№2^{Том 4}
2016

Фармакоэкономика

теория и практика

Pharmacoeconomics
theory and practice

№2^{Volume 4}
2016

- ❑ МЕТОДОЛОГИЯ АНАЛИЗА ЗАТРАТ
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- ❑ РЕПОРТАЖ С X НАЦИОНАЛЬНОГО КОНГРЕССА
С МЕЖДУНАРОДНЫМ УЧАСТИЕМ
"РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ
И ФАРМАКОЭПИДЕМИОЛОГИИ
В РОССИЙСКОЙ ФЕДЕРАЦИИ"
4-5 апреля 2016 года В НИЖНЕМ НОВГОРОДЕ

BUDGET IMPACT ANALYSIS OF TERIFLUNOMIDE (AUBAGIO) PROPOSED INCLUSION INTO THE PROGRAMME '7 HIGH-COST NOSOLOGIES' ON THE BUDGETS OF RUSSIAN FEDERATION FEDERAL AND REGIONAL PUBLIC AUTHORITIES IN THE FIELD OF HEALTHCARE TO ENSURE TREATMENT OF MULTIPLE SCLEROSIS PATIENTS

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Objective: Budget impact analysis of teriflunomide inclusion as first-line disease modifying drugs (DMD) therapy in the List to ensure patients with relapsing-remitting multiple sclerosis (RRMS) within the programme '7 high-cost nosologies' on the budgets of Russian Federation (RF) federal and regional public authorities in the field of health care.

Methods: Budget impact analysis was carried out from the perspective of federal and regional authorities of the RF, time horizon of the analysis: 5 years (treatment costs) and 2 years (effectiveness). Population of analysis: patients with RRMS in the RF. Data on clinical effectiveness of drugs was taken from meta-analysis carried out by the Canadian Agency for Drugs and Technologies of Health (CADTH, Comparative Clinical and Cost Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis, 2014). Within analysis two scenarios were considered: existing and new. In the existing scenario, teriflunomide is not financed within the programme '7 high-cost nosologies'. In this scenario, the drugs included in the List of drugs for provision of patients with multiple sclerosis in accordance with the Decision of the Government of the RF No. 2724-r: interferon beta-1a for intramuscular and subcutaneous injection, interferon beta-1b, glatiramer acetate and natalizumab are considered. In new scenario, teriflunomide is added to the above-listed drugs from 01 January 2017. Total costs for patient management are calculated as a sum of costs for therapy with DMD, costs for administration of DMD, costs for diagnosis and monitoring of MS, costs for relapse treatment. All costs are calculated on the basis of the standards of the Russian Ministry of Healthcare on the management of patients with MS, data from open auctions for purchase of DMDs in the framework of the programme '7 high-cost nosologies' as well as clinical guidelines (teriflunomide) and tariffs of Federal Compulsory Medical Insurance Fund. Proportion of patients with disability progression receiving each drug from the DMD group are calculated on the basis of Saint-Petersburg Center of Multiple Sclerosis data. In the performed budget impact analysis, changes in the structure of use of different DMD because of switching from one drug to another one were taken into account.

Results: The budget impact model was based on the assumption that, in new scenario, teriflunomide will be prescribed to the patients with disability rate increased within the range from 0,5 to 1,49 according to EDSS scale. The proportion of such patients as a result of comparison of average rate in 2015

with 2014 was 11,01%. For natalizumab 2 groups of patients were chosen. The first group - patients in whom EDSS rate has increased by 1,5 and more and there was one and more relapse per year (1,50%). The second group - patients in whom EDSS rate has increased within the range from 0,5 to 1,49 and there was one and more relapse per year (7,39%). In new scenario, natalizumab will be received by the patients from the first group. In existing scenario, it is assumed that natalizumab will be received by the patients from both groups. Total costs of federal and regional authorities for patient management in 2016 are equal to 13 235 940 849,78 RUB. Absence of teriflunomide in the programme is connected with total costs for patient management equal to 15 148 068 132,89 RUB in 2017 and 16 893 811 827,74 RUB in 2018. Inclusion of teriflunomide is connected with total costs for patient management equal to 14 908 830 663,19 RUB (2017) and 16 406 368 100,05 RUB (2018).

Conclusion: Inclusion of teriflunomide into the programme '7 high-cost nosologies' will cause total cost saving for budget of federal authorities of the RF in the field of healthcare of 268 666 174,08 RUB and 517 023 249,99 RUB in 2017 and 2018, respectively, and total costs of federal and regional authorities of the RF in the field of healthcare for provision of patients with multiple sclerosis will be reduced by 239 237 469,70 RUB in 2017 and by 487 443 727,70 RUB in 2018.

Keywords: budget impact analysis, teriflunomide, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic progressive autoimmune disease of the central nervous system observed in working-age population. This disease is characterized by constant increase of irreversible neurological deficit caused by two main pathological processes: immune inflammation and neurodegeneration.

In the world, prevalence rate of MS is 83 cases per 100,000 population, incidence rate is 4,3 cases per 100,000 population [1]. In Russia, these rates vary depending on geographical latitude and are equal to 35-70 cases per 100,000 population and 1-3 cases per 100,000 population, accordingly [2]. Annually, in Russia, approximately 5 thousand new cases of MS are registered [3], and total number of people affected by the disease is estimated at 70 to 150 thousand [2]. The disease is 1,5-2 times more common in women than in men [4]. Clinical manifestations of MS are various, at onset

of the disease the most frequent symptoms are visual impairment in the form of optic neuritis, sensory and motor disturbances. As disease progresses, progressive paresis of extremities, coordination impairment and autonomic dysfunction become leading neurological symptoms causing permanent disability in the patients. At the same time, intensity and severity of the disease symptoms in patients are determined by disease duration. In clinical picture of the disease, it is accepted to identify clinically isolated syndrome (CIS) during which still there are no signs of dissemination in time, relapsing-remitting, secondary progressive and primary progressive course of disease [5]. In 64,1% of multiple sclerosis cases relapsing-remitting course with relapses is observed [6]. Over time the disease converts into the stage of secondary progression when a permanent neurological deficit constantly increases while relapses may present. After 10 years from disease onset 30–37% of patients cannot walk independently, 50% have difficulties in the performance of professional duties, 80% are forced to leave their work because of different manifestations of the disease, and nearly half of them - during the first 3 years after MS diagnosis [7]. After 15 years from disease onset 50% of patients have problems with movement, 30% are unable independently to serve themselves and need a physical assistance [8].

Mortality of MS is equal to 2 cases per 100 thousand population per year [9]. In 50% of cases, infections of respiratory tract (pneumonias) and urinary tract (urosepsis) are the cause of death [9].

Costs for the treatment of MS are great: in 2007, according to Multiple Sclerosis International Federation, the economic burden caused by the disease was 41 334 USD per year per patient. In USA, average costs for one patient with early stage of MS are 8 500 USD per year without immunomodulating therapy, which costs about 12 000–15 000 USD per year, and on the later stages of disease - 77 938 USD [10]. Costs for management of patient with MS are proportional to patient disability degree. For example, in European countries, the cost of treatment of patient with mild degree of disability is 18 000 euro per year, with moderate degree - 36 500 euro per year, with severe degree of disability - 70 000 euro per year [10]. Total costs for the therapy of 1 patient during 2 years are equal to 72 120 USD that exceeds the costs for prevention of disease relapse - 56 594 USD [10].

Accordingly, the progressive nature of disease which causes an increasing evident disability of working-age people, reduced quality of life as well as increased medical and non-medical costs for management of such patients determine medical and social importance of MS [11].

The modern therapy of MS is based on pathogenetic therapy aimed at treatment of relapse periods (treatment courses with corticosteroids, rarely in severe cases - plasma exchange) as well as delaying disease progression with drugs which can modify the course of multiple sclerosis (disease-modifying drugs - DMD). The first DMD drugs with proved efficacy against MS were interferon-beta (INF- β) and glatiramer acetate (GA) that currently remain to have high significance for therapy. But this injection therapy has low efficacy (30%) and cannot fully inhibit the activity of disease in the majority of MS patients. According to the literature data, the low efficacy of interferon beta therapy in some of the patients could be caused by the development of neutralizing antibodies (Nab), the appearance of which occurs between 12–18 months after commencing therapy [14–18]. Depending on the preparation of interferon beta, the rate of Nabs development vary within the range 2–45%. High titers of Nabs cause clinical and radiological activity of multiple sclerosis that is accompanied with the increase in relapse rate by 50%, increase in burden of disease by 17,6%. All of this is accompanied by increased disease progression [15, 19–22].

Another widely discussed issue related to the therapy of any first-line injectable drugs is the adherence of MS patients to DMD treatment which relying on different published data, varies from 70–75% for interferon beta [23] to 49% for glatiramer acetate [24]. Among the most common reasons for patient refusal from the prescribed treatment are the unwillingness to use injection forms (20,4–21,1%) and complications related to the subcutaneous and intramuscular drug injections (32–32,9%) [22]. Also, in certain cases low adherence is related to inability of self-injection [25] that can be managed by the use of oral tablet forms [12]. Bad adherence to prescribed treatment is a key factor of efficacy of ongoing therapy and the remaining clinical and radiological activity of the disease.

During the last 5 years, for the patients with MS new therapies which have an effective influence on different components of pathogenesis were developed. One of such new drugs with a unique mode of action is teriflunomide registered in Russian Federation in 2014. In conducted international clinical trials, teriflunomide has demonstrated an efficacy profile similar to the drugs containing interferon beta and glatiramer acetate [12]. In two large phase III

randomized placebo controlled clinical trials (TEMPO and TOWER), statistically significant delay of neurological deficit progression confirmed over 12 weeks was proved for teriflunomide at the dose of 14 mg compared with placebo and clinically significant influence of the drug on relapse rate of MS at doses 7 and 14 mg [26, 27]. MRI studies data has confirmed clinical efficacy of teriflunomide. A direct comparative trial has demonstrated a comparable clinical efficacy of teriflunomide at the dose of 14 mg and high-dose INF-beta-1a for subcutaneous administration [28]. Review of cumulative data of teriflunomide use at the doses of 7 and 14 mg with totally 2400 patients included has proved that the drug is safe and well tolerated [13]. It is known that, currently, more than 30 000 patients in the world have received the treatment with Aubagio® within the framework of trials and real clinical practice [29].

Teriflunomide is registered and included into various international guidelines for MS treatment as first-line DMD as well as into the reimbursement programmes for the patients with relapsing forms of MS in USA and various European countries [12].

Despite the fact of high clinical relevance and existence of international guidelines, new therapeutic properties aimed to reduce the activity of pathological process and to delay the neurological deficit progression for preventing disability and increase in quality of life are not fully used in the Russian Federation because of the absence of new drugs in the List of drugs for the patients with hemophilia, cystic fibrosis, pituitary nanism, Gaucher's disease, malignancies of lymphoid, blood and related tissues, multiple sclerosis, persons after organ and (or) tissue transplantation (hereinafter referred to as List). The list of drugs is compiled not less than once in 3 years and is approved by the Decision of the Government of the Russian Federation. Purchase of drugs included in the List is financed from the federal budget (programme '7 high-cost nosologies'). Inclusion of the drug into the List makes it possible to use more widely the included drug in clinical practice.

This study is aimed at budget impact analysis of teriflunomide inclusion in the financing of Russian Federation federal and regional public authorities in the field of healthcare (hereinafter referred to as analysis of influence on budget) as a first-line DMD therapy in the List for relapsing-remitting multiple sclerosis patients.

Materials and methods of study

During the budget impact analysis principles of Good Research Practices developed by an International Society for Pharmacoeconomics and Outcomes Research for analysis of budget impact were used [30]. Within the framework of the study, analysis of costs, analysis of impact on budget as well as prediction of number of patients based on logarithmic trend line were done.

Point of view and time horizon of the analysis

Budget impact analysis was carried out from the point of view of federal (Ministry of Healthcare of the Russian Federation) and regional executive authorities of the Russian Federation in the field of healthcare (territorial programme of state guaranties for the citizens of free medical service). Time horizon of the analysis: 5 years. Analysis of treatment costs is carried out for the period from 1 January 2014 to 31 December 2018, effectiveness assessment - from 1 January 2017 to 31 December 2018.

Population of the analysis

The target population is patients with relapsing-remitting multiple sclerosis. On the basis of Federal State Statistics Service data [31] as well as data of All-Russian Organization of Disabled People with Multiple Sclerosis regarding the number of affected people in the Federal Registry of Persons with Multiple Sclerosis (82 700 patients), prevalence of MS in the Russian Federation was calculated (0,056% that is equivalent to 56 patients per 100 000 population). Incidence of multiple sclerosis used in experimental model is 2 per 100 000 population [9]. Number of patients receiving drug therapy within the framework of programme '7 high-cost nosologies' is calculated. It became known that, in 2016, approximately 30 712 (37,1%) patients will be provided with DMD therapy. Taking into account the prevalence of disease equal to 0,056%, the disease diagnosis rate is 96%.

Number of patients receiving disease-modifying drugs, included in the List of drugs for provision of persons affected by multiple sclerosis in accordance with the Decision of the Government of the Russian Federation No. 2724-r of 26 December 2015, is calculated on the basis of auction purchases of drugs for provision of multiple sclerosis patients organized by the Ministry of Healthcare of the Russian Federation in 2008–2015 and published on the Official web-site of United information system for purchasing activities [32] as well as plan-schedule of purchase orders for goods, performance of work, rendering services for state and municipal needs in 2016 (customer - Ministry

of Healthcare of Russia) and information included in the directions for use (table 1).

not less than 2 years according to the most significant criterion of clinical and economical evaluation - disability progression. During modeling of teriflunomide use, the assumption was taken into account that in new scenario the medication will be used by the patients with incomplete response on first-line therapy due to the following reasons:

Table 1. Absolute number of patients receiving different DMD therapy in accordance with data of auction purchases for the period of 2008-2017

Disease-modifying drugs	Actual data									Plan
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Teriflunomide 14 mg	0	0	0	0	0	0	0	0	0	0
Interferon beta-1a 30 µg		470	973	1554	1950	2016	1903	3283	2997	2928
Interferon beta-1b 250 µg	4872	5400	5946	5193	4894	5060	5518	6853	8090	8404
Glatiramer acetate	3836	4774	6020	7189	9175	10838	12788	12800	13246	13355
Interferon beta-1a 44 µg	1322	1615	2539	4015	4933	4901	6254	6378	5903	5355
Natalizumab	0	0	0	0	0	0	0	0	476	936
Total	10030	12259	15478	17951	20952	22815	26463	29314	30712	30977

The proportion of patients which were switched from one of first-line DMD to another one within the first-line therapy (interferon beta-1a, interferon beta-1b, glatiramer acetate) is calculated on the basis of data received from Saint-Petersburg Multiple Sclerosis City Center (hereinafter referred to as SPb MSCC) for 2014-2015 year (population size is 1596 patients). In the analysis, possible changes in the structure of use of different disease-modifying drugs in 2017 and 2018 are considered on the basis of prediction relating to the changes of treatment by the patient from one drug to another one. Relying on data of performed analysis, predictable number of patients who will be treated with any of DMD in 2018 was determined.

Scenarios

In the performed analysis two scenarios were considered: existing at the moment and a new one. In existing scenario teriflunomide is not financed from the state programme '7 high-cost nosologies'. In this scenario, for the treatment of adult patients with MS within the framework of the programme '7 high-cost nosologies' the following drugs are used:

- interferon beta -1a for intramuscular injection;
- interferon beta -1a for subcutaneous injection;
- interferon beta -1b for subcutaneous injection;
- glatiramer acetate;
- natalizumab for intravenous infusions from the second half of 2016.

In the formation of application of subjects of the Russian Federation on centralized procurement of medicines taking into account the additional requirements for 2016 and annual requirement for 2017 the Ministry of health of the Russian Federation recommended to use the following criteria to switch the patients with relapsing-remitting MS from first-line DMDs on a second-line drugs (international nonproprietary name – natalizumab, trade name - Tysabri):

- two or more relapses, which required corticosteroid therapy during the last 12 months;
- disability progression by 2 or more points according to EDSS scale during the last 12 months;
- appearance of one or more active lesions on T1-weighted images or two or more new T2-lesions.

Currently those patients with ineffectiveness of first-line drugs who do not reach the criteria of mentioned above activity and considered as not eligible for 2-nd line treatment are involuntarily switched from one injection drug to another one. Thus it is rarely possible to achieve the stability of process, and therapy escalation is carried out on the later stages of the disease. Existence of first-line drug with another mode of action, in this case teriflunomide, may contribute to the solution of this problem. Patient will continue the therapy with first-line drug, but with another mode of action and the severity of adverse events profile typical for second-line treatment will not increase.

For this reason, during the modeling of new teriflunomide drug prescription, it is proposed to use group of patients with incomplete clinical response to the therapy with interferons beta or glatiramer acetate conducted during

mid use, the assumption was taken into account that in new scenario the medication will be used by the patients with incomplete response on first-line therapy due to the following reasons:

- Nabs occurrence during the therapy with beta interferons;
- absence of adherence to injection therapy.

Due to the fact that at the moment to objectively assess the number of such patients is not possible, we assumed that the effect of the above mentioned variants in these patients may be a significant increase in the level of disability from 0.5 to 1.49 points per year compared with the previous year. We used the average value of increase of level of disability on the EDSS scale for the year in each patient due to the fact that multiple sclerosis occurs as an increase of EDSS level by increasing the activity of the disease, and decline during periods of remission. The range 0,5 – 1,49 points chosen due to the fact that mathematically it is rounded to units, which is a criterion for a review of the treatment of the patient.

The entire model for the purpose of natalizumab based on international criteria for therapy escalation [33] on the basis of which the proportion of patients requiring natalizumab treatment is more than in accordance with the criteria of Ministry of health of Russia. To simulate the use of natalizumab 2 groups of patients requiring therapy escalation were selected. The first group – patients with aggressive multiple sclerosis, who despite ongoing therapy of DMDs during the year have had an increase in disability EDSS score of 1.5 points or more, and experienced one or more relapses per year. The second group – patients with combination of two incomplete response to therapy criteria - the value of EDSS score increased in the range of 0.5 to 1.49 points and registered one or more relapses per year. All other drugs were used without changes, in accordance with the constructed forecast.

Costs

Costs for drug therapy using different drugs were calculated by summing up the costs for drug, its administration and therapy monitoring, relapse management (outpatient and inpatient). Costs for the DMD therapy are taken from the official web-site of United information system for purchasing activities. For teriflunomide and natalizumab the costs are calculated on the basis of maximum retail prices for these medications published in the State Registry of Maximum Retail Prices [34] because the prices for these drugs were registered in 2015 for natalizumab and in 2016 for teriflunomide and auctions for purchase of these drugs has not been carried out by the Ministry of Healthcare of the Russian Federation. Costs of annual therapy course for each drug were calculated as multiplication of number of annually needed packages of drug on the price of one package which is received on the basis of approximate initial contract price indicated in plan-schedule of applications for goods, performance of work, rendering services for state and municipal needs in 2016. The total costs on management of patients with multiple sclerosis were calculated in accordance with the Standard of primary healthcare approved by the Order of the Ministry of Healthcare of the Russian Federation No. 1542n of 24 December 2012 (hereinafter referred to as Standard). The costs for management

of 1 patient with multiple sclerosis in the remission stage were calculated on the basis of summing up the medical costs on the outpatient management of patient (costs for laboratory analysis and instrumental examination methods, costs for consultations of specialists, costs for other medical services) as well as costs on drug therapy during the reporting period - year (365 days) in accordance with the Standard. The calculation of costs for medical services rendered in outpatient conditions, for primary diagnosis and further management of patient was carried out on the basis of tariffs of medical service rendered in outpatient conditions approved from 1 April 2015 by the Ministry of Healthcare of Russia as exemplified by Territorial programme of Moscow Compulsory Medical Insurance [35]. In the model, changes of costs on patient management during the first year and future years of therapy are taken into account because of need for frequent clinical and diagnostic monitoring of therapy safety at the beginning of drug use.

Budget impact analysis and therapy effectiveness

During the modeling, the data on efficacy of different DMDs received from meta-analysis carried out by the Canadian Agency for Drugs and Technologies of Health was taken into account [12]. From this analysis the rates of annual relapse rates for different drugs (table 2) as well as data on disability progression were used (table 3).

Table 2. Annual relapse rate if disease-modifying drugs are used

Disease-modifying drugs	Annual relapse rate [confidence interval]
Teriflunomide 14 mg	0,68 [0,56, 0,83]
Interferon beta-1a 30 µg	0,87 [0,76, 0,98]
Interferon beta-1b 250 µg	0,67 [0,59, 0,77]
Glatiramer acetate	0,67 [0,60, 0,74]
Interferon beta-1a 44 µg	0,67 [0,59, 0,76]
Natalizumab	0,32 [0,26, 0,38]

Risks ratio, confidence interval (CI) 95%.

Table 3. Disability progression if different disease-modifying drugs are used

Disease-modifying drugs	Disability progression in comparison with placebo [confidence interval]
Teriflunomide 14 mg	0.80 [0.50, 1.15]
Interferon beta-1a 30 µg	0.87 [0.67, 1.09]
Interferon beta-1b 250 µg	0.74 [0.50, 0.97]
Glatiramer acetate	0.83 [0.65, 1.02]
Interferon beta-1a 44 µg	0.84 [0.61, 1.08]
Natalizumab	0.67 [0.40, 1.01]

Risks ratio, confidence interval (CI) 95%.

On the basis of received data the budget impact model was created in which the costs for both scenarios were calculated: costs for drugs, cost of their administration, therapy monitoring, relapse management (outpatient and inpatient). Also the calculation of total costs for therapy of patients included in the programme '7 high-cost nosologies' is carried out. For comparison of both scenarios, difference of cost between two scenarios is determined. In execution of Decree of the Government of the Russian Federation No. 871 of 28 August 2014 'On Approval of the Regulations for Preparation of the Lists of Drugs for Medical Use and the Minimum Range of Drugs Required for Rendering Medical Care' quantitative evaluation of clinical and economic effectiveness of medical technology is carried out. For this reason, deviation of costs indicator for the DMD therapy with inclusion of teriflunomide from the costs on the patient management without its use is calculated.

This indicator is calculated using the following formula: [Costs for patient management receiving natalizumab therapy in existing scenario in 2017 - Costs for patient management receiving teriflunomide therapy in new scenario in 2017 / (Costs for patient management receiving natalizumab therapy in existing scenario 2017)] * 100%.

Results

On the basis of the data about the auctions held by the Ministry of health of Russia and the schedule of procurement, and constructed prediction were calculated the number and proportion of patients receiving treatment for a variety of DMDs in 2016-2017. The results are presented in table 4.

Table 4. Proportion of patients receiving different DMDs in accordance with auction purchases for 2008-2016 as well as in accordance with plan-schedule of procurement held by the Ministry of Health of the Russian Federation (2017) and consumption prediction (2018)

Disease-modifying drugs	Auction purchases									Plan	Prediction
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Teriflunomide 14 mg	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%
Interferon beta-1a 30 µg	0,00%	3,83%	6,29%	8,66%	9,31%	8,84%	7,19%	11,20%	9,76%	9,45%	9,06%
Interferon beta-1b 250 µg	48,57%	44,05%	38,42%	28,93%	23,36%	22,18%	20,85%	23,38%	26,34%	27,13%	28,31%
Glatiramer acetate	38,25%	38,94%	38,89%	40,05%	43,79%	47,50%	48,32%	43,67%	43,13%	43,11%	40,16%
Interferon beta-1a 44 µg	13,18%	13,17%	16,40%	22,37%	23,54%	21,48%	23,63%	21,76%	19,22%	17,29%	18,94%
Natalizumab	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	0,00%	1,55%	3,02%	3,53%
Total	100,00%	100,00%	100,00%	100,00%	100,00%	100,00%	100,00%	100,00%	100,00%	100,00%	100,00%

The number of patients who will receive natalizumab and the proportion of patients receiving different DMDs with an increase of average disability score according to EDSS scale in 2015 compared with 2014 are calculated on the basis of data received from SPb MSCC. For analysis of the use of natalizumab 2 groups of patients were determined. The first group – patients whose EDSS score increased by 1.5 points or more, and experienced one or more relapses per year (1.5%). The second group – patients with increased EDSS score in the range of 0.5 to 1.49 points and registered one or more relapses per year (7.39%). In the new scenario, natalizumab will receive patients from the first group. In the existing scenario, the assumption was made that natalizumab will be received by the patients of both groups (table 5).

The number of patients, that in new scenarios will be treated with teriflunomide, and the proportion of patients receiving a variety of DMDs with the increase of the average value of EDSS disability score in 2015 compared with 2014 based on data received from the St. Petersburg MS Center were calculated. On the basis of total number of patients receiving DMDs therapy in the framework of the “7 high-cost nosologies” in 2016 and number of patients who in case of new scenario will receive teriflunomide in 2017-2018 was calculated and is equal to 3380 patients in Russia.

In accordance with data transfer from one drug to another DMD the proportion of patients receiving the variety of DMDs in existing and new scenarios was calculated. In the model it is assumed that the switch to teriflunomide and natalizumab will be gradual because of the need to supply medical establishments with equipment, as well as sharing relevant knowledge and experience with the medical staff. In the simulation used it was assumed that in 2017 teriflunomide will be assigned to 50% of patients from the calculated amount, and in 2018, 100% of patients (3380) will be switched to teriflunomide. In its turn on natalizumab 33% patients of 2 group will be switched in 2017 and 66% patients of 2 group will be transited in 2018 of the total number of 2 group patients who need natalizumab prescription.

Table 5. Proportion of patients if different disease-modifying drugs are used in existing scenario

Disease-modifying drugs	2014	2015	2016	2017	2018
Teriflunomide 14 mg	0,00%	0,00%	0,00%	0,00%	0,00%
Interferon beta-1a 30 µg	7,19%	11,20%	9,76%	9,27%	8,73%
Interferon beta-1b 250 µg	20,85%	23,38%	26,34%	26,61%	27,37%
Glatiramer acetate	48,32%	43,67%	43,13%	41,97%	38,09%
Interferon beta-1a 44 µg	23,63%	21,76%	19,22%	16,69%	17,86%
Natalizumab	0,00%	0,00%	1,55%	5,46%	7,96%

In new scenario of standard therapy, from 1 January 2017, it is proposed to add teriflunomide (table 6):

Table 6. Proportion of patients in case if different disease-modifying drugs are used in new scenario

Disease-modifying drugs	2014	2015	2016	2017	2018
Teriflunomide 14 mg	0,00%	0,00%	0,00%	5,46%	9,91%
Interferon beta-1a 30 µg	7,19%	11,20%	9,76%	8,79%	7,85%
Interferon beta-1b 250 µg	20,85%	23,38%	26,34%	25,96%	26,19%
Glatiramer acetate	48,32%	43,67%	43,13%	40,58%	35,56%
Interferon beta-1a 44 µg	23,63%	21,76%	19,22%	16,20%	16,96%
Natalizumab	0,00%	0,00%	1,55%	3,02%	3,53%

Costs

Costs for annual therapy course with teriflunomide are calculated on the basis of the registered price of teriflunomide 14 mg No. 28 in State Registry of Maximum Retail Prices [34] which is equal to 43 358,00 RUB without VAT (with VAT – 47 693,80 RUB). The maximum contract price for the delivery of the drug for planning of costs for provision of 1 patient with annual therapy course is equal to 620 019,40 RUB.

Costs for management of patients receiving different DMDs is carried out. The minimum total costs and costs for drug therapy were received for Interferon beta-1b (subcutaneous) – 270 288,56 RUB and 218 334,60 RUB, accordingly, maximum – for natalizumab (intravenous) – 1 337 232,00 RUB and 1 284 153,00 RUB.

Total costs for 1 patient management during the reporting period of 365 days with teriflunomide were 671 973,36 RUB. During the calculation of costs for patient management using this drug, additional costs recommended by the manufacturer (directions for use) [35] as well as experts of demyelinating diseases section of All-Russian Society of Neurologists and Executive Committee of the Council of Russian Multiple Sclerosis Researchers Committee (RMSRC) [36], were considered and were equal to 14 301,50 RUB, (table 7). Accordingly, the total costs for patient management during 365 days were 686 274,86 RUB.

Table 7. Costs for additional examination methods and consultation of specialists for the purpose of therapy safety (RUB)

Name	Costs, RUB
Laboratory methods of analysis	12820,95
Instrumental methods of examination	870,36
Consultation of specialists	610,19
Total costs for patient management, RUB	14301,5

Costs for management of 1 patient with multiple sclerosis during relapse without hospitalization (inpatient) in accordance with the tariffs of medical service provided in conditions of day hospital within the framework of Territorial programme of Moscow Compulsory Medical Insurance and Appendices No. 6 and 10 to Tariff agreement for 2016 of 25 December 2015 [37], including drug therapy with methylprednisolone 1000 mg daily IV during 5 days (average duration of treatment) were equal to 10 547,7 RUB.

Costs for management of patients with multiple sclerosis in exacerbation stage with hospitalization (hospital) in accordance with the tariffs of medical service provided in conditions of hospital for completed disease treatment cases within the framework of Territorial programme of Moscow Compulsory Medical Insurance for 2016, including drug therapy with methylprednisolone 1000 mg daily IV during 9 days (average duration of hospitalization) were equal to 64 641 RUB.

Total costs for management of patients with multiple sclerosis in outpatient conditions for different DMDs are given in table 8.

Costs for disease-modifying drugs in 2016 for both scenarios were 11 457 225 174,87 RUB; in 2017, for scenario without inclusion of teriflunomide – 13 253 905 219,70 RUB, with inclusion of teriflunomide – 12 985 239 045,62 RUB; in 2018, without inclusion of teriflunomide – 14 884 667 527,32 RUB, with inclusion of teriflunomide – 14 367 644 277,33 RUB.

Saving of costs of federal budget for use of disease-modifying drugs in case of teriflunomide inclusion into the programme ‘7 high-cost nosologies’ will be 268 666 174,08 RUB in 2017 and 517 023 249,99 RUB in 2018, respectively.

Total costs for patient management including drug therapy with disease-modifying drugs, costs for drug administration and therapy monitoring as well as costs for relapse management at outpatient and inpatient stages of patient management) in 2016 are equal to 13 235 940 849,78 RUB. Absence of teriflunomide in the therapy is connected with costs for patient management equal to 15 148 068 132,89 RUB in 2017 and 16 893 811 827,74 RUB in 2018. Inclusion of teriflunomide into the programme ‘7 high-cost nosologies’ is connected with costs equal to 14 908 830 663,19 RUB in 2017 and 16 406 368 100,05 RUB in 2018. Therefore, the inclusion of teriflunomide will result in saving of 239 237 469,70 RUB and 487 443 727,70 RUB in 2017 and 2018, accordingly (table 9).

Table 8. Costs for management of patients with multiple sclerosis in outpatient conditions, RUB

Name	Drug products					
	Teriflunomide, tablets	Interferon B-1a (IM)	Interferon B-1a (SC)	Glatiramer acetate (SC)	Interferon B-1a (SC)	Natalizumab (IV)
Costs for laboratory methods of analysis, RUB	4 985,6	4 985,6	4 985,6	4 985,6	4 985,6	4 985,6
Costs for instrumental methods of examination, RUB	12 751,5	12 751,5	12 751,5	12 751,5	12 751,5	12 751,5
Costs for consultations of specialists, RUB	2 468,86	2 468,86	2 468,86	2 468,86	2 468,86	2 468,86
Costs for drug therapy, RUB	620 019,40	223 735,20	218 334,60	400 982,40	533 950,56	1 284 153,00
Costs for medical services, RUB	31 748,00	31 748,00	31 748,00	31 748,00	31 748,00	32 873,04
Total costs for management of 1 patient during the reporting period of 365 days, RUB	671 973,36	275 689,16	270 288,56	452 936,36	585 904,52	1 337 232,00
Costs for additional measures recommended by manufacturer, RUB	14 301,50					
Total costs for management of 1 patient during the reporting period of 365 days taking into account additional costs (according to the opinion of expert and manufacturer), RUB	686 274,86	275 689,16	270 288,56	452 936,36	585 904,52	1 337 232,00

Table 9. Comparative evaluation of costs of new and existing scenarios

Costs for drugs, RUB	2014	2015	2016	2017	2018
With teriflunomide	10 091 514 586,77	10 474 094 197,06	11 457 225 174,87	12 985 239 045,62	14 367 644 277,33
Without teriflunomide	10 091 514 586,77	10 474 094 197,06	11 457 225 174,87	13 253 905 219,70	14 884 667 527,32
Difference	0,00	0,00	0,00	268 666 174,08	517 023 249,99
Costs for drug administration, RUB	2014	2015	2016	2017	2018
With teriflunomide	0,00	0,00	593 429,47	1 234 342,59	1 533 224,88
Without teriflunomide	0,00	0,00	593 429,47	2 231 995,32	3 456 334,79
Difference	0,00	0,00	0,00	997 652,73	1 923 109,92
Costs for therapy monitoring, RUB	2014	2015	2016	2017	2018
With teriflunomide	1 374 025 243,26	1 481 288 441,10	1 588 628 095,22	1 720 927 303,63	1 823 487 340,79
Without teriflunomide	1 374 025 243,26	1 481 288 441,10	1 588 628 095,22	1 696 377 777,58	1 803 148 499,79
Difference	0,00	0,00	0,00	24 549 526,05	20 338 841,00
Costs for relapse management, RUB	2014	2015	2016	2017	2018
With teriflunomide	169 857 966,82	181 577 578,07	189 494 150,22	201 429 971,35	213 703 257,05
Without teriflunomide	169 857 966,82	181 577 578,07	189 494 150,22	195 553 140,28	202 539 465,85
Difference	0,00	0,00	0,00	5 876 831,06	11 163 791,21
Total costs, RUB	2014	2015	2016	2017	2018
With teriflunomide	11 635 397 796,84	12 136 960 216,23	13 235 940 849,78	14 908 830 663,19	16 406 368 100,05
Without teriflunomide	11 635 397 796,84	12 136 960 216,23	13 235 940 849,78	15 148 068 132,89	16 893 811 827,74
Difference	0,00	0,00	0,00	239 237 469,70	487 443 727,70

Indicator deviation of costs reduction for disease-modifying drugs with teriflunomide inclusion in comparison with the costs for patients treatment without its use is calculated using the following formula:

[Costs for natalizumab therapy in existing scenario in 2017 - Costs for teriflunomide therapy in new scenario in 2017 / (Costs for natalizumab therapy in existing scenario 2017)] * 100% = [(1693 patients * 1 284 135 RUB) - (1690 patients * 620 019,40 RUB) / 1693 persons * 1 284 135 RUB] * 100% = **51,80%**.

Sensitivity analysis

- In case of 10% price discount for all drugs except teriflunomide:
- In case of 10% discount for all drugs except teriflunomide, inclusion of teriflunomide into the programme '7 high-cost nosologies' for use of analysis in the population provides reduction of costs for purchase of drugs by 131 488 032,01 RUB in 2017 and by 252 467 812,95 RUB in 2018 for federal budget and savings in amounts by 102 059 327,62 RUB

and 222 888 290,66 RUB, accordingly, for budgets of federal and regional bodies of state authority of the Russian Federation in the healthcare field.

- In case of 17.5% price discount for all drugs except teriflunomide:

In case of 17.5% discount for all drugs except teriflunomide, inclusion of teriflunomide into the programme '7 high-cost nosologies' for use of analysis in the population provides reduction of costs for purchase of drugs by 28 604 425,45 RUB in 2017 and by 54 051 235,18 RUB in 2018 for federal budget and savings in amounts by 24 471 712,88 RUB in 2018 for budgets of federal and regional public authorities of the Russian Federation in the field of healthcare. In such case, the use of teriflunomide in 2017 will be more expensive by 824 278,93 RUB.

Discussion

For the first time, in the conditions of Russia, budget impact analysis of teriflunomide (Aubagio) inclusion in the budgets of federal and regional public authorities of the Russian Federation in the field of healthcare to provide support for patients with relapsing-remitting multiple sclerosis as a first line therapy was conducted. Two scenarios were compared:

- existing (without teriflunomide use) when natalizumab is prescribed to all patients on first-line DMD therapy with EDSS disability score increase from 0,5 to 1,49 points and at least one registered relapse and to patients with EDSS score increase on 1,5 or more points and one or more registered relapse per year;
- new when teriflunomide was prescribed to the patients with EDSS score increase from 0,5 to 1,49 points, and natalizumab was prescribed to the patients with EDSS score increase on 1,5 or more points and one or more registered relapses per year.

Costs for drug therapy using different drugs were calculated through summing up the costs for: drug, its administration and therapy monitoring, relapse management (outpatient and inpatient). As a result, it was shown that the costs for disease-modifying drugs in 2016, in both scenarios, were 11 457 225 174,87 RUB, in 2017, for the scenario without inclusion of teriflunomide - 13 253 905 219,70 RUB, with inclusion of teriflunomide - 12 985 239 045,62 RUB; in 2018, without inclusion of teriflunomide - 14 884 667 527,32 RUB, with inclusion of teriflunomide - 14 367 644 277,33 RUB. In 2016, costs for patient management including costs for drug therapy with disease-modifying drugs are equal to 13 235 940 849,78 RUB. Absence of teriflunomide in the therapy is connected with the costs for patient management equal to 15 148 068 132,89 RUB in 2017 and 16 893 811 827,74 RUB in 2018. Inclusion of teriflunomide in the programme '7 high-cost nosologies' is connected with costs for therapy equal to 14 908 830 663,19 RUB in 2017 and 16 406 368 100,05 RUB in 2018.

Conclusions

1. Inclusion of teriflunomide into the programme '7 high-cost nosologies' and its use in the patients with multiple sclerosis with EDSS score increase from 0,5 to 1,49 points is economically more profitable than its absence in this programme.
2. Saving of costs for the use of disease-modifying drugs in case of inclusion of teriflunomide into the programme '7 high-cost nosologies' will be 268 666 174,08 RUB in 2017 and 517 023 249,99 RUB in 2018.
3. Inclusion of teriflunomide will cause total cost saving 239 237 469,70 RUB and 487 443 727,70 RUB in 2017 and 2018, accordingly.
4. Indicator deviation of costs reduction for disease-modifying drugs with teriflunomide inclusion in comparison with the costs for patient management without its use is equal to 51,80%.

Model restrictions

During presenting the results of this study, it is necessary to take into account the model restrictions:

1. Clinical effectiveness data were taken from Canadian meta-analysis because of the most full presentation of results of comparative evaluation of all analyzed drugs. In the meta-analysis, data of TOWER study, in which teriflunomide 14 mg has shown higher efficacy in terms of Average Annual Relapse Rate and Disability Consistent Progression over 12 weeks, were not included. In the meta-analysis, it was not taken into account that in TEMSO study only 91% of patients had relapsing-remitting multiple sclerosis, and 9% of patients had secondary progressive MS and primary progressive MS, for this reason teriflunomide 14 mg effectiveness data (Average Annual Relapse Rate and Disability Consistent Progression over 12 weeks) can be lower than in the populations studied without secondary progressive MS and primary progressive MS.

2. Costs of patient management were calculated on the basis of Moscow Compulsory Medical Insurance Fund data. In other regions, these costs can be lower, but it does not influence on the analysis results.
3. Proportions of patients and costs were calculated on the basis of 2016-2018 data (population: 3380 patients).
4. In the model, inflation and discounting were not considered. It is also assumed that the medical service price will remain the same in 2017 and 2018, and the population of the Russian Federation and the incidence of multiple sclerosis will not change in Russia.

References

1. Miroshnikova V. V., Saranov, A. A., Arakelyan A. S., Rybak V. A. Modern therapy of multiple sclerosis // . – 2013. – No. 1 (49). – Vol. 7.
2. Boiko A. N. Comparative analysis of clinical and demographic parameters of the PC with an early debut in two populations (Moscow, Russia and Vancouver, British Columbia, Canada) I A. N. Boiko, O. V. Bykova, S. N. Fedosova, etc. II Neuroimmunology. — 2003. No. 1. — P. 38-44.
3. Electronic resource: http://www.center-hc.ru/diseases/multiple_sclerosis/epidemiology_of_multiple_sclerosis.htm. (available at: 29.02.2016)
4. Schmidt, T. E., Yakhno N. N. Multiple sclerosis: a guide for physicians. – M: MEDpress-inform, 2010.
5. Lublin F., Reingold S.C., Cohen J.A. et al. Defining the clinical course of multiple sclerosis. Neurology 2014; 83:278-286.
6. Electronic resource: <http://www.dissercat.com/content/epidemiologiya-i-klinicheskaya-kharakteristika-rasseyannogo-skleroza-v-g-irkutskke>. (available at: 29.02.2016)
7. Global economic impact of multiple sclerosis. Literature Review Prepared for Multiple Sclerosis International Federation London, United Kingdom.
8. Munschauer F. et al. Rationale for early treatment with interferon beta-1a in relapsing-remitting multiple sclerosis Clin Ther. 1997;19:868.
9. Zavalishin I. A., Piradov M. A., Boyko A. N., Nikitin S. S., Spirin N. A., Peresedova A. V. "Autoimmune disease in neurology" vol. 1. Regional Public Organization of Disabled People "Human Health", Moscow 2014.
10. Likhachev S. A., Bunyak A. G. Pharmacoeconomic studies of the drugs with immunomodulatory effects in the treatment of multiple sclerosis // Medical news. – 2012. – No. 1. – P. 45-49.
11. Schwartz G. J. Pharmacoeconomic rationale for the use of drugs for preventive treatment in some patients with multiple sclerosis I G. J. Schwartz II Neurological journal. — 2001. No. 1. — P. 43-47.
12. CADTH Therapeutic Review: Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis, October 2013 Volume 1, Issue 2B Updated March 2014.
13. Leist T, Freedman MS, Kappos L et al. Pooled safety data from three placebo-controlled teriflunomide studies. Mult Scler 2013; 19: 74 P633.
14. Bertolotto A., Capobianco M., Amato M.P. et al. Guidelines on the clinical use for the detection of neutralizing antibodies (Nabs) to IFN beta in multiple sclerosis therapy: report from the Italian Multiple Sclerosis Study group // Neurol. Sci (2014) 35:307-316.
15. Sorensen P.S., Deisenhammer F., Duda P., Hohlfeld R., Myhr K.M., Palace J., Polman C., Pozzilli C., Ross C. (2005) Guidelines on use of anti-IFN beta antibody measurements in multiple sclerosis: report of an EFNS Task Force on IFN-beta antibodies in multiple sclerosis. Eur J Neurol 12:817–827.
16. Polman C.H., Bertolotto A., Deisenhammer F., Giovannoni G., Hartung H.P., Hemmer B., Killestein J., McFarland H.F., Oger J., Pachner A.R., Petkau J., Reder A.T., Reingold S.C., Schellekens H., Sorensen P.S. (2010) Recommendations for clinical use of data on neutralizing antibodies to interferon-beta therapy in multiple sclerosis. Lancet Neurol 9(7):740–750.
17. Paolicelli D., D'Onghia M., Pellegrini F., Drenzo V., Iaffaldano P., Lavalpe V., Trojano M. (2013) The impact of neutralizing antibodies on the risk of disease worsening in interferon b-treated relapsing multiple sclerosis: a 5 year post-marketing study. J Neurol 260(6):1562–1568.
18. R.A. Farrel, G. Giovannoni. Current and future role of Interferon beta in therapy of Multiple Sclerosis. J Int Cyt Res 2010; 30 (10): 715-726.
19. Hartung H., Munschauer F. Assessment and management of neutralizing antibodies in patients with multiple sclerosis // J. Neurol. – 2004. – Vol. 251 (Suppl. 2). – P. 40-42.
20. Rudick R., Simonian N., Alam J. et al. Incidence and significance of neutralizing antibodies to interferon beta-1b in MS// Neurology. – 1998. – Vol. 50. – P. 1266-1272.
21. Sorensen P., Ross C. et al. Clinical importance of neutralizing antibodies against interferon beta in patients with relapsing-remitting multiple

- sclerosis // *Lancet*. – 2003. – Vol.362. – P.1184-1191.
22. Vartanian T., Sorensen P., Rice G. Impact of neutralizing antibodies on the clinical effect of interferon beta in multiple sclerosis // *J. Neurol.* – 2004. – Vol. 251 (Suppl. 2). – P.25-30.
23. Devonshire V., Lapierre Y., Macdonell R., Ramo-Tello C., Pattie F., Fontoura P., Suchet L., Hyde R., Balla I., Frohman E.M., Kieseier B.C. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis // *European Journal of Neurology* 2010.
24. Oura A., Kovac L., Sasa-Sega. Adherence to disease-modifying therapies and attitudes regarding disease in patients with multiple sclerosis // *Clinical Neurology and Neurosurgery* 115S (2013) S6–S11.
25. Sidorenko T. V. Commitment to long-term therapy with drugs that modify the course of multiple sclerosis: extended abstract of Cand. Sci. (Medicine) Dissertation: 14.00.13 – nervous diseases/ Sidorenko Tatiana Valerievna. – M., 2009. – 22p.
26. O'Connor P., Li D., Freedman M. et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. *Neurology*. 2006; 66(6): 894-900
27. O'Connor P., Wolinsky J.S., Confavreux C. et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *The New England Journal of Medicine*. 2011;365(14):1293-1303
28. Tallantyre E., Evangelou N., Constantinescu C.S. Spotlight on teriflunomide. *The International MS Journal* 2008; 15: 62-68
29. Press release Genzyme to Feature Multiple Sclerosis Pipeline and Present New Data on Aubagio and Lemtrada at ECTRIMS 2014. September 8, 2014
30. Sullivan S., Mauskopf J., Augustovski F., Penna P., Barrios J.M., Shau W.Y. Budget Impact Analysis – Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force // *Value in Health* 17 (2014) 5-14.
31. Electronic resource: <http://www.gks.ru/>. (available at: 1.03.2016)
32. Electronic resource: <http://zakupki.gov.ru/>. (available at: 1.03.2016)
33. Gold R et al. Therapeutic goals of platform and escalation therapies for relapsing-remitting multiple sclerosis. *Aktuel Neurol*. 2012;39 (7): 342-350.
34. Electronic resource: <http://grls.rosminzdrav.ru/>. (available at: 03.03.2016)
35. Instruction for medical application of Aubagio (teriflunomide). Electronic resource: <https://health.mail.ru/drug/abadzhio/>. (available at: 1.03.2016)
36. Electronic resource: <http://ructrims.itdevelopers.ru/> (available at: 29.02.2016)
37. Electronic resource: <http://www.mgfoms.ru/>. (available at: 1.03.2016)