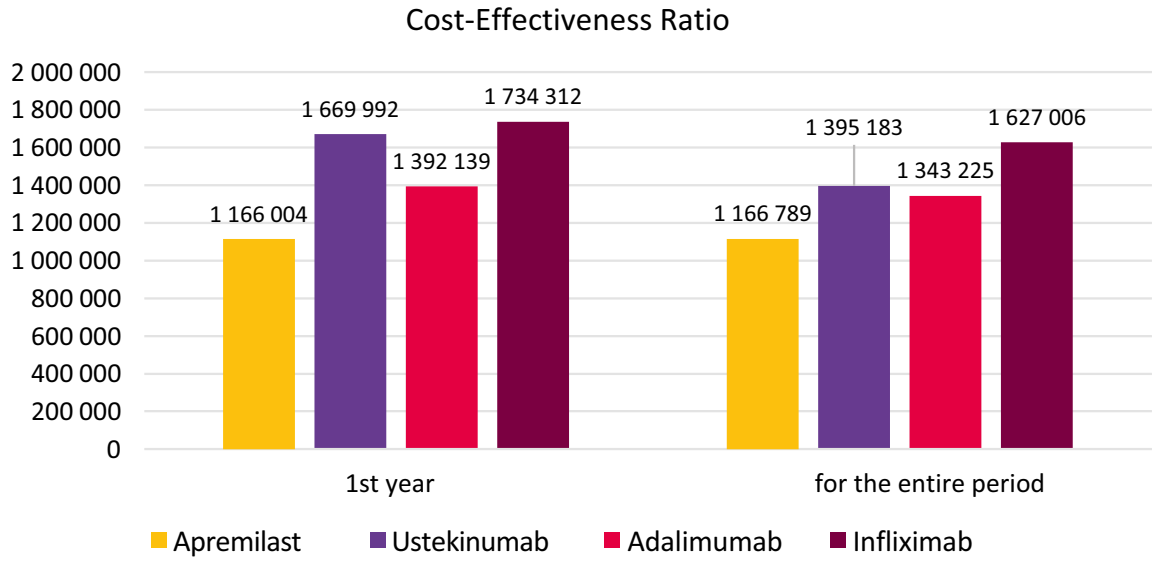

Figure 2. Results of the cost - effectiveness analysis:

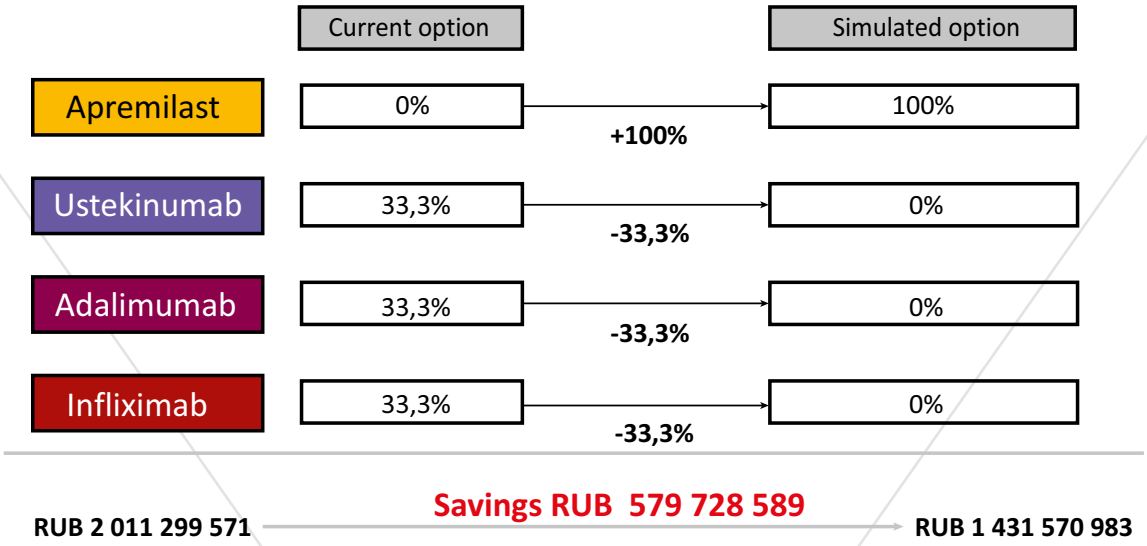

Figure 3. Results of the budget impact analysis

Table 5. Results of costs analysis per one patient taking into account the time horizon and discount

INN	Number of injections	Pharmacotherapy	Introduction	Monitoring	Side effects	Cost amount
Costs for the entire period of the study - 2 years (without discount)						
Apremilast		RUB 1,505,873	RUB 0	RUB 26,677	RUB 984	RUB 1,533,535
Ustekinumab	10	RUB 1,912,000	RUB 390	RUB 26,677	RUB 2,749	RUB 1,941,816
Adalimumab	54	RUB 1,836,000	RUB 2,106	RUB 26,677	RUB 4,718	RUB 1,869,501
Infliximab	15	RUB 2,613,541	RUB 10,410	RUB 26,677	RUB 1,718	RUB 2,652,346
Costs for the entire period of the study - 2 years (with discount)						
Apremilast		RUB 1,405,749	RUB 0	RUB 24,903	RUB 919	RUB 1,431,571
Ustekinumab	10	RUB 1,784 872	RUB 364	RUB 24,903	RUB 2,567	RUB 1,812,706
Adalimumab	54	RUB 1,713,926	RUB 1,966	RUB 24,903	RUB 4,404	RUB 1,745,199
Infliximab	15	RUB 2,439,768	RUB 9,718	RUB 24,903	RUB 1,604	RUB 2,475,993
Costs for the first year						
Apremilast		RUB 752,420	RUB 0	RUB 13,339	RUB 492	RUB 766,251
Ustekinumab	6	RUB 1,147,200	RUB 234	RUB 13,339	RUB 1,375	RUB 1,162,147
Adalimumab	28	RUB 952,000	RUB 1,092	RUB 13,339	RUB 2,359	RUB 968,790
Infliximab	8	RUB 1,393,888	RUB 5,552	RUB 13,339	RUB 859	RUB 1,413,638

Thus, the budget impact analysis showed that switching 1,000 patients to apremilast treatment from ustekinumab, adalimumab and infliximab treatment results in maximum cost savings of RUB 579,728,589 for the whole time horizon of 2 years, as well as costs reduction in the 1st year (on average) of RUB 289,864,294. The budget cost savings per patient are: RUB 579,729 for the whole time horizon, RUB 289,864 for 1 year (on average).

Conclusions

Pharmacoeconomic analysis of apremilast application in the treatment of psoriatic arthritis showed:

1. According to the cost analysis results, the presented cost of treatment with apremilast during the study period of 2 years is on average 27% lower than the cost of treatment with the reference drugs: ustekinumab, adalimumab and infliximab, and the presented cost of the annual treatment with the Otezla reference drug in the 1st year of therapy is 34% lower than the cost of treatment with the Stelara reference drug, 21% lower than that for Humira and 46% lower than that for Remicade.
2. The assessment of costs and efficiency (the ratio of the drug and the reference drugs) showed that treatment with apremilast is characterized by a lower cost per unit of effectiveness QALY demonstrating reduction in the cost-effectiveness indicator for apremilast relative to the indicators of ustekinumab, adalimumab and infliximab both during the first year of treatment and throughout the whole time horizon.
3. The use of the Otezla drug reduces the total direct costs of healthcare under the program of state guarantees of free medical assistance (budget influence) by 29% compared to the use of the following drugs: Humira, Remicade and Stelara.

References

1. Musina F. S. et al. Features of clinical picture and treatment of psoriatic arthritis // 2011. Vol. 4. No. 52. P. 32-36.
2. Taradin G. G. et al. Modern concepts of pharmacotherapy of psoriatic arthritis // 2009. P. 83-91.
3. Bojke L. et al. Modeling the cost-effectiveness of biologic treatments for psoriatic arthritis // 2011. P. 39–47.
4. Rodgers M. et al. for the treatment of psoriatic arthritis : a systematic review and economic evaluation // 2011. V. 15. № 10.
5. Woolacott N. et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technology Assessment 2006; Vol. 10: No. 46
6. PsA Network Meta-Analysis, Celgene 2015 (Data on file. 2016)
7. Kulikov A. Yu., Pochuprina A.A.Pharmacoeconomic evaluation of of treatment with abatacept in patients with rheumatoid arthritis, with inadequate response to methotrexate treatment in the Russian Federation // Pharmacoeconomics: theory and practice. -2016. - Vol. 4, No. 1. - P. 116-122.
8. The state register of maximum sale prices [Electronic resource]. URL http://grls.rosminzdrav.ru/pricelims.aspx (date accessed: 01.12.2016)
9. Federal clinical practice guidelines for the management of patients with psoriatic arthritis. 2015. P.41
10. Shostak N. et al. Decision-making algorithm for choice of tactics management // 2015. V. 9. Pp. 39-46.

11. Mughal F. et al. Cost-effectiveness of Apremilast in Psoriatic Arthritis in Scotland, ISPOR, Milan, 2015 – PMS62
12. Schafer P.H. et al. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. British Journal of Pharmacology (2010), 159, 842–855.
13. Federal Fund of obligatory medical insurance. The tariffs for medical services [Electronic resource]: http://www. mgfoms.ru/strahovye-kompanii/tarifi (date accessed: December 1st 2016)
14. L Gossec et al. Clinical and epidemiological research: Extended report: European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis 2016;75:3 499-510
15. Yagudina R.I., Kulikov A. Yu., Serpik V. G. Discounting during conducting pharmacoeconomic studies // Pharmacoeconomics. Modern pharmacoeconomics and pharmacoepidemiology. 2009. No. 4 p. 10-13.
16. Arthritis Foundation. Psoriatic Arthritis Diagnosis [Электронный ресурс]. URL: http://www.arthritis.org/about-arthritis/types/psoriatic-arthritis/diagnosing.php.
17. Korotaeva T.V. et al.. Psoriatic arthritis: classification,clinical picture, diagnostics, treatment // 2014. Vol. 52, No. 6. P. 650-659.
18. Capri S. et al. Cost-Utility Analysis of Apremilast for the Treatment of Psoriatic Arthritis in the Italian Setting, ISPOR, Milan, 2015 – PMS70
19. Mease, P.J., Gladman, D. D. et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial. Arthritis & Rheumatism, 52: 3279–3289. doi:10.1002/art.21306
20. Mease P.J. et al. Apremilast: A Phosphodiesterase 4 Inhibitor for the Treatment of Psoriatic Arthritis. Rheumatology and Therapy. 2014;1(1):1-20. doi:10.1007/s40744-014-0005-4.
21. Antoni, C. E., Kavanaugh, A. et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis & Rheumatism, 52: 1227–1236. doi:10.1002/art.20967
22. Ritchlin C., Rahman P. et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal anti-body, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological antitumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Annals of the Rheumatic Diseases. 2014;73(6):990-999. doi:10.1136/annrheumdis-2013-204655.
23. Kavanaugh A. et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis 2014;0:1–7. doi:10.1136/annrheumdis-2013-205056
24. Yagudina R. I., Sorokovikov I. V. Methodology of analysis “cost-utility” in conducting pharmacoeconomic research. Pharmacoeconomics Vol. 5, No. 2, 2012 – Pp. 9-12
25. Kubanov A. A., Zyryanov S. K., Belousov D. Yu. Clinical and economic analysis of the effectiveness of biological drugs for the treatment of psoriasis // Qualitative clinical practice. 2015. No. 3, P. 1-8
26. Sizova L. V. Assessment of quality of life in modern medicine // Scientific-practical rheumatology. 2003. No. 2 P. 38-46
27. Instructions for use of the medicinal product for medical use Otesla [Electronic resource]: http://grls.rosminzdrav.ru
28. Instructions for use of the medicinal product for medical use Enbrel [Electronic resource]: http://grls.rosminzdrav.ru
29. The incidence of the entire population of Russia in 2015. Statistics. The Ministry of health Of The Russian Federation. [Electronic resource]: https://www.rosminzdrav.ru (date accessed: 1 December 2016)
30. Nikiphorou E. et al. Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol. 2014 May;33(5):609-14
31. Mease P.J., Ory P. et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year da-ta from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis 2009;68:702–709. doi:10.1136/ard.2008.092767
32. Kavanaugh A., Puig L. et al. Maintenance of Clinical Efficacy and Radiographic Benefit Through Two Years of Ustekinumab Therapy in Patients With Active Psoriatic Arthritis: Results From a Randomized, Placebo-Controlled Phase III Trial. Arthritis Care & Research Vol. 67, No. 12, December 2015, pp 1739–1749 DOI 10.1002/acr.22645
33. Instructions for use of the medicinal product for medical use of Humira [Electronic resource]: http://grls.rosminzdrav.ru
34. Instructions for use of the medicinal product for medical use of Stelara [Electronic resource]: http://grls.rosminzdrav.ru
35. Instructions for use of the medicinal product for medical use of Remicade [Electronic resource]: http://grls.rosminzdrav.ru
36. Menter A., Korman N.J., Elmets C.A. et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol 2009;61:451–85.
37. Burden A.D., Hilton Boon M., Leman J. et al. Diagnosis and management of psoriasis and psoriatic arthritis in adults: summary of SIGN guidance. BMJ 2010;341:c5623.
38. Coates LC., et al. GRAPPA 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis Rheumatol. 2016 May;68(5):1060-71. Link to the text
39. https://www.ncbi.nlm.nih.gov/pubmed/26749174
40. A. L. Bakulev. The strategy of «treating to target» in psoriasis. Actual questions of resistance to biological therapy. Bulletin of dermatology and venereology 2016; (5): 32-38.