UDK 616.933.162-07/09

EVALUATION OF CHANGES IN INTERLEUKIN-4 LEVELS WHEN USING THE IMMUNOMODULATOR GEPON IN THE TREATMENT OF PATIENTS WITH CUTANEOUS LEISHMANIASIS

Rakhmatov O.B.
Bukhara State Medical Institute

Summary,

Observations were carried out in 43 patients with cutaneous (zoonotic) leishmaniasis aged 2 to 44 years. In all infected patients, the diagnosis of cutaneous (zoonotic) leishmaniasis was confirmed by clinical, epidemiological and parasitological methods.

In 10 healthy individuals, 12 patients with cutaneous leishmaniasis who received conventional medical treatment (control group) and 43 patients after 15 days of local and oral administration of Gepon immunomodulator (main group patients), the levels of Interleukin-4 in the blood were studied. showed changes.

Key words: *cutaneous (zoonotic) leishmaniasis, Hepon immunomodulator, Interleukin-4.*

Relevance of the topic:

In more than 80 countries of the world, many studies are being conducted to improve the treatment methods of cutaneous leishmaniasis and shorten its duration [1,2,3,9,11,12].

In recent years, the increase in warm weather around the world has led to the expansion of the geography of the disease and the extension of the duration of the season. For example, in Uzbekistan, the occurrence of the disease occurred in August-October, but in the last 2-3 years, this period corresponds to June-November [1,2].

The results, the positive effect of local application of methylene blue with the ALT-Vostok model-03 apparatus and Gepon immunomodulator prolonged the nodular and erosive stages of zoonotic leishmaniasis, shortened the duration of the gastric ulcer period, the total period [1,2] .

Cutaneous leishmaniasis, which has been relevant in Central, Western, Eastern, Northern, and Southern Asian countries since ancient times, is endemic and in some cases epidemic, causing economic damage to many countries in their development. Seasonal occurrence and long-term persistence of the disease causes social problems among the population. Since the foci of this disease are rodents living in endless deserts and steppes, and there are mosquitoes that transmit it, preventive measures to prevent this disease are not enough. Treatments performed for short-term treatment of the disease are not effective enough. One of the urgent problems is the fact that the production of drugs that affect leishmaniasis and are less harmful has not been established [5,6,8,9,10].

When the results of local and general use of Gepon, an immunomodulatory drug, were studied separately, the effect on the absolute and relative indicators of lymphocytes in the blood was significant. It was found that the effect on the relative and absolute index of lymphocytes in the blood was more pronounced in patients who were recommended to drink the drug Gepon and locally for 15-16 days compared to only drinking and only locally recommended for 15-16 days [1].

Intravenous laser therapy in patients with zoonotic leishmaniasis did not have adverse effects. Due to the positive effect on the amount of cytokines, wound healing was accelerated and caused a faster transition to the scarring period [3,7,9].

The increase of tourism and migration of the working population among the population will also play an important role in the spread of the disease in the future [11].

Enhances the synthesis of antibodies against any antigen of infectious etiology. The drug significantly increases the effectiveness of protective immunity against various infections and conditionally pathogenic microorganisms. In addition, peptides have antiviral activity in human cells infected with viruses, have antiviral activity against hepatitis C, herpes types 1 and 2, rabies, sexually transmitted infections, and in acute purulent diseases and postoperative infections. Can also be used in treatment [13, 14, 15].

Form highly modified vacuoles inside phagocytes, and their properties of reproduction and persistence are preserved [15, 16, 21,22].

Disruption of cellular cytokine transmission and other signaling pathways to avoid invasion by phagocytes is often considered a survival strategy of parasites.

Parasites enter macrophages, each of them has its own way of reducing macrophage activity. Some types of Leishmania change the communication system of infected macrophages or stop the production of cytokines and microbicidal molecules (nitric oxide, active oxygen species) and disrupt antigen presentation [16, 17, 18, 19, 21, 23, 27].

Inflammatory reaction is a non-specific protective part of the body, which is manifested by an increase in the number of granulocytes, macrophages and lymphocytes in the focus of inflammation. The first step in the induction of an inflammatory response is associated with the activation of anti -inflammatory cytokines (in particular, α-tumor necrosis factor (α-TNF)) [4].

α-TNF and ß-TNF are two structurally related cytokines able to destroy sensitive cells (mostly tumor cells) in vitro [20].

α-TNF is a major proapoptogenic cytokine. They cause apoptosis of blood cells. Synthesis of α-TNF by macrophages increases during various diseases. These cytokines interact with interleukin-2 using CD2 or CD3 receptors when activated, it is also produced in peripheral blood T-cells [25].

α-TNF is considered as an important polypeptide mediator of inflammation and cellular immune response [26].

When the results of local and general use of Gepon were studied separately, the effect on the relative and absolute index of B-lymphocytes in the blood ($SD19^+$) changes in the absolute and relative indicators of the amount of natural killer cells - (Natural killer cells (NK-$SD16^+$)) were significant [28].

30% of patients had serum levels of IL-4 > 1 pg/ml, which is consistent with other authors' data on the presence of this cytokine in the blood of 21-38% of patients with systemic scleroderma [29,30].

Of the Th2-dependent cytokines, possibly involved in the development of scleroderma fibrosis [31].

Inflammatory cytokine IL-4 have been reported in patients with lacunar and phlegmonous forms of the disease and complications such as parathyroid gland abscess, as well as in patients with moderate and severe forms of the disease [32].

The effect of IL-4 on the skin with scleroderma has been proven to stimulate collagen synthesis by fibroblasts, activation of fibronectin and tenascin synthesis [33, 34].

Purpose of work:

IL-4 levels in healthy individuals and in patients with cutaneous leishmaniasis treated with traditional medical treatments before wounding and 15 days after wounding and scarring .

Wounding period in patients with cutaneous leishmaniasis to determine the amount of interleukin-4 (IL-4) in the blood after 15 days of local and oral administration of Gepon immunomodulator according to the number of wounds and the age of the patient.

Materials and styles:

A total of 53 patients aged 2 to 44 years, whose diagnosis of cutaneous (zoonotic) leishmaniasis was confirmed by clinical, laboratory and epidemiological methods in the studied areas of Bukhara region in the summer-autumn period of 2018-2022, were studied.

IL-4 content in 10 healthy individuals, 10 patients with cutaneous leishmaniasis before wounding, on the 15th day after wounding, and during scarring (control group).

IL-4 in the blood serum after giving the immunomodulator Gepon 10 mg once orally and topically applying 2 mg once to the wounded area for 15 days from the time of wounding) to study changes in the dynamics of the amount (the main group of patients).

The amount of interleukin-4 in the blood was determined with an immunoenzyme analyzer using the "Interleukin-4-IFA-BEST" kit.

Statistical methods. To study the reliability of the data obtained as a result of studies, A.A. Vorobyov and I.P. M-mean, m-mean error, r-reliability difference were found using the criterion methods proposed by Ashmarin. The R-reliability difference is obtained from the Steward table.

Results obtained:

IL-4 in blood serum were studied before injury and on the 15th day after injury, during the period of scarring and after complete recovery (control group). It showed changes (Xmin-Xmax) of 6-14 pg/ml in healthy individuals, 15-24 pg/ml in pre-injury period, 20-42 pg/ml in the 15th day of injury and 18-28 pg/ml in the period of scarring.

Blood interleukin-4 in the main group of patients who received Gepon for 15 days gave the following results: 22-44 pg/ml in 8 patients with up to 3 ulcers, 28-48 pg/ml in 7 patients with 3-6 ulcers , in 6 patients with more than 6 lesions, it was 32-66 pg/ml.

In patients aged 11-20 years, 24-46 pg/ml in 6 patients with up to 3 lesions, 28-50 pg/ml in 4 patients with 3-6 lesions, 34-50 pg/ml in 3 patients with more than 6 lesions A result of 72 pg/ml was obtained.

In patients aged 21-40, the level of interleukin-4 in the blood was 26-54 pg/ml in 6 patients with up to 3 ulcers, 28-52 pg/ml in 4 patients with 3-6 ulcers, and more than 6 ulcers 2 patients had values of 38-72 pg/ml. The obtained results are reflected in Table 1.

Table 1

Interleukin-4 levels in patients with cutaneous leishmaniasis

Content learned	Inspection period	N (number of patients)	Xmin-Xmax	X±m	P
IL-4 (pg/ml)	In control group patients				
	Healthy persons	10	6-14	12±0,7	<0,001
	Until the injury period	12	15-24	22 ±0,6	<0,001
	Injury 15 of the era - on the day		20 - 42	28±1,7	<0,001
	Scarring during		18-28	23 ±0,8	<0,001
	Gepon after 15 days of topical and oral administration (main group)				
	In patients under 10 years of age				
	Wounds is up to 3 when	8	22-44	34±1,7	<0,001
	Wounds is 3-6 when	7	28-48	31 ± 1,5	<0,001
	Wounds is 6 a lot when	6	32-66	38 ± 1,0	<0,001
	In patients aged 11-20 years				
	Wounds is up to 3 when	6	24-46	32±1,2	<0,001
	Wounds is 3-6 when	4	28-50	37 ± 0,8	<0,001
	Wounds is 6 a lot when	3	34-72	41 ± 2,0	<0,001
	In patients aged 21-40 years				
	Wounds is up to 3 when	6	26-54	41 ± 1, 6	<0,001
	Wounds is 3-6 when	4	28-52	36 ± 1,3	<0,001
	Wounds is 6 a lot when	2	38-72	41 ± 2,0	<0,001

Comment: Reliability between the main and control groups was presented in the obtained results.

Table 2 shows the analysis of indicators of changes in interleukin-4 levels after local and general administration of Gepon drug for 15 days.

In order to clarify the results and determine changes in the dynamics, the dynamic changes in the amount of IL-4 in the blood of each group of patients were determined on the 1st-2nd day of the treatment and on the 15th-16th day of the treatment.

The obtained results showed that IL-4 levels in the blood serum of patients who did not receive Gepon immunomodulator were 17,75±0,001 on the 1st-2nd day of injury, and 22,06±0,02 on the 15th day of injury. This indicator in the blood serum of those who received Hepon immunomodulator was equal to 33,26±0,64 on 15-16 days after injury.

Table 2

The amount of IL-4 in the blood serum of patients who did not receive the immunomodulator Gepon (control group) and received it (main group)

Groups	Control group (n = 12) $M_1 \pm m_1$		The main group (n = 43) $M_2 \pm m_2$	
Periods of illness	In the pre-injury period	On the 15th day of injury	In the pre-injury period	On the 15th day of injury
IL-4 is opg/ml	22 ±0,6	28 ± 1,7	29±0,03	36±0,64

Comment: Reliability between the main and control groups was presented in the obtained results.

IL-4 levels in the blood before and after starting topical and oral administration of Gepon immunomodulator for 15 days, according to the number of wounds, gave the following results. It was 36±0,6 in 20 patients with up to 3 ulcers, 38±1,6 in patients with 3-6 ulcers, and 40±0,8 in patients with more than 6 ulcers.

Table 3

Serum IL-4 levels in patients with cutaneous leishmaniasis in relation to the number of lesions (day 15 of lesions)

IL-4 opg/ml relative to the number of lesions		
Up to 3 wounds	3-6 wounds	More than 6 wounds
36±0,6	38±1,6	40±0,8

When comparing the blood IL-4 level of patients with cutaneous leishmaniasis in relation to age and the number of wounds in the patient, it was found that the number of wounds in the patients with more than 6 and the number of wounds in persons under the age of 20 years is less and the number of wounds increases more than in those aged 20-40 . Instead, it was concluded that the large number of wounds accelerates the formation of cellular and humoral immunity against the disease.

Conclusion: When studying IL-4 levels in the blood before and after the start of topical and oral administration of Gepon immunomodulator for 15 days, compared to the control group patients, it was found that the IL-4 content in the blood serum of the

main group patients significantly changed in people with a large number of wounds and in those under 20 years of age.

Changes of the above indicators were determined reliably (R<0.05<0.001).

References:

1. Teri leyshmaniozi bilan kasallangan bemorlarda gepon Immunomodulyatorini qo‘llaganda qondagi limfotsitlarning o‘zgarishiga baxo berish. *Raxmatov O.B., Obloqulov A.R. Jurnal Tibbiyotda yangi kun 2022 yil 2(40)son 76-81 betlar.*
2. 2022/03/01/15-2-40-2022-Raxmatov.O.B. Obloqulov.A.R.,-yevaluation-of-changes-in-blood-lymphocytes-when-using-gepon-immunomodulators-in-patients-with-skin-leis’hmaniosis.
3. Improving the principles of treatment in patients with zoonotic leis’hmaniasis with the immunomodulator gepon and methylene blue using the alt-vostok device. Olim Bobomurodovich Rakhmatov, 2021/9, jurnal 湖南大学学报 (自然科学版) tom 48, nomer 9.
4. Intravenous laser blood irradiation in the complex treatment of patients with cutaneous leis’hmaniasis. Farxod A Maxmudov, Olim B Raxmatov, Ixtiyor I Latipov, Mirabbos K Rustamov, Gulnoza S’harapova, data publikatsii 2021/9, jurnal 湖南大学学报 (自然科学版), tom 48, nomer 9
5. Дранник Г.Н. Клиническая иммунология и аллергология: пособие / Г.Н. Дранник. - 4-е изд., доп. – К.: Полиграф плюс, 2010.- 547 с.
6. The use of “Sulfatcet-r”–gel in combination with zinc ointment to determine its yeffectiveness against acne disease. O.B Raxmatov, N.D Xayitova, 2021/12/4, Central asian journal of medical and natural sciences, tom 2, nomer 6, str. 227-230.
7. To identify genetic tendency of tendency of teenagers to acne and to yevaluate the yefficiency of zinc for the purpose of it’s prophylactic. O.B Raxmatov, N.D Xayitova, 2020, jurnal Новый день в медицине 4, стр. 129-132.
8. Analysis of registered patients diagnosed with gonorrhea in bukhara region and a method for comparing the yeffectiveness of the drugs used depending on the clinical course of . J.H Ozodov, O.B Raxmatov, 2020, jurnal novyy den v meditsine 4, str. 293-297.
9. Patients with a diagnosis of gonorrhea are registered in bukhara region and depending on the clinical course of the disease, separation into age and gender. O.B Raxmatov, J. X Ozodov, N.D Xayitova, data publikatsii, 2020, jurnal novыy den v meditsine №1, stranisы 347-350

10. Buxoro viloyatida atopik dermatit kasalligi bilan kasallanganlarning yoshga va jinsga nisbatan ajratilishi O.B Raxmatov, D.A Yusupov, 2021, jurnal scientific progress, tom-2, №6, stranisy 1718-1729.

11. Improving the principles of treatment in patients with zoonotic leis'hmaniasis with the immunomodulator gepon and methylene blue using the alt vostok apparatus. Rakhmatov Olim Bobomurodovich, Khus'hvaktova Madina Farkhodovna, data publikatsii 2021/1/31, jurnal the american journal of medical sciences and pharmaceutical research, tom-3, №01, str. 147-151.

12. Assessment of skin and mucosal changes during acute illness and remission of Covid-19 patients. M.F Xus'hvaqtova, O.B Raxmatov, data publikatsii 2021/10/30, jurnal Central asian journal of medical and natural sciences, str. 288-291.

13. Ранняя диагностика и совершенствование принципов лечения у болных с кожным лейшманиозом. Олим Бобомуродович Рахматов, Мадина Фарходовна Хушвақтова, дата публикации 2018, журнал Биология и интегративная медицина, №11.

14. Leyshmanioz, epidemiologiya, klinik namoyon bo'lishi, diagnostika va davosi. A.Yu. Rodin, A.V. Smirnov. Vestnik VolGMU 181-183 betlar.

15. Synthetic and natural immunomodulators acting as interferon inducers. Silin, D.S., Lyubomska, O.V., Yers'hov, F.I., Frolov, V.M., Kutsyna, G., Current pharmaceutical design, 2009. 15(11): p. 1238-1247. DOI: 10.2174/138161209787846847.

16. Иммуномодуляторы Иммуномакс и Гепон в комплексном лечении болных с острой гнойной хирургической инфекцией Чадаев, А.П., Нурписов, А.М., Пичугин, А.В., Атауллаханов, Р.И.,. Русский медицинский журнал, 2004. 12(24): п. 1427-1433.

17. Experimental and clinical study of immunomodulators Immunomax and Gepon in complex treatment of acute purulent surgical infection.Chadaev, A.P., Nurpisov, A.M., Antibiotiki i khimioterapiia [Antibiotics chemoterapy], 2004. 49(7): p. 9-16.

18. The biogenesis and properties of the parasitophorous vacuoles that harbour Leis'hmania in murine macrophages. *(Antoine J. C., Prina Ye., Lang T., Courret N.* (angl.) // Trends in microbiology. — 1998. — Vol. 6, no. 10. — P. 392—401. — PMID 9807783.)

19. Subversion of host cell signalling by the protozoan parasite Leis'hmania. *(Gregory D. J., Olivier M.* (angl.) // Parasitology. — 2005. — Vol. 130 Suppl. — P. 27—35. — doi: 10.1017/S0031182005008139. — PMID 16281989.)

20. The immunopathogenesis of atopic dermatitis and strategy of immunotherapy. Maxmudov, F. A., & Latipov, I. I. (2019). *Новый день в медицине*, (4), 53-57.

21. Hoofnagle J.H. Therapy of viral hepatitis / J.H. Hoofnagle // Digestion. — 1998. — № 59. — P. 563—578.

22. Evaluation of the quality of life of vitiligo patients by the yeffectiveness of combination therapy using the dermatology life quality index (dlqi). Latipov, I. I., Axmedovich, M. F., & Hamza o'g'li, O. J. (2021). *Web of Scientist: International Scientific Research Journal*, *2*(10), 55-63.

23. Атопический дерматит: иммунопатогенез и стратегия иммунотерапии. Махмудов, Ф. А., & Латипов, И. И. (2019). *Новый день в медицине*, (4), 195-200.

24. Karimkulovich, R. M., & Axmedovich, M. F. (2021). The use of Retinoids in the Approach to the Cosmetic Treatment of Acne. *Central Asian Journal Of Medical And Natural Sciences*, *2*(6), 44-48.

25. Шаропова Г.С. (2022). Изучит эффективности экстракта Алое при местном применения Зоонозного Лейшманиоза. *CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES*, *3*(1), 216-220.

26. Yoshikawa H., N Akajima Y., T Asaka K. Glucocorticoid supress autocrine survival of mast cells by inhibiting IL-4 production and ICAM-1 expression. J.Immunol., 1999, 162(10), 6162-6170

27. Щичкин В.П. Патогенетические значения цитокинов и перспективы цитокиновой (антицитокиновой) терапии /В.П. Шичкин// Иммунология. — 1998. — №2. — С. 9—13.

28. Analysis of registered patients diagnosed with gonorrhea in bukhara region and a method for comparing the yeffectiveness of the drugs used depending on the clinical course of . J.H Ozodov, O.B Raxmatov, 2020, журнал Новый день в медицине 4, стр 293-297.

29. O. B. Rakhmatov, Support of the Immunomodulator Hepon in Patients with Skin Leukemia in the Blood Analysis of Changes in B-lymphocytes and Natural Killer Cells, *American Journal of Medicine and Medical Sciences*, Vol. 12 No. 5, 2022, pp. 502-505. doi: 10.5923/j.ajmms.20221205.11.

30. Needlem an B.W., F Redrick M.W., Stair R.W. Interleukin-1, interleukin-2, interleukin-4, inteiieukin-6, tum or necrosis factor a, and interferon-y levels in sera from patients with scleroderma. A Rthr. Rheum., 1992, 35(1), 67-72.

31. Szegedi A., C zirjak L., U nkeless J.C . Serum cytokine and tion and anti-FC gamma R autoantibody measurements in patients with systemic sclerosis. Acta. Derm. Venerol., 1996, 76(1), 21-23

32. Salmon-Ehr V., Serpier H., Nawrocki B. Expression of IL-4 in scleroderma skin speciements and scleroderm a fibroblast cultures. Potential role in fibrosis. Arch. Derm atol., 1996, 132(7), 802-806.

33. Nagoeva M.X., Marjoxova M.Yu., Afashagova M.M. Izuchenie roli sitokinovogo profilya pri bakterialnyx anginax // Sovremennye problemy nauki i obrazovaniya.–2015. – № 6. ; URL:

34. Kuroda K., Shinkai H. Dow nregulated of decorin expression in dermal fibroblasts by interleukin-4. Arch. Derm atol. Res.,1997, 289, 476-480.

35. Lee K.S., Ro Y.J., Ryoo Y.W., Kwon H.S. Regulation of interleukin-4 on collagen gene expression in systemic sclerosis fibroblast culture. J. D erm atol. Sci., 1996, 12(2), 110-117.

36. Khushvaktova Madina Farkhodovna, & Achilova Donokhon Nutfilloevna. (2023). CLINICAL AND IMMUNOLOGICAL CHARACTERISTICS OF ATOPIC DERMATITIS IN CHILDREN LIVING IN THE TERRITORY OF OIL REFINERIES. RESEARCH AND EDUCATION, 2(2), 59–65. https://doi.org/10.5281/zenodo.7693042