

The Results Of A Clinical Study In Relation To A New Antihistamine Medication Theoritin In The Treatment Of Patients With Chronic Spontaneous Urticaria

G.N. Gildeeva¹, A.V. Belostotsky¹, O.V. Gridnev¹, V.I. Yurkov²

1 Dr. Ph.Sci., Professor of the Department of organization and management in the field of drug circulation

1 Dr. habil. med., associate professor, head of the Department of organization and management in the field of drug circulation

1 Dr. habil. med., Professor of the Department of organization and management in the field of drug circulation

2 Candidate of biological sciences, Medical Advisor (contact, e-mail – vy@mda-cro.com)

1- Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University)

2- LLC «Medical Development Agency», Russia

Abstract

Since the middle of the last century, there has been an increase in the prevalence rate of allergic diseases, which also continues in recent years. The projected further growth of the allergic diseases frequency requires the development of new approaches in order to find solution for this problem, in particular the use of new modern medicines. The article presents the pharmaceutical characteristics and results of an open-label randomized clinical trial in relation to the effectiveness and safety (phase III) of a new anti-allergic medical product, Theoritin, in comparison with the reference preparation Aerius (desloratadine). This clinical trial involved 164 patients with chronic spontaneous urticaria (CSU). The research results indicate the noninferiority and comparable safety of the medical product Theoritin in relation to changes (decrease) in the severity of CSU symptoms after 14 days of therapy.

Keywords: Theoritin, chronic spontaneous urticaria

INTRODUCTION

Despite the fact that the medical practice includes quite wide antihistamines nomenclature as anti-allergic medical products, the search for new H₁-histamine receptor blockers remains an urgent task due to the fact that most existing medical products of this class are not without disadvantages, such as: short-term effect, the side effects for the Central nervous system, and others [1,2].

The antihistamines are in clinical practice since the 1950s in order to treat various types of allergic diseases. With consideration of the fact that especially patients with allergy have symptoms of the individual sensitivity to certain antihistamines, a quite wide range of anti-allergic medical products is necessary for the effective treatment. In this regard, it is particularly relevant to find the original antihistamine (anti-allergic) medical products with a new chemical structure.

In the beginning of the 21st century, the Russian scientists synthesized and studied a large group of 1- and 7-derivatives of xanthine, the most active compound was succinate 3-methyl-7 - [4-(4-benzhydrylpiperazinyl-1) butyl] xanthine (7 - [4 - (4-benzhydrylpiperazinyl-1) butyl] - 3-methylxanthine succinate), called Theoritin [3]. In order to form the structure of Theoritin we applied to the following considerations:

1. The molecule of the new medical product should include a benzhydrylpiperazinoalkyl fragment, which is the main pharmacophore part of the structure in a number of modern H₁-histamine receptor blockers of the second generation – cetirizine, meclozine, etc.
2. One planned to use the biogenic structure of xanthine, which is the basis of some medical products and natural compounds, as a transport system for the

benzhydrylpiperazinoalkyl fragment.

The structural modification of major pharmacologically active substances is still one of the main approaches in the development of new medical products. In this regard, one selected a very available 3-methylxanthine as the original compound for the preparation of a new medical product (for a number of technological and economic reasons). It is popular within the synthesis of many medical products that do not have sedative properties that are undesirable for antihistamines [4].

The study of Theoritin general pharmacological properties within the framework of preclinical studies has shown that it does not have an adverse effect on the main systems and functions of the body within the doses that correspond to antihistamines and antiallergic medical products. One can observe the major antimuscarinic effect of Theoritin in doses that are in 3-4 orders of magnitude higher than antihistamines [3]. In accordance with the studies of Theoritin central effects one can conclude that this medical product, like cetirizine and in contrast to antihistamines (anti-allergic) medicines of the 1st generation, does not have inhibitory action on the central nervous system.

As one of the possible clinical applications for the new medical product, one proposed the condition of chronic spontaneous urticaria - it is among the most common allergic diseases within almost all age groups. The chronic urticaria is the spontaneous symptoms of itchy blisters that do not disappear for at least 6 weeks and usually relapse for several years. If one cannot determine the exact cause of the condition, one can traditionally determine the chronic urticaria as idiopathic, or spontaneous.

The prevalence rate of CSU is 0.5-3 % within the overall

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population [5-7]. The Itches and blisters are the leading signs and symptoms of CSU. Sometimes, angioedema is the additional symptom. The patients with acute illness complain about sleep disorders (due to itches) and decreased activity in the daytime (due to the bad external view of blisters). These signs and symptoms lead to deterioration in the quality of life [8,9].

Within the registration procedure of a new medical product, one successfully conducted clinical trials (CI) of phases I-III, one can find the main results of CI phase III below.

MATERIALS AND METHODS

The purpose of the research was to maintain efficiency and safety assessment of the medical product Theoritin® (2 mg tablets, ЗАО «ОХФК», Russia) in comparison with the medical product Aeriус® (5 mg film-coated pills, Schering Plau Labo N.V., Belgium) among adult patients with CSU.

The design of study is a multi-center prospective open-label randomized trial in order to make the assessment of efficacy and safety. Clinical trial protocol №: TEORITIN-03, trial registration № 26, date of registration – 23.01.2017.

The study corresponds to the principles of the Declaration of Helsinki and GCP (Good Clinical Practice). The ethics committee examined and approved its Protocol and patient's informed consent. The study included a screening period of up to 7 days, a therapy period of 14 days, and an observation period of up to 8 days, the total time of patients participation constituted maximum 29 days. The study consisted of 5 visits – a screening visit, a visit for randomization/initiation of therapy, a visit for interim assessment of therapy efficiency, final therapy visit, and the final visit of observation period.

The study involved 164 patients, among them 161 completed all of its procedures. All the patients passed the briefing about the purpose and nature of the study, and signed the informed consent for participation in the study.

Key criteria of inclusion:

1. Patients of both sexes in the age from 18.
2. Sterile women or women who use one or more barrier methods of contraception.
3. The absence of contraindications to the prescription of the test medical product/comparator agent.
4. The availability of clinical documentation, which confirms the duration of CSU for more than 6 weeks.
5. Patients with CSU within the period of disease recurrence.
6. Patients who have passed a "washout" period, during which it is forbidden to take any medical products.
7. Patients who suffer a condition of intermediate severity within the initial period.

Key criteria of non-inclusion:

1. Clinically significant changes in the ECG.
2. Pregnant or nursing women.
3. Alcohol and / or drug addiction within the medical history.
4. The local or systemic viral and bacterial infections in 2 weeks before the screening.

5. Hypersensitivity to any components of the test medical product/comparator agent.
6. Lactose intolerance, lactase deficiency, glucose-galactose malabsorption.
7. Any cardiovascular, neurological, hepatic, renal, or other conditions in the medical history that may affect the absorption, metabolism, or excretion of the medical products under study.
8. The usage of ketoconazole, fluconazole, Itraconazole, or other azole antifungal medical products, or any macrolide antibiotics during the 2 months before the screening.
9. The local inhalation or systemic glucocorticoid therapy during 21 days before the screening period.
10. The usage of deposited glucocorticosteroids in the period of 2 months before the screening.
11. The usage of long-term antihistamines during 7 days before the first intake of the test medical product.
12. The usage of leukotriene receptor blockers for 14 days before the first intake of the test medical product.

Patients who correspond to all the selection criteria passed the randomization procedure into 2 groups under a ratio of 1:1, and they got the prescription of medical product Theoritin® at a dose of 4 mg as the study therapy. As a comparison therapy, there was a prescription of the medical product Aeriус® at a dose of 5 mg. The intake of medical products under comparison was oral, once a day for 14 days. In order to register the clinical symptoms and signs of CSU, the patients received a specially designed diary and they filled it on the daily basis. The assessment of treatment efficacy occurred after 1 and 2 weeks of the treatment.

Outcome measures

The primary outcome measure of the therapy was the mean change in the severity assessment of itch (by the scale for severity assessment of symptoms and signs of CSU (**Total symptom score, (TSS)**), made in the morning/evening over the past 12 hours (AM/PM PRIOR TSS) during 14 days of therapy in comparison with the baseline level.

The secondary outcome measures included:

- The mean change in the morning/evening severity score of itch (AM/PM NOW TSS) during 14 days of therapy.
- The mean change in the severity of CSU by the scale for severity assessment of symptoms and signs of CSU on Day 7 and Day 14 of therapy.
- The overall assessment of CSU treatment efficacy on Day 7, Day 14, made by the researcher.
- The mean change in the 12-hour reflexive assessment of the effect on sleep and daily activities during 14 days of therapy.
- The frequency of the additional medical products use in order to relieve the condition.

The scale for severity assessment of symptoms and signs of CSU

There is the calculation of points for each of the following symptoms and signs of CSU: skin itch, the number of urticary skin rashes (blisters), and the size of the largest urticary lesion.

Points	Severity of skin itch	The number of urticarial rash	Size of the largest urticarial rash, (cm)
0	Absent	None	0
1	The condition of itch is light, clearly defined, but causes minimal concern and is easy to carry.	from 1 to 6	≤1,0
2	The condition of itch is moderate,	from 7 to 12	1,0-2,5

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	causes anxiety, but is possible to carry.		
3	The condition of itch is apparent, difficult to bear.	>12	>2,5

The patients assessed the severity of itch, the number of urticary rashes, and the size of the largest urticary rash in the previous 12 hours ((AM/PM PRIOR TSS)) and directly at the time of assessment (AM/PM NOW TSS) during all days of the study. The assessment occurred after the patient's awakening in the morning (before the medical product intake) and 12 hours later, in the evening, with a general assessment of all the parameters under evaluation.

Also, during all days of the study, patients were under reflexive assessment (for the previous 12 hours) of the impact on sleep (in the morning) and the impact on daily activities (in the evening) on the basis of scale for severity assessment of sleep disorders/daily activities:

- 0- no, sleep/daily activities are without disorders
- 1- light disorder
- 2- moderate disorder
- 3- apparent disorder

The severity assessment of CSU:

The CSU severity assessment included the calculation of points by the assessment scale of the symptoms and signs. The sum from 0 to 3 points correspond to light severity level, 4-6 points – moderate severity level, 7-9 points – heavy severity level.

The researcher made the *overall assessment of therapy effectiveness* in accordance with the following scale:

- 1- no response (the symptoms have not changed or worsened);
- 2- slight relief (there are symptoms that cause anxiety without noticeable improvement);
- 3- moderate relief (there are symptoms, but the condition slightly improved);
- 4- significant relief (there are symptoms, but they significantly improved, almost without reasons for concern);
- 5- full response (no symptoms).

Security evaluation criteria

The assessment in relation to safety and tolerance of the drug occurred by the frequency and severity of adverse events (AE). All performance and safety data passed statistical processing by means of NCSS 11.0 software.

RESEARCH RESULTS

Efficiency

There was the statistical analysis of efficacy within the ITT population (163 patients: 81 patients in group T (Theoritin) and 82 patients in group R (Aerius)) and within the PP population (161 patients: 80 patients in group T and 81 patients in group R).

The diagnosis of physical, chemical, environmental and other causes of CSU among the patients under study showed no indications of them, which helped to make the accurate diagnosis. In particular, the medical records of patients included information about skin tests with non-infectious allergens or information about examinations of specific class E immunoglobulins for certain most common allergens. The results of these tests were negative.

All the patients under randomization corresponded to the inclusion/non-inclusion criteria and were comparable in both groups by the analyzed initial parameters of the condition. The differences of the average values for these indicators between the groups are not statistically significant ($p > 0.05$). The groups within both populations also were mainly in

balance by the main vital indicators, results of laboratory tests (clinical blood analysis, biochemical blood analysis, clinical urine analysis)

In accordance with Protocol of the study, the primary outcome measure is the mean change in the severity score of itch condition (AM/PM PRIOR TSS) within 14 days of therapy in comparison with the baseline level on the basis of patient's diaries.

As a result of repeated measures analysis of variance in relation to the severity assessment of itch condition AM/PM PRIOR TSS during 14 days of therapy, there were no statistically significant differences between the groups of patients that that the medical product T and R ($p=0.886$). Within the groups T and R, statistically significant differences were in the reflexive severity assessment of the itch condition during 14 days ($p=0.000$). There was a statistically significant decrease in the values of the reflexive severity assessment of the itch condition during 14 days. The figure 1 shows the average values of the reflexive severity assessment of the itch condition.

Secondary outcome measures

- The mean change in the morning/evening severity score of itch (AM/PM NOW TSS) during 14 days of therapy.

As a result of repeated measures analysis of variance, there were no statistically significant differences between the groups of patients who took the medical product T and R (p -value=0.916).

- The mean change in the severity of CSU by the scale for severity assessment of symptoms and signs of CSU on Day 7 and Day 14 of therapy.

The statistical analysis showed no statistically significant differences between the groups of patients that take the medical product T and R ($p = 0.888$). Within the groups T and R, statistically significant differences were in the severity assessment of the itch condition ($p=0.000$). There was a statistically significant decrease in the severity of CSU on Day 7 and day 14 of the therapy in comparison with Day 0.

- The overall assessment of CSU treatment efficacy on Day 7, Day 14, made by the researcher.

The research analysis of overall therapy efficiency assessment on Day 7 did not reveal statistically significant differences between the groups of patients under the medical product T and R ($p = 0.708$). The research analysis of overall therapy efficiency assessment on Day 14 also did not reveal statistically significant differences between the groups of patients under the medical product T and R ($p = 0.078$).

- The mean change in the 12-hour reflexive assessment of the effect on sleep and daily activities during 14 days of therapy.

A repeated measures analysis of the effect variance on sleep during 14 days of therapy did not reveal statistically significant differences between the groups of patients under the medical product T and R ($p = 0.920$). Within the groups T and R, statistically significant differences were in the severity assessment of the effect on sleep during 14 days ($p=0.000$). The analysis of the effect on daily activities did not reveal statistically significant differences between the groups of patients under the medical product T and R ($p = 0.905$).

- The frequency of the additional medical products intake in order to relieve the condition

During the study, 2 patients from the main group and 4

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patients from the control group took additional medical products in order to relieve the condition. There were no statistically significant differences between groups T and R ($p>0.05$).

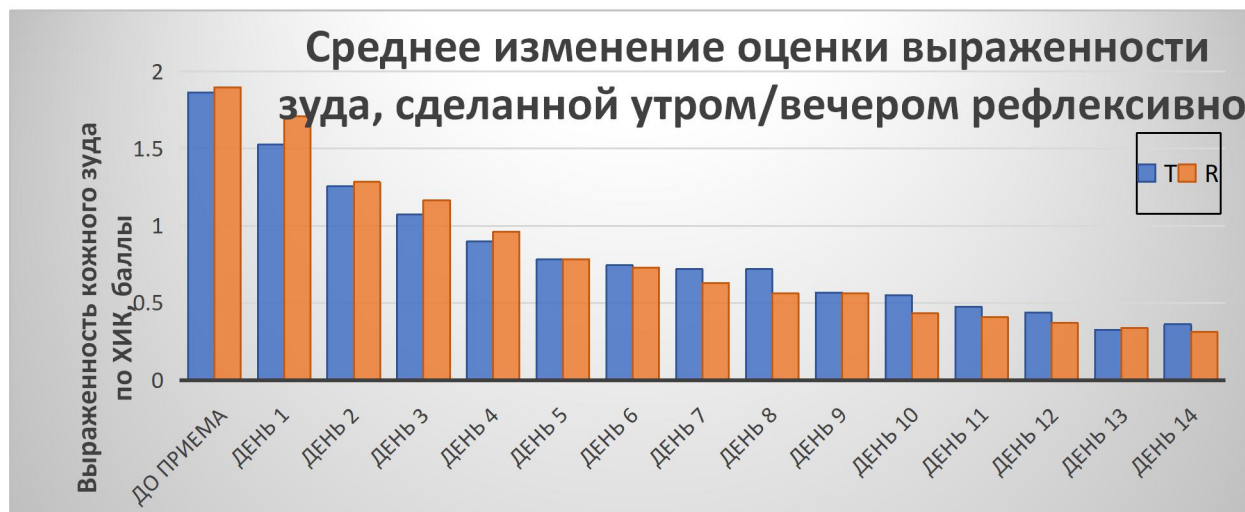
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All registered adverse effects were under analysis. There was

products.

Physical examination, vital signs

The results of the physical examination did not reveal any differences between the groups during any of visits under analysis. There were no statistically significant differences between the medical product under the study in terms of their



division of these effects into groups by frequency, severity, and their relationship with the use of the medical products under study.

Within the clinical trial there were 191 of AE (96 of AE in the group of patients under the research medical product Theoritin, and 95 of AE in the group of patients under the medical product Aerius). In total, 90 patients had AE (47 patients in the group with intake of medical product Theoritin and 43 patients in the group with intake of medical product Aerius).

Throughout the study, the intake of medical products under study was good within the group of patients. During the study, there were no registered cases of deaths, and there were no cases of serious adverse events (SAE).

The most common AE were deviations of laboratory parameters (clinical and biochemical blood tests, clinical urine analysis). One registered them on Visit 4. In accordance with the researchers, these deviations had a mostly doubtful connection with the intake of medical

effect on vital indicators of heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure and body temperature ($p>0.05$). It allows us to assume that the intake of the medical product Theoritin is comparable to the intake of the medical product Aerius by these parameters.

The indicators of clinical, biochemical blood tests, clinical urine analysis

On the basis of the results obtained both at Visit 1 and at Visit 4, there were observations of minor hematological abnormalities, as well as deviations in the clinical urine analysis among patients of both groups with a similar frequency, which were random and not clinically significant in accordance with the researchers ($p0, 05$).

ECG

On the basis of ECG there were no statistically significant differences between groups T and R ($p>0.05$).

Figure 1. Severity of skin itch (AM/PM PRIOR TSS)

DISCUSSION AND CONCLUSIONS

The chronic urticaria refers to a heterogeneous and widespread group of diseases. In accordance with modern international recommendations for the diagnosis and treatment of urticaria, the antihistamines are the first-line drugs (level of evidence I++, recommendation level A) [10,11]. They block the action of mast cell mediators (prostaglandins, cytokines) the main effector cells in relation to target organs and receptors of IgE. The new antihistamines are essential for the treatment of patients with chronic urticaria, and should have a proven high effectiveness in symptoms relief of the disease and good tolerance even in case of increased doses without sedative effect.

The developed antihistamine Theoritin demonstrated good results within the framework of the study. In comparison with the popular and respective medication of desloratadine (Aerius), one found that the treatment groups under analysis were comparable both in terms of the main and additional effectiveness parameters.

For the primary outcome measure, the lower limit of 95% CI for the difference in the mean values of AM/PM PRIOR TSS of the main and control groups constituted -0.177, this value does not cross the limit of noninferiority -0.74, which

indicates the noninferiority (**non inferiority**) of the study medical product Theoritin in comparison with the medical product Aerius in relation to the severity of itch among the patients with CSU after 14 days of therapy. As for the secondary outcome measures, there were also no differences between the groups under comparison. In accordance with the results of the analysis, one can also conclude that the medical product Theoritin is safe because it has no severe negative effect by the results of the study in relation to laboratory and instrumental methods within the dynamics (before and after a course of medical product) and does not lead to negative changes in the organs and organ systems by physical examination. The medical product Theoritin does not have a significant effect on vital signs and is not worse in safety to the comparator agent Aerius.

Thus, in accordance with the results of the conducted clinical study, one can conclude that the medical product Theoritin has noninferiority in comparison with the medical product Aerius in terms of change (decrease) in the severity of itch among the patients with CSU after 14 days of therapy with the medical products under study.

CONCLUSION

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The relevant problem of modern medicine is the ineffectiveness of standard antihistamine therapy among about the half of patients with CSU, despite the developed and approved treatment standards [10,11]. In this regard, the appearance of a promising new medical product on the market is important for patients with such disease.

The effective relief of CSU symptoms with the medical appointment of Theoritin already occurs in the first days of treatment, continues for the entire period of treatment by the medical product and consists of rapid and persistent decrease of rashes, itches, improvement of sleep and activity among the patients during the daytime, i.e. the medical treatment by Theoritin in case of chronic urticaria leads to a significant improvement in the quality of life among the patients. The high degree of safety and good tolerance give reason to recommend the latest antihistamine Theoritin for the treatment of patients that suffer from chronic urticaria. The medical product successfully passed registration procedures and received permission from the Ministry of Health of the Russian Federation for the clinical management.

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