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The Burden of Migraine in Real Clinical Practice: Clinical and Economic Aspects

M. V. Naprienko,^{1,2} L. V. Smekalkina,² M. I. Safonov,² E. G. Filatova,^{1,2} N. V. Latysheva,^{1,2}
E. V. Ekusheva,¹ A. R. Artemenko,² V. V. Osipova,^{2,3} and L. I. Baiushkina¹

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Objectives. To assess the value of using different treatment schemes in chronic migraine by comparing clinical results and the economic burdens of disease in real clinical practice. **Materials and methods.** The study included 66 patients attending the Academician Aleksandr Vein Headache and Autonomic Disorders Clinic: 60 women and six men aged 28–51 years with diagnoses of chronic migraine. The patients were divided into three groups: group 1 ($n = 22$) consisted of patients who received three months of oral prophylactic therapy with topiramate at doses of up to 100 mg/day; patients of group 2 ($n = 20$) received 12 sessions of acupuncture with three procedures per week; patients of group 3 ($n = 24$) received injections of botulinum toxin type A (Botox, BTA) at a dose of 155–195 U. The observation period was three months. Treatment efficacy was assessed using the following methods: clinical-neurological assessment, the Headache Impact Test HIT-6 questionnaire, and a subjective points questionnaire assessment for treatment satisfaction and tolerance. **Results.** BTA was the most effective of the three treatment methods studied in patients with chronic migraine. As compared with oral prophylactic therapy and acupuncture, BTA produced the fastest and strongest actions on the frequency of headache, promoting regression of chronic migraine and recovery of the episodic nature of headache (the numbers of headache days in group 1, 2, and 3 were 16.1 ± 0.1 , 18.0 ± 0.02 , and 13.9 ± 0.3 , respectively, at one month). BTA also produced significantly faster and more effective recovery of quality of life and was better tolerated (good in 51%, 75%, and 85% in groups 1, 2, and 3, respectively; satisfactory in 35%, 25%, and 15% in groups 1, 2, and 3, respectively; poor in 14% in the oral prophylaxis group). Most patients in the BTA group achieved satisfactory treatment results more quickly. Despite the greater direct costs as compared with topiramate, the direct costs associated with the use of BTA (29931.51 and 32085.87 rubles, respectively, the predicted cost per non-headache day in the BTA group was the lowest, at 652.15 rubles (692.86 and 1017.60 rubles in the oral prophylaxis and acupuncture groups, respectively). **Conclusions.** The efficacy and cost data obtained here for the different methods of prophylaxis of chronic migraine may help specialists and patients select the most optimal therapeutic approaches.

Keywords: chronic migraine, cost, topiramate, acupuncture, botulinum toxin type A (Botox).

The primary headaches have the highest incidences in the population and are linked with enormous social and economic costs to the community. The most serious maladapt-

tation and, thus, economic losses come from chronic headaches where the frequency of headache days ranges from 15 per month to daily episodes of pain for more than three months [1].

The most widespread of the chronic types of daily headache is chronic migraine (CM). CM is widespread around the world, as in Russia [2, 3], and is linked with significant decreases in quality of life and everyday activities, as well as marked maladaptation [4].

¹ Vein Headache and Autonomic Disorders Clinic, Moscow, Russia; e-mail: mv_naprienko@mail.ru.

² Sechenov Moscow State Medical University, Moscow, Russia.

³ Solov'ev Scientific Psychoneurology Center, Moscow Health Department, Moscow, Russia.

CM is a serious economic burden for patients and the healthcare system as a whole. The results of an economic analysis based of internet data were published in 2012. The aim of the study was to run a comparative analysis of the direct medical costs to patients with episodic migraine (EM) (up to 14 days of headache per month) and CM (15 or more headache days per month for three months) in five European countries [5]. The parameters evaluated included social-demographic indicators and information on the use of healthcare resources and medications. Unit cost data collected from publicly available sources were analyzed for each type of service stratified by type of migraine: EM or CM.

Patients with CM made more visits to out-patient healthcare institutions and emergency rooms; they received more diagnostic tests; medical costs per CM patient were three times those of EM patients. Annual costs per patient were the greatest in the UK and Spain, somewhat lower in France and Germany. In all countries, CM required greater medical resources and total costs than EM. Thus, it became evident that medical strategies and approaches decreasing the incidence of headache could significantly decrease the clinical and economic burden of migraine in Europe.

Analysis of the “cost of disease” involves assessment of the direct and indirect costs, expressed in monetary terms. Direct costs include the expenses of keeping the patient in therapeutic institutions and the costs of providing services; indirect costs are economic losses due to decreased work productivity and the absences from work due to illness, as well as loss of family income [5]. Despite the fact that direct healthcare costs on migraine treatment differ in each country, 70–90% of the expenses in all countries are indirect costs [6].

Research on the costs of migraine is constantly under way in different countries, though extrapolation of these data is impossible because of differences in the ways healthcare systems are organized and differences in the costs of medical services and medications. For example, the cost of sumatriptan in the Russian Federation is 10 times greater than in India, so the total treatment cost is also greater [7].

Studies by Russian authors included pharmaco-economic evaluation of the “burden” of migraine (without division into clinical forms) in the Russian Federation and Moscow: the total costs in Moscow was 109.03 billion rubles, while state expenses of the treatment of migraine per year for Moscow was 84.4 billion rubles; the annual cost per patient living in Moscow was 28432.64 rubles (around 2400 rubles per month) [8]. Migraine is clearly an “expensive” disease and optimization of the use of personal and public financial resources is an important task.

A valuable tool for optimizing resources and improving patients’ quality of life is provided by studies of the efficacy of treating CM in real clinical practice. No previous studies of this type have been reported in the Russian Federation. Two agents are recommended for the prophylaxis of CM in the world in general and the Russian Federation in particular,

both with high evidence levels (A): the anticonvulsant topiramate and the botulinum toxin type A formulation onabotulotoxin (BTA). BTA can be used when previous courses of prophylactic treatment have been ineffective or as first-line therapy when there are contraindications to oral drugs, when drugs are ineffective, and when the patient expresses preference; it is compatible with these drugs [9].

In scientific studies it is not always possible to reproduce and consider the clinical capabilities and features of the use of different methods of treating headache, such that there is interest in experience of the treatment of CM, its efficacy and cost, and the level of demand in real clinical practice [10–13]. A significant number of Russian patients with CM attend the Academician A. Vein Headache and Autonomic Disorders Clinic – the oldest specialized clinic for the study and treatment of headache in Russia. Thus, of the 2500–3000 new patients attending the Clinic each year, 80% are diagnosed with CM. The Clinic has accumulated extensive experience in the treatment of patients with CM using a variety of approaches. Among the most frequent causes of patient attendances are the desire to obtain specific help, i.e., treatment with BTA, which has been used in the Clinic since 2000. The proportion of patients asking for this treatment in 2013–2014 was 18% and reached 28% in 2017. The number of patients responding to primary and repeat treatment with BTA (decrease in number of headache days by more than 50%) increased proportionately [14].

Considering the large flow of patients with CM receiving adequate prophylactic treatment in the Clinic and the opportunity to analyze treatment efficacy, the aim of the present work was to evaluate the advisability of using different CM treatment schemes by comparing the clinical results and economic burden of disease in real clinical practice.

Materials and methods. A prospective, observational cohort study was run at the Vein Headache and Autonomic Disorders Clinic which included 66 patients with CM: 60 women and (mean age 40.1 ± 11.2 years, mean duration of disease 11 ± 8.1 years) and six men (mean age 39.3 ± 8.1 years, mean duration of disease 12 ± 4.3 years). Diagnoses of CM were established in accordance with the diagnostic criteria of the International Classification of Headache Disorders ICHD-3, 2018.

All patients were divided into three groups: patients of group 1 ($n = 22$) were prescribed three-month courses of oral prophylactic therapy (OPT) with topiramate at doses of up to 100 mg/day; patients of group 2 ($n = 20$) received 12 sessions of acupuncture (ACU) at a rate of three procedures per week; patients of group 3 ($n = 24$) received injections of BTA (Botox) at doses of 155–195 U in accordance with the PREEMPT protocol. The patient observation period was three months.

The efficacies of the three prophylactic methods were evaluated using the following methods: 1) clinical neurological assessment (detailed characteristics of headache, history, analysis of factors provoking attacks, migraine chroni-

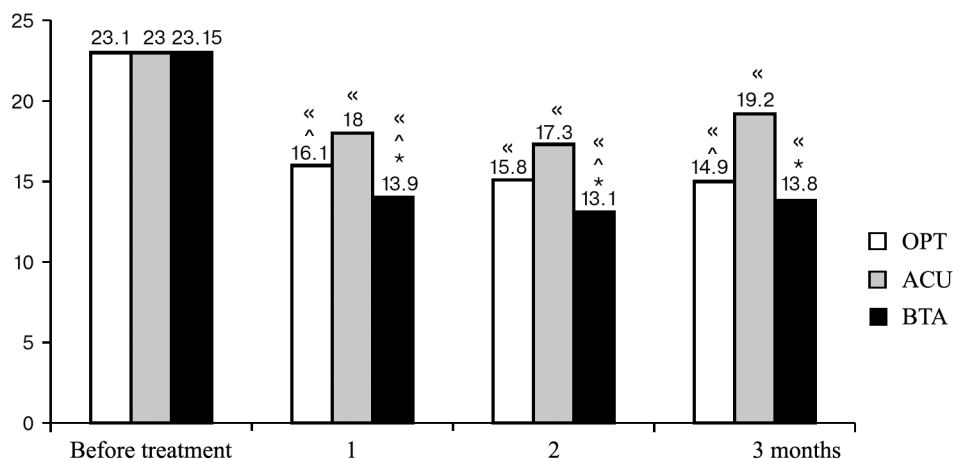


Fig. 1. Dynamics of the numbers of headache days per month in patients with CM receiving different types of preventive therapy. < Difference in results before and after treatment; ^ difference in treatment results in the OPT and ACU groups; * difference in treatment results in the ACU and BTA groups; x difference in treatment results in the OPT and BTA groups ($p < 0.05$).

cization factors, etc.); 2) completion of headache diaries during the three months of treatment (with determination of the number of headache days, the numbers of drugs taken to treat headache, and side effects due to use of drugs); 3) the Headache Impact Test HIT-6 questionnaire, which provides evaluation of the effects of headache on patients' general wellbeing and daily activity; 4) a subjective points questionnaire assessment for treatment satisfaction (0–100%) and 5) evaluation of treatment tolerance during the observation period (poor, satisfactory, good).

The main parameters of clinical efficacy were a decrease in the number of headache days and improvements in measures of quality life using these scales. The economic burden associated with the treatment of CM was determined for each patient by counting the direct financial expenses, which included: costs of first consultation with the neurology headache specialist, the costs of the main treatment (OPT, ACU, BTA), drugs for controlling attacks of pain, and such additional costs as consultations, investigations, and treatment on top of the basic elements.

Data were analyzed statistically in Statistica 10.0. Results are presented as mean \pm standard error of the mean. The critical level of significance for verification of hypotheses in the study was 0.05.

Results. The patients included in the study suffered essentially daily headache: the mean number of headache days per month was 23 ± 5.2 , of which 12.5 ± 2.3 days per month involved severe, intense attacks which patients evaluated as migraine attacks. Most patients (92%) fulfilled the diagnostic criteria for medication-induced headache (ICHD-III) [1]. Attacks were ameliorated by giving patients a variety of drugs: simple analgesics and non-steroidal anti-inflammatories (NSAID) (mostly ibuprofen) in 19% of cases, combined analgesics (mostly Pentalgin: paracetamol, naproxen, caffeine, Drotaverine hydrochloride, pheniramine maleate) in 42%, and triptans (mostly sumatriptan) in 39% of cas-

es. Psychometric testing before treatment showed that CM had significant effects on patients' quality of life: the HIT-6 score was 62.01 ± 5.82 points.

Comparative analysis of the efficacy of three types of treatment yielded the following results (Fig. 1): all groups showed improvements, with decreases in headache frequency. Stable reductions in headache frequency were seen in the OPT and BTA groups, and attacks were significantly less frequent in patients receiving BTA ($p < 0.05$). Treatment in the ACU group was less effective, such that episode frequency started to increase by the third month of observation. It should be noted that only the BTA group showed a sufficiently significant decrease in headache frequency to allow the "goalpost" to be moved to 15 days a month, i.e., return to the initial level – EM. Only this group showed such rapid improvement: the frequency of headache corresponded to the frequency in the episodic form of migraine (10–14 days/month) by one month after BTA injections. For comparison: the decrease in headache frequency in the OPT group to 15 days/month was achieved only by three months of treatment, and there was no "moving the goalpost" to EM in this group. In the ACU group, despite some improvement, the frequency of headache over the whole observation period remained 15 days/month and above.

All groups on the background of treatment showed significant decreases in the numbers of doses of analgesics of any group used, which was greatest by the end of the first month of treatment. The smallest analgesic intake was in patients of BTA group: 4.02 ± 2.1 doses of combined analgesics and 6.2 ± 2.6 tablets of triptans, as compared with the OPT group (5.7 ± 2.8 doses and 8.2 ± 3.7 tablets) and ACU (6.7 ± 2.7 doses and 10.2 ± 5.6 tablets). It should be emphasized that on the background of BTA, there were significantly greater decreases in the numbers of analgesics taken at the ends of both the first and second months of treatment as compared with the OPT group. While this tendency was

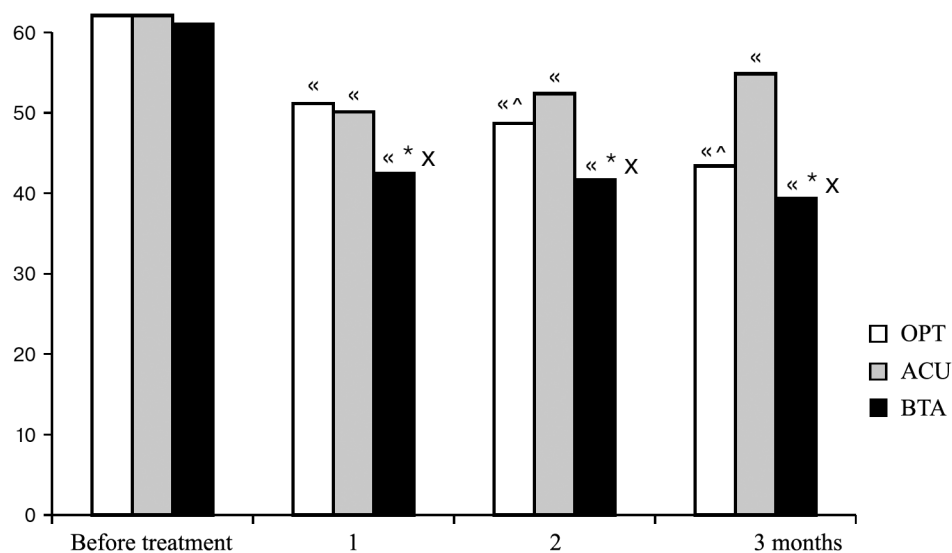


Fig. 2. Comparative characteristics of the effects of headache on the quality of life of patients with CM (HIT-6, points). «Difference in results before and after treatment; ^ difference in treatment results in the OPT and ACU groups; * difference in treatment results in the ACU and BTA groups; X difference in treatment results in the OPT and BTA groups ($p < 0.05$).

stable throughout the whole of the observation period in the OPT and BTA groups, consumption of analgesics in the ACU group by the third month of treatment gradually increased in accordance with the increase in the number of headache days.

All groups showed reductions in the quantities of combined analgesics taken. The fact of termination of medicinal drug abuse for ameliorating headache in most patients with CM was indicative. After three months of treatment, patients of the OPT group were taking 5.2 ± 2.7 doses of simple analgesics/NSAID, 1.03 ± 0.2 doses of combined analgesics, and 4.6 ± 2.1 doses of triptans for treating attacks of CM; the numbers in the ACU group were 9.7 ± 4.1 , 5.3 ± 3.1 , and 8.2 ± 4.6 doses, respectively, which were significantly greater than those in the other groups; in the BTA group, the numbers were 3.4 ± 1.21 , 1.1 ± 0.1 , and 3.6 ± 2.02 doses, respectively, which were the smallest values and allowed patients of this group to avoid drug-induced headache.

Assessment of the effects of headache on overall well-being and daily activity of patients on the HIT-6 scale showed that use of BTA had more marked positive influences on patients' quality of life than other treatment methods at all stages of the observation period (Fig. 2).

Overall, patients demonstrated adequate satisfaction on use of different therapeutic schemes. It should be noted that the only group in which treatment results at the end of the first month were satisfactory in more than half the patients was the BTA group; by the end of the third month the proportion of such patients reached 83%. For comparison, the maximum levels of satisfaction among patients in the OPT and ACU groups were 71% and 38%, respectively. Thus, while the level of satisfaction increased when OPT and BTA were used, it decreased on use of ACU (Fig. 3).

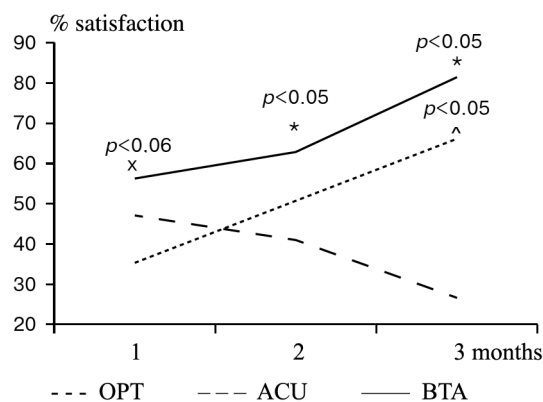


Fig. 3. Satisfaction of CM patients with different treatment schemes. ^ Difference in treatment results in the OPT and ACU groups; * difference in treatment results in the ACU and BTA groups; X difference in treatment results in the OPT and BTA groups ($p < 0.05$).

Among side effects, the OPT group most frequently showed complaints of memory loss, difficulty concentrating, feelings of stiffness in the limbs, drowsiness, and impaired sensation, which were noted at different periods of treatment and required additional treatment to be prescribed (nootropic substances, vascular drugs, and group B vitamins). Patients in the ACU group did not display any side effects. In the BTA group, adverse events were noted in two cases: myalgia in one patient and mild asymmetry of the eyebrows in the other, which resolved over a period of two weeks. Overall, better treatment tolerance was noted in patients in the ACU and BTA groups (Fig. 4).

Assessment of the direct costs of patients of each group involved summing the three-month costs of basic and additional treatments, consultations with specialists, and diag-

TABLE 1. Total Costs of Treatment in Groups over the Whole of the Observation Period

Group	Basic treatment, rubles	Additional treatment, rubles	Specialist consultations, rubles	Diagnostic procedures, rubles	Cost of drugs for treating attacks, rubles	Total costs for 3 months of treatment, rubles	Number of headache-free days	Predicted cost of headache-free day, rubles
OPT	10665	5150	7400	4150	2566.51	29931.51	43.2	692.86
ACU	30000			3150	2974.93	36124.93	35.5	1017.60
BTA	31040				1045.87	32085.87	49.2	652.15

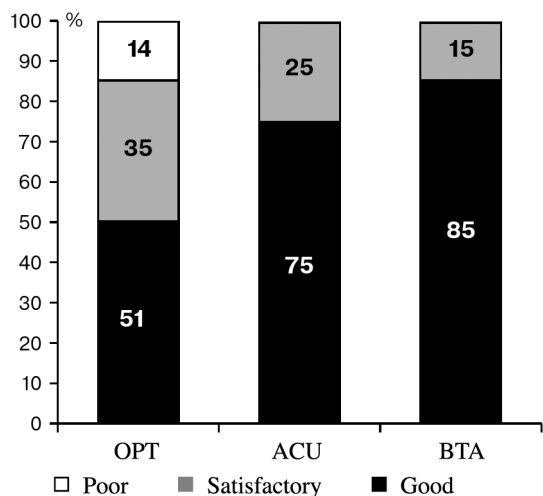


Fig. 4. Subjective assessment of treatment tolerance in groups (%).

nostic procedures, as well as the costs of drugs for treating attacks. The mean prices of drugs for basic therapy and analgesics were calculated from data on www.AptekaMos.ru (accessed November 7, 2018) and the prices of medical services from the price list of the Academician A. Vein Headache and Autonomic Disorders Clinic (2018). Determination of the total cost of treatment for CM in all groups showed that any prophylactic treatment of CM is expensive (see Table 1).

Prescription of OPT to patients requires an additional visit to the treating doctor for determination of treatment details (correction of side effects), while some patients in the OPT and ACU groups underwent additional diagnostic investigations at their insistence because of poor treatment tolerance and dissatisfaction with treatment results. Determination of the predicted cost per headache-free day gave the smallest total in the BTA group.

Discussion. We report here the Russian Federation's first study of the efficacy and cost of different approaches to the prophylaxis of CM in real clinical practice. Features of the development and course of CM specific to the Russian Federation were found. Thus, most of our patients had long histories of migraine and suffered from medication-induced headache (92%), probably due to diagnostic and treatment errors of headache patients in the Russian Federation [15]. Indicators of medication-induced headache were higher than

in other, non-Russian, studies [3], but corresponded to data from some Russian studies [16]. Previous studies showed that late establishment of diagnoses of CM and prolonged inadequate treatment promote chronicization of the disease and are the main causes of the higher incidence of chronic daily headache and CM in the Russian Federation than other countries [2, 15]; furthermore, patients attending specialist headache clinics are mainly those with chronic forms of cephalalgia [3].

Although in our study the use of ACU was less effective than the use of OPT or BTA, patients showed a decrease in the number of headache days per month at one month and a decrease in the quantity of medication taken to treat headache. A study by a Korean group, Yang et al. [17], demonstrated analogous positive effects of ACU on the course of medication-induced headache and emphasized that the management of patients with severe medication abuse is extremely difficult. Thus, ACU can be recommended for patients with CM with contraindications for the use of BTA and OPT, including those with medication-induced headache and in patients who do not want to use medication.

Comparative analysis of different approaches to the prophylactic treatment of CM showed similar efficacies for the anticonvulsant topiramate and BTA, which is consistent with previous data [17–19]. Treatment with BTA in patients produced the greatest number of headache-free days and the lowest predicted cost per headache-free day.

More detailed analysis of the efficacy and tolerance of BTA in comparison with the other approaches was interesting. In patients with CM receiving treatment in our Clinic, BTA showed high efficacy and safety, greater than for OPT and ACU. A published analysis of the use of BTA in nine European countries showed that there is a significant relationship between the efficacy of botulinum therapy and the level of experience, the qualifications of the doctor, and the availability in the clinic of publications on this method; it is emphasized that that with these factors, patients show smaller numbers of side effects and complications [20].

Pain is a subjective experience, so the patient's personal assessment of treatment satisfaction and tolerance is a major criterion for the efficacy and safety of any therapy. Our data indicate that despite the greater costs of BTA in CM as compared with topiramate, the level of treatment satisfaction was significantly higher than on treatment with OPT during all three months of observation.

Our data showing high levels of satisfaction with the prophylactic effect of using BTA and its increase in the first months after the first injection are consistent with previously published results showing increases in patients' satisfaction with repeated courses of BTA [21, 22]. Satisfaction with the use of BTA was greater than in the other groups; as compared with the OPT group, there was a tendency to significance ($p < 0.06$) at the beginning of treatment, which was greater than in the ACU group in the other months, which increases patients' treatment compliance and provides the opportunity to overcome clinical difficulties.

Patients' subjective assessments indicated that the tolerance of BTA was also better than that of OPT, as side effects in the BTA group were seen rarely and did not persist more than two weeks after injections. Treatment of OPT, conversely, was linked primarily with decreased cognitive functions forcing patients to withdraw from therapy and the doctor to prescribe additional investigations and treatment [23]. Counting of the direct costs to patients for treatment of CM showed that all types of treatment of CM are expensive, which is consistent with data from studies in other countries [24].

Thus, BTA was the most effective of the three treatment methods for CM studied here. As compared with OPT and ACU, BTA produced faster and stronger actions on pain, promoting regression of chronic daily headache and restoring the episodic nature of headache, faster and more effective restoration of quality of life, and better tolerance; most patients reported rapid achievement of satisfactory treatment results. The rate at which patients' status improved and the strength and stability of the analgesic action of BTA were absolute advantages in selecting the treatment method for many CM patients. This determines the view of BTA as a contemporary, highly effective and much demanded treatment method, confirming the rapidly increasing requests for botulinum treatment of CM according to data from Russia's oldest specialist headache clinic. Data on the efficacy and cost of different methods for the preventive therapy of CM were obtained and these may help specialists and patients to select the optimum therapeutic approach. Choice of appropriate and economic methods for the prophylaxis of CM leads to significant reductions in personal and public financial resources, decreasing the clinical and economic burden of CM.

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The authors have no conflicts of interests.

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