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Economic Effectiveness Of Interferon Gamma In The Treatment Of Tuberculosis.

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ABSTRACT

Tuberculosis is a socially significant disease in Russia. One of the ways to improve the effectiveness of its treatment is to use interferon gamma as a part of antibacterial therapy; clinical studies demonstrated that this drug is highly effective for the treatment of tuberculosis. The aim of this study was to evaluate the economic effectiveness of interferon gamma in a complex therapy of tuberculosis. Pharmacoeconomic analysis showed that interferon gamma lead to the increase of quality adjusted life expectancy by 2.1 QALY; up to 284 million RUB savings for the Russian budget; or up to 27.3% savings for the treatment of this group of patients.
Keywords: tuberculosis, interferon gamma, budget impact analysis, QALY.

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INTRODUCTION

In 2016, about 78,000 new cases of active tuberculosis were diagnosed in Russia. The morbidity was 53.2 per 100,000 population, while the mean annual morbidity was 71.9 per 100,000 population. [1]
Figure 1 presents the dynamics of tuberculosis morbidity in Russia. The highest morbidity in the last decade was observed in Siberia and in the Russian Far East. [1]

Figure 1. The dynamics of tuberculosis morbidity in Russia. [1]

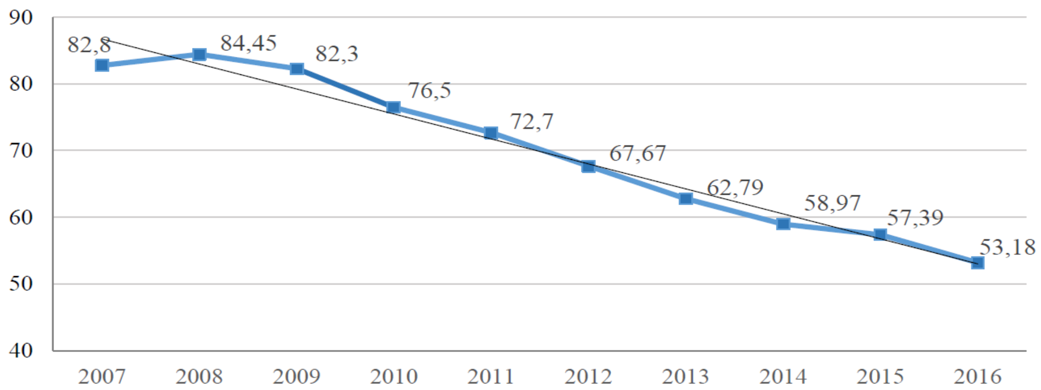

Table 1. The highest rate of Tuberculosis morbidity in Russia. [1]

	Region	General population			Rural population		
		Morbidity	Change in 2014-2016, %	Mean annual morbidity in 2006-2015	Morbidity	Change in 2014-2016, %	Mean annual morbidity in 2006-2015
	Russian Federation	53.18	−10.4	71.88	58.04	−9.1	77.36
1	Tyva Republic	178.25	23.0	212.07	161.91	6.4	222.65
2	Chukotka Autonomous Okrug	172.25	28.8	109.91	336.85	24.9	197.59
3	Primorsky Krai	127.80	−4.4	169.48	152.34	−0.5	199.38
4	Jewish Autonomous Oblast	126.75	−5.5	160.93	136.17	−15.7	175.87
5	Irkutsk Oblast	108.33	−11.0	133.82	109.05	1.8	124.60
6	Khabarovsk Krai	102.81	−3.0	123.45	122.80	−8.3	145.16
7	Kemerovo Oblast	102.16	−5.6	128.22	98.69	−8.7	128.75
8	Altai Krai	99.76	−6.4	121.37	96.05	6.9	106.51
9	Novosibirsk Oblast	97.95	−6.6	120.48	116.02	3.8	129.36
10	Kurgan Oblast	96.67	9.4	122.29	95.22	22.4	124.67
11	Astrakhan Oblast	96.28	1.9	93.23	111.93	38.1	99.07

The general mortality from tuberculosis in 2017 declined by 16% compared to 2016, and by 55.8% compared to the year 2005, when the peak value (22.6 per 100,000 population) was observed [1].

One of the main obstacles in the treatment of tuberculosis is the rapid development of strains resistant to the current antimicrobial therapy. The creation of new classes of anti-tuberculosis drugs can significantly improve the results of treatment. Patients infected with drug-resistant strains of mycobacteria are a separate problem. [2-5] The results of treatment also depend on concurrent diseases (HIV etc.), living conditions, and social status of patients. [2-8] The groups of highest risk include inmates of the Federal Penitentiary Service of Russia (FSIN) and HIV positive persons.

Active search for new therapeutic agents has been performed in the last decades in order to increase the effectiveness of the existing anti-tuberculosis therapy and to overcome the problem of drug resistance interferon gamma is one of the medical drugs that can change the progression of fibrocaseous tuberculosis as a part of a comprehensive antimicrobial therapy. [2-9] Its effectiveness was studied in several randomized clinical trials. A meta-analysis of nine clinical trials demonstrated a statistically significant effect of interferon gamma as an additional drug in the treatment of tuberculosis [10]. The studies with interferon gamma aerosol showed statistically significant advantages revealed by negative conversion of sputum culture and chest X-ray examination. A total relative risk (RR) for the conversion was 1.97 (95% CI: 1.20—3.24; p = 0.008) after 1 month of treatment; 1.74 (95% CI, 1.30—2.34; p = 0.0002) after 2 months of treatment; 1.53 (95%, CI 1.16—2.01; p = 0,003) after 3 months of treatment; 1,57 (95% CI 1.20—2.06; p = 0,001) after 6 months of treatment, and 1.55 (95% CI 1.17—2.05; p = 0,002) in the end of treatment. Total RR for chest X-ray examination was 1.38 (95% CI 1.10—1.17; p = 0,006) in the end of treatment [9]. A meta-analysis for intramuscular administration of interferon gamma included three studies and showed a significant improvement of negative conversion of sputum culture after two months of treatment. A randomized controlled trial of aerosol and subcutaneous administration of interferon gamma showed a significant decrease of fever, crackles, and night sweats after one month of treatment compared to the control group. Its authors concluded that the adjuvant therapy with interferon gamma, especially in a form of aerosol, may be useful for patients with tuberculosis [10].

MATERIALS AND METHODS

Several types of analyses were performed. On the first stage, the impact of the addition of a recombinant human interferon gamma to the therapy of tuberculosis was assessed for the health care system. To do this, the cost of the treatment with this drug, and its effect on the reduction of hospital stay were compared. Clinical data were taken from a clinical trial of recombinant human interferon gamma in patients with newly diagnosed tuberculosis with lung destruction (A. A. Maslennikov, N. I. Obolonkova, 2012). The data on the cost of hospital stay were obtained from the work by Yu.M. Markelov et al. [11]. The cost of basic therapy was excluded from the cost of a bed day; it was assumed to be equal in groups with and without interferon gamma. The costs were then recalculated to the prices of 2016 using the information on the dynamics of consumer price index. It was assumed that patients are discharged from hospitals, if they are abacillary according to smear microscopy. After that, a probable duration of hospital stay was defined based on the data of the clinical trial. These results included the time when patients became abacillary according to smear microscopy; therefore if was assumed that the discharge occurs once a month. This assumption was used to evaluate the costs of hospital stay. Within three months of observation, all patients in the group of recombinant human interferon gamma (Ingaron) became abacillary according to the results of smear microscopy. However, this was not the case in the group of standard therapy. An attempt was made to evaluate possible duration of hospital stay for the rest of patients based on average time of hospital stay. To do this, the duration of hospital stay in the last group was iteratively changed until the average time was 73.5 bed days as in Yu. M. Markelov et al. [11]. The cost of hospital stay per patient was then assessed in compared groups with consideration for the cost of therapy with the studied drug. The data on the cost of therapy were obtained from the registered price of interferon gamma according to the List of Vital and Essential Drugs (http://grls.rosminzdrav.ru/). It was 4341.6 RUB per a pack of five flasks of lyophilizate for the preparation of solution containing 500,000 ME of recombinant human interferon in one flask. In the clinical study, the recombinant human interferon gamma was administered every second day for one month. Accordingly, a course consisted of fifteen injections or five packs of the drug.

The number of patients with potential indications for the treatment with recombinant human interferon gamma was calculated based on the characteristics of patients, who received this therapy in the clinical study, i.e. lung destruction and newly diagnosed tuberculosis. In 2016, there were 24,497 such patients in Russia according to official statistics.

In order to evaluate the long-term effectiveness of the drug expressed in universal values (quality-adjusted life years), a Markov model was built that included three main states, i.e. active tuberculosis, cured tuberculosis and death. The transition from active form of tuberculosis to the cured state was modeled based on the data on absence of mycobacteria of tuberculosis in sputum culture in the clinical trial. To obtain information on the distribution of time to recovery, the data in the clinical trial were subject to a parametric survival analysis (analysis of time to recovery) using LIFE REG procedure of SAS University Edition system (not all patients were completely cured in the end of trial; they were considered as censored observations). It was found that the data are better approximated with exponential distribution, and this type of distribution was used to create a model.

The model included several parametric distributions, which were used to form a matrix of transitions, i.e. time to recovery in control groups (p1) and administration of recombinant human interferon gamma (p4), and survival time. To define the survival time in the group of patients with active tuberculosis (p2), data by V. M. Kolomiyets et al. [12] were used. It was assumed that the life duration of cured patients is the same as in the general population. Respective distribution parameters (p3) were evaluated based on a life expectancy of persons of the same age as the average age of participants in the clinical trial (data from Zdravookhraneniye v Rossii [Health in Russia] statistical compilation) [13]. The pattern of the model for patients in the group that received recombinant human interferon gamma is shown in Figure 2.

The utilities of the states of active and cured tuberculosis were taken from a study by L. Wolfson et al. [14]. According to the recommendations of this article, the utilities were lower in the first year after recovery. The utilities for the calculation of quality-adjusted life years were discounted with 3% annual rate. The horizon of the model was 50 years.

Markov model was implemented in heemod package [15] in R system for Windows (version 3.3). The budget impact analysis and the calculation of the cost of compared therapies with respect of the duration of hospitalization were calculated in Microsoft Excel.

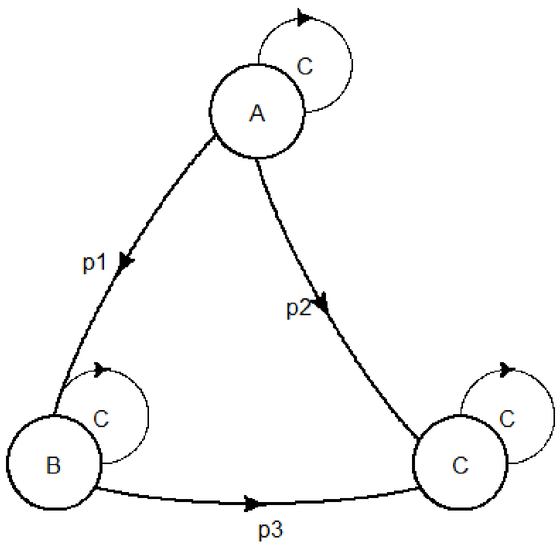

Figure 2. The pattern of the model (A — active tuberculosis, B — cured tuberculosis, C — death).

RESULTS

Initially, the evaluation of costs of therapy with recombinant human interferon gamma was performed for the health care system. Based on the data of clinical trial, it was established that the total cost of therapy and hospital stay was 40,979 RUB in group of recombinant human interferon gamma (Ingaron), and 56,386 in the group without this drug (standard therapy not included). Therefore, the drug was more cost-effective, and a budget impact analysis was possible (Table 2).

Table 2. Budget impact analysis

Value	Source data	Budget savings, million RUB/year
Difference in costs (RUB/person) in case of administration of recombinant human interferon gamma (Ingaron)	15,407 (to the advantage of the administration of the drug)	
Number of new cases	24,497	
Frequency of use:		
10%		37.74
20%		75.48
50%		188.71
75%		283.07

Table 2 shows that the budget savings depend on the frequency of the use of the drug in the therapy of tuberculosis with lung destruction. Budget savings will be 37.7 million RUB if the drug is used in one tenth of all patients with newly diagnosed tuberculosis, if indicated. If three fourths of such patients receive the drug, the savings will be 283.7 million RUB. In this case, the reduced of duration of hospital stay alone may result in up to 27.3% budget savings.

The administration of the studied drug appeared to be a dominant strategy, therefore cost-efficiency analysis was unnecessary. However, the effectiveness of the drug from the point of impact on life quality was assessed, which was expressed as a quality-adjusted life years (QALY). The result of this assessment is shown in Table 3.

Table 3. The results of modelling

Value	Recombinant human interferon gamma (RHIG) with standard therapy	Standard therapy only
Quality-adjusted life years (QALY)	8.65	6.55
Years of life	17.67	13.37
Difference in QALY between RHIG and control groups	2.1	

Table 3 shows that the use of recombinant human interferon gamma as an additional therapy of newly diagnosed tuberculosis with lung destruction leads to 2.1 more quality-adjusted life years, and to the increase of life duration.

CONCLUSIONS

The analysis showed that the use of recombinant human interferon gamma in Russia as a part of comprehensive therapy of newly diagnosed tuberculosis with lung destruction leads to an increase of quality-adjusted life duration (2.1 QALY). It also results in up to 284 million RUB savings for the Russian budget, or 27.3% lesser cost of treatment in this group of patients.

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