MARIAM GOGOTISHVILI[1], NINO ABASHIDZE [2], NINO KORSANTIA[3], NATO KORSANTIA[4]

IMMUNOMODULATORY AND CLINICAL EFFECTIVITY OF THE DRUG "LAZOLEX" IN TREATMENT OF RECURRENT APHTHOUS STOMATITIS (RAS)

[1]Batumi Shota Rustaveli State University,
[2]TSMU, Department of Periodontology and Oral Mucosal diseases;
[3]TSMU, Department of Odontology;
[4]TSMU, Department of Dermatology and Venereology; Georgia

მარიამ გოგოტიშვილი [1], ნინო აბაშიძე [2], ნინო კორსანტია [3], ნატო კორსანტია [4]

პრეპარატ „ლაზოლექსის“ იმუნომამოდულირებელი და კლინიკური ეფექტურობა მორეციდივე აფთოზური სტომატიტის მკურნალობის დროს

[1]ბათუმის შოთა რუსთაველის სახელმწიფო უნივერსიტეტი,
[2]თსსუ, პაროდონტოლოგიისა და ლორწოვანი გარსის დაავადებათა დეპარტამენტი,
[3]თსსუ, ოდონტოლოგიის დეპარტამენტი,
[4]თსსუ, კანისა და ვენერიულ სნეულებათა დეპარტამენტი, საქართველო

რეზიუმე

მოცემული კვლევის მიზანი იყო მორეციდივე აფთოზური სტომატიტით დაავადებულ პაციენტებში ქართული სამამულო პრეპარატის „LAZOLEX“-ის იმუნომამოდულირებელი და კლინიკური თვისებების შესწავლა. კლინიკური და იმუნოლოგიური პარამეტრები შესწავლილ იქნა 50 პაციენტში. შედეგებმა აჩვენა ნათელი კორელაცია იმუნური სისტემის მდგომარეობასა და დაავადების სიმძიმეს შორის, კერძოდ, ყველაზე მწვავე იმუნოდეპრესია დაფიქსირდა დაავადების მძიმე ფორმის მქონე პაციენტებში. "LAZOLEX"-ის 5% გელის გამოყენებამ აჩვენა ტრადიციული თერაპიის მსგავსი მაღალი კლინიკური ეფექტურობა, თუმცა LAZOLEX-ის იმუნომაკორეგირებელი თვისებების არსებობა გამოიხატა პაციენტის მკურნალობის ხარისხის გაუმჯობესებაში: ეპითელიზაციის დროის შემცირებასა და რემისიის გახანგრძლივებაში. ჩატარებული კლინიკური, ლაბორატორიული და იმუნოლოგიური კვლევები საშუალებას გვაძლევს რეკომენდაცია გავუწიოთ პრეპარატ „LAZOLEX“-ს სტომატოლოგიურ პრაქტიკაში, მორეციდივე აფთოზური სტომატიტის მკურნალობაში აქტიური გამოყენებისათვის.

The Greek term “Aphthae” was initially used in relation to disorders of the mouth and was first mentioned by Hippocrates (460-370 BC) [12]. Today, recurrent aphthous ulceration, or recurrent aphthous stomatitis (RAS), is recognized as the most common oral mucosal disease known to human beings. According to WHO, it affects up to 20% of the population. The onset of RAS seems to peak between the ages of 10 and 19 years before becoming less frequent with advancing age [13].

The most characteristic symptom of the disease is the recurrent onset of single or multiple painful small, round or ovoid erosions and ulcers with circumscribed margins, erythematous haloes, and yellow or gray floors, covered with fibrous coating, with a development cycle of 7-10 days. They appear mainly on unattached oral mucosa of the lips, cheeks and tongue. Occasionally the lesions may also be observed on strongly keratinized palatal and gingival mucosa [14].

Patients complain of burning sensation and pain, which is sharply increased when eating, talking. Often the general condition of the patient worsens, manifesting headaches, insomnia, possible addition of subfebrile temperature. It can be considered not only as an independent local process, but also as a manifestation of some disease of the body. Up to now, the etiopathogenesis of this condition remains unclear; it is, however, considered to be multifactorial. The potential trigger factors, that modify the immunologic response in RAS and provoke relapses of the disease include: trauma of the oral mucosa, stress, gastrointestinal disorders and hormonal level

fluctuations, hypothermia, genetic predisposition, systemic diseases, vitamin and microelement deficiencies, food allergies, viral and bacterial infections, HIV. There are many different theories about the origin of RAS, such as viral, immune, infectious, allergic, neurogenic [8, 15].

As the etiopathogenesis of the condition has not been clearly defined, the treatment is mainly symptomatic and not very effective. Discovering the direct etiopathogenetic factors in RAS may in future help to predict the risk of the disease occurrence and to develop the effective, causative management.

Intensive research is continuing in our country to find and implement new natural medicinal preparations produced from ecologically pure endemic plants of Georgia, according to traditional medicine recipes, using the latest biotechnological approaches. An example of such studies is a local drug - LAZOLEX (extract of the pericarpium of an unripe walnut), produced by the "Iveria-Pharma" company. LAZOLEX passed the necessary preclinical tests and was successfully used in the clinic as an antiviral agent [1, 4, 9]. This time, we studied its clinical effects in patients with recurrent aphthous stomatitis (RAS) [2].

Results of In vitro tests in cell cultures, as well as in laboratory animals, have shown that the extract for the production of LAZOLEX has the protective properties against the herpes simplex virus. In addition, under the same experimental conditions, as well as on healthy volunteers, positive immunotropic effects of LAZOLEX were also found [4].

The purpose of this study was to study the immunomodulatory and clinical properties of the drug in patients with RAS.

Material and methods

In order to assess the effect of the LAZOLEX on the clinical course of RAS, 2 groups of patients were formed (In total 50 patients):

1) The first group (control), which included 20 patients, who received a traditional treatment (application of A and E vitamins, cedar oil, Solcoseryl dental adhesive paste);

2) The second group (main), which included 30 patients, who were treated with LAZOLEX. (5% gel was applied to the damaged areas of the lips and oral mucosa, daily for 10 days).

In addition, depending on disease form, each group was divided into 3 subgroups - Fibrinous (a) – 12 patients (24%), Necrotic (b) – 32 (64%) and Glandular (c) – 6 (12%). Depending on the severity of the disease – mild (A) – 20 (40%), moderate – 20 (40%), severe – 10 (20%).

The therapeutic effect was assessed on the basis of the timing of the disappearance of subjective and objective signs of RAS, time of epithelialization and remission.

Clinical symptoms were assessed daily. Clinical research methods included taking anamnesis, examining the oral cavity for the presence of RAS aphids, palpation of the oral mucosa to assess the pain of the rash, time of epithelialization.

To assess the immune status of the organism, we used the following adequately responding indicators of the T- and B-lymphocyte system, phagocytosis, interferon in the blood, secretory immunoglobulin A and lysozyme in saliva (in total, about 15 parameters). Since some of them were comparatively less informative, in our discussion we stopped at 6 parameters, which were the most dynamic, informative and reliable: interferon system - αIFN and γIFN, index of immunoregulation (Ii), phagocytic index (PhI), sIgA and lysozyme [7].

The state of immune homeostasis of patients was assessed in dynamics, i.e., at the first visit to the clinic, as well as on the 10-13th day of treatment. Table 1 (first visit) combines data from all 50 patients, depending on the severity of stomatitis. In the second table, the immunological aspects of the two treatment approaches (Traditional/LAZOLEX), depending on the severity of RAS and the results of treatment, were assessed separately and comprehensively, and a generalizing analysis of the data obtained was made.

The processing of the results was carried out using a special program on an IBM PC by the method of variation statistics, with the calculation of the criterion for the significance of the Students' difference.

Results and its discussion

Examination of patients with RAS revealed noticeable changes in the immune system, affecting all its factors, which largely depended on the severity of the process, i.e., the most severe immunosuppression was recorded in patients with severe stomatitis.

***Table 1**. Immunological parameters in patients with RAS (admission to the clinic)*

Parameters	Severity of the disease (A – mild; B – moderate; C – severe).				Control (n=30)
	Total (n=50)	A (n=20)	B (n=20)	C (n=10)	
αIFN (U/ml)	*25.05	*28.1	*26.7	*20.2	**41.3**
γIFN (U/ml)	*13.3	*17.6	*13.5	*8.8	**28.6**
Ii	*1.7	2.1	*1.76	*1.24	**2.28**
PhI	*3.88	4.75	*3.8	*3.1	**4.9**
sIgA (g/l)	0.27	*0.39	0.27	*0.14	**0.28**
Lyz (%)	*33.6	40.6	34.5	*25.7	**41.9**

Note: * indicates a significant difference with the control - Practically healthy volunteers.

As can be seen from the table 1, mild RAS proceeded against the background of the compensatory reaction of the body, due to the humoral link. Important is a significant increase in the digestive capacity of blood leukocytes (4.75) and an increase in the concentration of secretory IgA (0.39g/l) and lysozyme (40.6%) in saliva, the most important factors of local protection of the oral cavity. The interferon system turned out to be especially sensitive (decrease, αIFN to 28.1 units/ml, - γIFN to 17.6 units/ml). However, with the deterioration of the clinical condition of patients, there was a depletion of compensatory capabilities and a cascade inhibition of almost all the factors studied.

With moderate severity of RAS, almost all parameters undergo further suppression: phagocytic index - 3.8; αIFN - 26.7 U/ml; γIFN - 13.5 U/ml. It should be emphasized that with this form of stomatitis, the content of lysozyme in saliva significantly decreased - 34.5%, and slightly below the norm - the amount of sIgA (0.27 g/l). In other words, with a moderate degree, we can no longer talk about compensatory mechanisms on the part of the immune system, which was characteristic of mild stomatitis.

A serious immunodeficiency state is formed with a severe degree, all the studied parameters turned out to be significantly lower than normal. Thus, these studies, which were, as it were, preliminary, indicate a serious immuno-pathological state of the body, which accompanies moderate and severe forms of stomatitis.

Therefore, the obtained fact was a sufficient justification for the use of immunomodulatory agents as adjuvant therapy, in a particular case - LAZOLEX. We note that this drug significantly increases the effectiveness of traditional treatment, and from an immunological point of view, we can reasonably assert that it contributes to the immunorehabilitation of patients (see table 2).

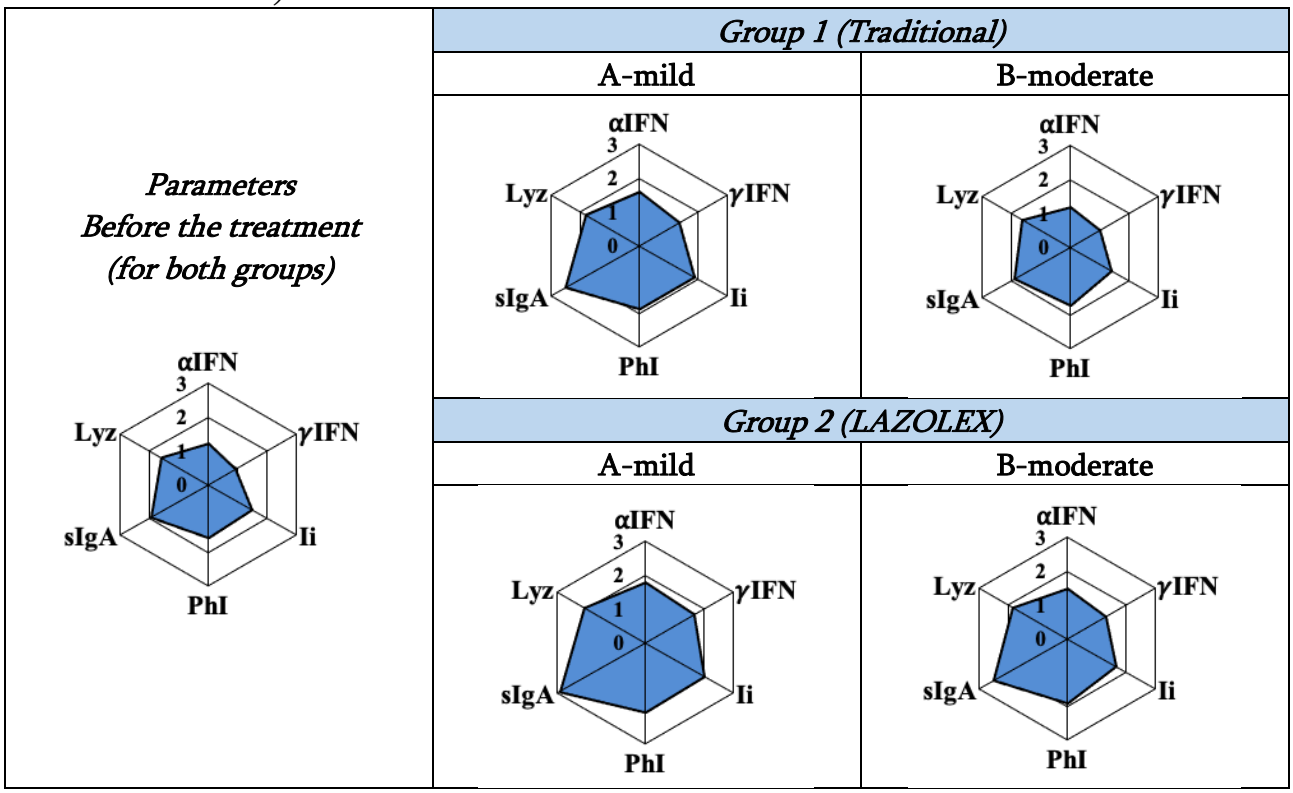
For a better perception of this data, we used immunograms, in which the control information is presented in the form of a regular hexagon. The shaded (irregular) polygon reflects the dynamics of immunological indicators from different groups (for example, different severity of the disease, treatment, units of measurement).

***Table 2**. Immunological parameters in patients with RAS (10-13 days after treatment)*

Parameters	Severity of the disease (A – mild; B – moderate; C – severe).								Control (n=30)
	Before treatment (n=50)		A (n=20)		B (n=20)		C (n=10)		
	Group 1 n=20	Group 2 n=30	Gr 1 n=7	Gr 2 n=13	Gr 1 n=8	Gr 2 n=12	Gr 1 n=5	Gr 2 n=5	
αIFN (U/ml)	*24.7	*25.4	*32.55	36.9	*24.8	*30.7	*22.1	*26.1	**41.3**
γIFN (U/ml)	*13.7	*12.9	*19.6	24.4	*14.8	*18.8	*9.3	*9.9	**28.6**
Ii	*1.68	*1.72	2.17	2.31	*1.6	*1.9	*1.31	*1.34	**2.28**
PhI	*3.85	*3.9	4.65	5.1	*4.2	*4.7	*3.9	*4.4	**4.9**
sIgA (g/l)	0.28	0.25	*0.35	*0.41	0.26	*0.35	*0.16	*0.19	**0.28**
Lyz (%)	*33.5	*33.7	38.05	43.2	*34.1	38.6	*28.1	*29.3	**41.9**

Note: * indicates a significant difference with the control - Practically healthy volunteers.

***Immunograms**. Immune status of patients with RAS after treatment in Group 1 and 2 (comparison with control - line 2).*



Thus, the determination of the state of different links of immunity in patients with RAS is of great practical importance, since it allows predicting the course and outcome of an infection of the oral cavity. It is known that timely and pathogenetically justified therapy can achieve almost complete compensation for violations of homeostatic mechanisms [5, 10, 11]. In case of irrational treatment of patients, the indices of the body's immunocompetence may remain altered for a long time, which increases the likelihood of a torpid course of the disease and the occurrence of complications as a result of the activation of other pathogenic factors. Therefore, along with specific treatment, complex therapy is of decisive importance, including means aimed at restoring immune homeostasis (LAZOLEX).

Clinical efficacy was assessed according to the following criteria: [I] Time of epithelialization; [II] Duration of remission.

The results of a study showed that the use of LAZOLEX (Group 2) was accompanied by a significant improvement: Time of epithelization – depending on a disease form - Fibrinous (a) – 3-6 days, Necrotic (b) – 7-14 days and Glandular (c) – 9-14 days, compared to traditional treatment (Group 1) - (a) – 7-14 days, (b) – 10-21 days and (c) – 14-20 days.

Period of remission in group 2 was also improved: Fibrinous (a) – 6-9 months, Necrotic (b) – 4-6-7 months and Glandular (c) – 3-5 months, compared to traditional treatment (Group 1) - (a) – 3-4 months, (b) – 2-4 months and (c) – 1-2 months.

Specifically speaking about LAZOLEX, which was previously used by us for herpetic stomatitis as an adjuvant agent, and now for treatment of RAS, we can talk about the double action of the drug, it significantly increases the effectiveness of direct antiviral treatment, and from the immunological point of view, it contributes to the immunorehabilitation of patients. This opinion is based on the fact of a clear correlation between the clinical state of patients and the dynamics of immunological parameters [3, 6]. The drug is especially effective in showing its immunomodulatory properties in case of mild disease, when almost all parameters approach the control level. The action of LAZOLEX with an moderate form of stomatitis is quite reliable.

Our studies have convincingly shown that LAZOLEX can be successfully used to selectively neutralize the immunosuppressive effect of the herpes virus. We can talk about the various mechanisms of the indicated abilities of the drug, but the following seems to be the most acceptable to us with herpes, a hormonal imbalance is formed in the body, general and cellular hypoxia develops, destructive processes lead to intoxication. All these phenomena arise either against the background of an already existing immunopathology, or lead to it. In other words, with herpes, and also with RAS at least all four of these factors are present - hormonal imbalance, hypoxia, intoxication, immunopathology, with mutually reinforcing effects. In our opinion, these effects are realized due to physiologically active substances contained in the extract (antibiotic Juglon and flavonoids; trace elements; complex of vitamins C, E, PP), which enhance functional activity of immunocompetent cells. Therefore, the Juglone herbal extract tested by us (for the production of LAZOLEX) can be classified as active natural remedies that can be successfully used for the prevention and treatment of viral and bacterial infections, purulent-inflammatory diseases, as well as other pathological conditions that require an improvement in metabolic and adaptation processes [9, 16].

Conducted clinical, laboratory and immunological studies allow us to recommend LAZOLEX for active use in dental practice for RAS.

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МАРИАМ ГОГОТИШВИЛИ [1], НИНО АБАШИДЗЕ [2], НИНО КОРСАНТИЯ [3], НАТО КОРСАНТИЯ [4]

ИММУНОМОДУЛЯТОРНАЯ И КЛИНИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ПРЕПАРАТА «ЛАЗОЛЕКС» В ЛЕЧЕНИИ РЕЦИДИВНОГО АФТОЗНОГО СТОМАТИТА (РАС)

[1]Батумский Государственный университет им. Шота Руставели; [2]ТГМУ, Департамент заболеваний пародонта и слизистой ротовой полости; [3]ТГМУ, Департамент Одонтологии, [4]ТГМУ Департамент Дерматологии и Венерологии; Грузия.

РЕЗЮМЕ

Целью данного исследования было изучение иммуномодулирующих и клинических свойств грузинского препарата «ЛАЗОЛЕКС» у пациентов с рецидивирующим афтозным стоматитом (РАС). Клинико-иммунологические показатели были изучены у 50 пациентов, результаты показали корреляцию между состоянием иммунной системы и тяжестью РАС, т.е. наиболее тяжелая иммуносупрессия была зафиксирована у пациентов с тяжелым стоматитом. 5% гель «ЛАЗОЛЕКС» по сравнению с традиционной терапией показал такую же высокую клиническую активность, но наличие иммунокорригирующих свойств у ЛАЗОЛЕКС проявилось в улучшении качества лечения пациентов, уменьшении времени эпителизации и значительном увеличении продолжительности ремиссии. Проведенные клинические, лабораторные и иммунологические исследования позволяют рекомендовать ЛАЗОЛЕКС для активного использования в стоматологической практике при РАС.

MARIAM GOGOTISHVILI[1], NINO ABASHIDZE [2], NINO KORSANTIA[3], NATO KORSANTIA[4]

IMMUNOMODULATORY AND CLINICAL EFFECTIVITY OF THE DRUG "LAZOLEX" IN TREATMENT OF RECURRENT APHTHOUS STOMATITIS (RAS)

[1]Batumi Shota Rustaveli State University, [2]TSMU, Department of periodontal and oral mucosa diseases; [3]TSMU, Department of Odontology; [4]TSMU, Department of Dermatology and Venereology; Georgia

SUMMARY

The purpose of this study was to study the immunomodulatory and clinical properties of the Georgian drug “LAZOLEX” in patients with Recurrent Aphthous Stomatitis (RAS). Clinical and Immunological parameters were studied in 50 patients, the results showed the correlation between the condition of immune system and the severity of the RAS, i.e., the most severe immunosuppression was recorded in patients with severe stomatitis. 5% Gel of “LAZOLEX” compared to traditional therapy, showed the same high clinical activity, but the presence of immunocorrective properties in LAZOLEX manifested itself in an improvement in the quality of patient treatment: decrease of time of epithelization and a significant increase in the duration of remission. Conducted clinical, laboratory and immunological studies allow us to recommend LAZOLEX for active use in dental practice for RAS.

Keywords: lazolex, aphthous stomatitis, immunomodulatory effectivity, treatment