

Evaluation of uveitis activity in Behcet's disease patients using BOS24

V.V. Neroev — Corresponding member of RAS, Dr. Med. Sci., professor, director¹
G.A. Davydova — MD, Cand. Med.Sci., researcher, department of retina and optic nerve pathology¹
L.A. Katargina — Dr. Med. Sci., professor, deputy director¹
T.A. Lisitsyna — Dr. Med. Sci., leading researcher, laboratory of systemic rheumatoid diseases²
Z.R. Khatagova — MD, ophthalmologist¹
Z.S. Alekberova — Dr. Med. Sci., leading researcher, laboratory of systemic rheumatoid diseases²

¹ Moscow Helmholtz Research Institute of Eye Diseases, 14/19, Sadovaya-Chernogryazskaya St., Moscow, 105062, Russia

² V.A. Nasonova Research Institute of Rheumatology, 34A, Kashirskoe shosse, Moscow, 115522, Russia

Purpose: to estimate the change of uveitis activity using Behcet's disease ocular attack score 24 (BOS24) during anti-inflammatory and immunosuppressive therapy of Behcet's disease (BD) patients. **Material and methods.** 144 (70.2 %) out of 205 patients with confirmed BD diagnosis (according to the criteria set out in ISGBD, 1990) had ocular lesions, 83 (57.6 %) of 144 had acute uveitis, 145 eyes displayed active inflammation. Uveitis activity was estimated in dynamics using BOS24 score, which consisted of 6 parameters with the maximum level of 24 points. **Results.** The initial average BOS24 score for 145 eyes with active uveitis was 7.38 ± 0.71 points. The most pronounced inflammatory changes were revealed in posterior pole areas — mostly in retina periphery, less frequently in the area of fovea and the optic disc. All patients with uveitis exacerbation received systemic therapy including glucocorticoids, cyclosporine and/or azathioprine. After 9.43 ± 2.47 months of therapy, the average BOS24 score dropped significantly ($p < 0.001$) to 1.86 ± 0.48 . The most notable positive changes were revealed in the anterior chamber ($p < 0.001$), the vitreous ($p = 0.002$) and in retinal periphery ($p < 0.001$). **Conclusion.** BOS24 is a reliable tool allowing a quantitative assessment of uveitis activity in BD patients and its change after anti-inflammatory and immunosuppressive therapy.

Keywords: Behcet's disease, uveitis activity index, therapy.

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Behcet's disease (BD) is a systemic vasculitis, or progressive damage of the eye, which often leads to the disability of the patient [1, 2]. According to data represented in literature, eyes are affected by this pathology in 50–70% of the patients with BD [1–4]. Inflammation can be detected in all parts of the choroid and is manifested by iritis, iridocyclitis, chorioretinitis, retinal vasculitis, retinal vein occlusion, optic neuritis, retinal neovascularization and vitreous hemorrhage [5]. In BD, it is most common to observe generalized or posterior uveitis; isolated anterior uveitis is detected only in 10% of patients [5]. According

to the recommendations of EULAR, glucocorticoids (GK), cyclosporin A, azathioprine and colchicine are successfully used to reduce the activity of the intraocular inflammatory process during BD [6]. Treating refractory uveitis during BD with inhibitors of tumor necrosis factor- α (TNF- α), in particular infliximab and adalimumab, significantly reduced the amount of acute uveitis (AU) cases and saved the majority of patients' vision [7–13]. Evaluating the degree of uveitis' activity and the effectiveness of therapy in patients with this cardiovascular disease is traditionally based on measuring the frequency

of AU, changes in visual acuity, localization of the inflammatory process (posterior and generalized uveitis are more serious than the anterior one), on the presence or absence of severe inflammatory manifestations (hypopyon; involvement of the retina, macula, or the optic nerve disc), and on the doctor's opinion about the severity of each exacerbation (mild, moderate, severe) [5]. However, AU does not always reflect the degree of its activity. To assess the overall activity of BD, the index of BDCAF (Behcet Disease Current Activity Form) is used. BDCAF takes into account only the presence of AU, and the degree of intraocular inflammation cannot be calculated from this index due to the subjectivity of the indicators reflected in the index [14, 15].

In 2014, the Japanese research group for the study of ophthalmic manifestations of the BD (the Ocular Behcet's Disease Research Group of Japan) highly valued and recommended the use of a new index, BOS24 (Behcet's disease Ocular attack Score 24), for assessing the activity of the current uveitis. The authors suggest using this index to assess the severity of each AU when seeking consultation from an ophthalmologist. If AU is observed in both eyes, the BOS24 index is calculated for each eye separately. When calculating the index, only objective data confirming the current inflammation is taken into account, and visual acuity is not taken into account, as it often does not correlate with the presence of AU. The signs of chronic inflammation, such as "old" cells in the anterior chamber of the eye or the destruction of the vitreous body and macular edema, are also often not considered. BOS24 is suggested for use in both prospective and retrospective studies, as well as in the clinical practice of an ophthalmologist dealing with uveitis [5].

The **PURPOSE** of this work was to evaluate the activity of the current uveitis and its changes while undergoing anti-inflammatory and immunosuppressive therapy using the BOS24 index in patients with BD.

MATERIAL AND METHODS

The study included 205 patients diagnosed by BD according to the classification criteria of the international group ISGBD 1990 [16]. All patients signed informed consent forms to participate in the study. The study was approved by the Ethical Committee of the V.A. Nasonova Research Institute of Rheumatology. All patients underwent a combined clinical, laboratory, and instrumental examination at V.A. Nasonova Research Institute of Rheumatology and at Moscow Helmholtz Research Institute of Eye Diseases.

Among the patients, there were more men (64.4%). The mean age of the group was 33.1 ± 0.77 years old; the mean duration of BD was $137.3 \pm$

8.21 months (about 11 years). Patients varied in ethnicity: 68.2% of them were natives of the North Caucasus and Transcaucasia, mostly ethnic Dagestanis (36.7%) and Chechens (10.9%), and 17.2% Russians. Among the 115 patients tested for being carriers of the HLA-B5 (51) antigen associated with BD, 69 (60.0%) had a positive result. In most cases, the diagnosis of BD was recognized late — in the 8th–9th year of the disease. The activity of BD was assessed using the BDCAF index [15], and the severity of BD evaluated according to the Ch. Zouboulis classification [17]. At the beginning of the experiment, the majority of patients (67%) had a high degree of severity the disease and a moderate ongoing disease activity (BDCAF averaged 3.39 ± 0.15 points). Adequate therapy of BD before hospitalization at the V.A. Nasonova Research Institute of Rheumatology was not performed in most cases. The average duration of the constant therapy of BD was 3.05 ± 0.46 years.

144 (70.2%) out of 205 patients had a damaged eye. 83 (57.6%) out of 144 patients with affected eyes were diagnosed with AU as BD became more severe. AU was considered as an acute appearance of intraocular inflammation with distinctive patient complaints (eye redness, floating opacities before the eyes, decreased visual acuity, etc.) and clinical manifestations of uveitis, which are revealed by biomicroscopy and ophthalmoscopy [5].

The activity of uveitis was assessed using the BOS24 index [5]. The maximum score for this index can be 24 points. A high score of BOS24 is characteristic of inflammatory retinal damage, especially in its posterior pole and foveal zone. When calculating the index, the intensity of inflammatory changes in 6 different areas of the eye is taken into account: "fresh" cells in the anterior chamber (maximum 4 points), vitreous transparency (maximum 4 points), damage to the periphery of the fundus (maximum 8 points), damage to the posterior pole (maximum 4 points), foveal lesions (maximum 2 points) and damage to the DZN (maximum 2 points) (Figure 1, Table 1). The severity of inflammation in

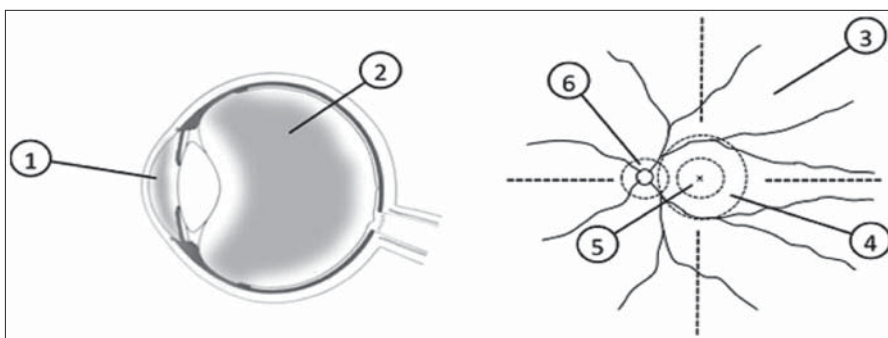


Fig. 1. Behcet's disease Ocular attack Score 24 (BOS24) [5].

1. Anterior chamber cells — 0, 1, 2, 3, 4 point. 2. Vitreous haze — 0, 1, 2, 3, 4. 3. Peripheral retina lesions — 0, 2, 4, 6, 8. 4. Posterior pole lesions — 0, 2, 3, 4. 5. Foveal lesions — 0, 2. 6. Optic disc lesions — 0, 2.

Total 24 points

Note. For scoring retina inflammatory signs the retinal field is divided into posterior pole (areas inside of arcade vessels) and peripheral retina (areas outside of arcade vessels) divided into 4 areas for each quadrant: temporal superior, temporal inferior, nasal superior, and nasal inferior.

Table 1. Behcet's disease Ocular attack Score 24) (BOS24) [5]

1	Anterior chamber cells (max 4 points, are graded using the grading scale presented by the SUN [18]): Cells: 0 – 0; 0,5+ or 1+ - 1; 2+ - 2, 3+ - 3; 4+ or hypopyon – 4 points
2	Vitreous haze (max 4 points, are graded using the grading scale presented by SUN and R. Nassenblatt [18, 19]): Haze: 0 – 0; 0,5+ or 1+ - 1; 2+ - 2, 3+ - 3; 4+ – 4 points
3	New inflammatory peripheral fundus lesions (max 8 points): give each 2 points in each quadrants of peripheral retina if new inflammatory changes (exudates, hemorrhages, vasculitis) are seen
4	New inflammatory posterior pole lesions (max 4 points): The percentage of areas occupying new inflammatory changes in the posterior pole of retina: 0 % - 0; > 0 and < 10 % – 2; ≥ 10 and < 25 % – 3; ≥ 25 % – 4 points
5	New inflammatory foveal lesions (max 2 points): give 2 points if new inflammatory changes (exudates, hemorrhages, vasculitis) are seen in the fovea
6	New inflammatory optic disc lesions (max 2 points): give 2 points if new inflammatory optic disc changes (redness and edema, sometimes accompanied by hemorrhages, exudates and edema of retina surrounding the optic disc) are seen

the anterior chamber of the eye is determined in the index by the number of cells in accordance with the slightly modified recommendations of the Standardization of Uveitis Nomenclature ((SUN) Working Group) [18]. The transparency of the vitreous body (maximum damage – 4 points) is estimated according to the scale proposed by R. Nussenblatt, et al. [19], with a minor modification.

To calculate the inflammatory changes on the retina, the latter is conditionally divided into the posterior pole (the zone between the temporal vascular arcades) and the peripheral retina (the zone outside the temporal vascular arcades). This quotient is then further divided into 4 more zones — the upper-temporal, lower-temporal, nasal, lower-nasal. When assessing the peripheral retina, 2 points are added for each quadrant with new inflammatory changes, specifically, exudate or hemorrhages (a maximum of 8 points is possible). Macular edema is often a manifestation of chronic inflammation; however, the absence of other signs of inflammation is not included in the calculation. When assessing the posterior pole of the retina, the percentage of the region with new inflammatory changes (hemorrhages, exudate) is considered excluding the macular edema zones. A score of 2 points is set if the zone of inflammatory changes does not exceed 10 %; 3 points are set if more than 10 % but less than 25 % is observed; if 25 % or more is measured, 4 points are set.

The fovea (the central part of the macula) is the most important prognostic feature for patients with BD, so any new hemorrhage or exudate in this area adds 2 points to the total score. New inflammatory changes in the area of the optic nerve disk (papilledema, accompanied by hemorrhages, exudate, or swelling of the peripapillary retina) are counted as 2 points in the calculation of the optic nerve disk abrasions.

For the statistical processing of the material, the parametric and nonparametric methods were used in the statistics programs Statistica 6.0 and SPSS. The results are presented in the form $M \pm m$, where M is the arithmetic mean and m is the standard error (standard deviation of each group's mean) and the median with interquartile range [Me (25th and 75th percentile)]. When comparing the groups averages, the dispersion analysis was used, which takes into account the size of the groups being

compared and the character of distribution of the feature studied. To check some of the calculations, when the use of parametric statistics methods could be incorrect, comparisons were made between groups using similar nonparametric methods with the Mann – Whitney test. The reliability of the frequency's differences was determined using the χ^2 test. A correlation analysis was carried out using the Fisher coefficient and Spearman's nonparametric correlation coefficient. Differences were considered significant at $p < 0.05$.

RESULTS

Patients with BD and AU did not differ in age from healthy patients (31.3 ± 1.58 and 35.30 ± 1.47 years), the age of BD's appearance (20.80 ± 1.41 and 22.10 ± 1.62 year), the age at the time of BD's diagnosis (29.30 ± 1.61 and 30.30 ± 1.45 years), duration of BD (124.2 ± 15.7 and 141.9 ± 13.9 months) and sex (men 71.7 and 65.0 % respectively). The eye infection duration in patients with AU was significantly less than in patients without AU (3.39 ± 0.57 and 6.94 ± 1.21 years, respectively, $p = 0.009$). The amount AU cases for the previous year was significantly higher in the group of patients who had AU at the time of examination (2.70 ± 0.43 and 0.24 ± 0.09 , respectively, $p < 0.001$). The overall activity of BD with respect to BDCAF did not differ significantly in the groups of patients (4.00 ± 0.35 and 3.24 ± 0.24 , respectively, $p = 0.17$). The duration of therapy with BD was significantly less than duration of BD, and in patients with OS it was significantly less than without OS (1.51 ± 0.52 and 4.34 ± 0.76 years, respectively, $p = 0.005$). The duration of glucocorticoid therapy (GK) was significantly less (1.0 (0; 12) and 10.0 (0; 36) months, respectively, $p = 0.015$), and the number of parabular GK injections in the last year was significantly higher in the group of patients with AU (5.50 ± 1.48 and 0.18 ± 0.17 , respectively, $p = 0.001$) (Table 2).

Active inflammation was detected in 145 eyes out of 83 patients with AU. 59 (71 %) patients had uveitis in general, 24 (29 %) patients — isolated posterior uveitis, and 59 (71 %) patients had bilateral lesions.

The average BOS24 score for 145 eyes with active uveitis at the time of enrollment in the study was 7.38 ± 0.71 (2 to 20) points. The average score for each

Table 2. Baseline characteristics of enrolled BD patients

Parameters	Patients with current ocular attack, n = 83	Patients without current ocular attack, n = 61	p
Gender (male/ female) (n /%)	60/23 (72/ 28)	40/21 (65/35)	n/s
Age, years (M ± m)	31.30 ± 1.58	35.30 ± 1.47	n/s
Age of BD manifestation, years (M ± m)	20.80 ± 1.41	22.10 ± 1.62	n/s
Age of BD diagnosis, years (M ± m)	29.30 ± 1.61	30.30 ± 1.45	n/s
Age of eyes involvement, years (M ± m)	25.30 ± 1.64	27.40 ± 1.85	n/s
BD duration, months (M ± m)	124.2 ± 15.7	141.9 ± 13.9	n/s
Duration of diagnosis, years (M ± m)	3.39 ± 0.57	6.94 ± 1.21	0.009
Duration of eye lesions, years (M ± m)	2.70 ± 0.43	0.24 ± 0.09	< 0.001
Number of ocular attack for the last year (M ± m)	8.42 ± 1.33	8.00 ± 1.09	n/s
BD current activity (BDCAF), point (M ± m)	4.00 ± 0.35	3.24 ± 0.24	n/s
Hs CRP, mg/l [Me (25%; 75%)]	1.76 (0.7; 16.1)	4.5 (1.4; 14.3)	n/s
Any treatment duration, years (M ± m)	1.51 ± 0.52	4.34 ± 0.76	0.005
Corticosteroid treatment duration, months [Me (25%; 75%)]	1.0 (0; 12)	10.0 (0; 36)	0.015
Current oral prednisone dose, mg/day (M ± m)	6.50 ± 1.22	7.89 ± 0.84	n/s
Parabulbar injections number per year (M ± m)	5.50 ± 1.48	0.17 ± 0.17	0.001

Note. n/s — difference is not significant, n — number of patients.

of the six parameters of the BOS24 index was as follows: 1) cells in the anterior chamber — 0.90 ± 0.14 ; 2) opacity of the vitreous body — 1.23 ± 0.14 ; 3) damage to the peripheral retina — $3,19 \pm 0,46$; 4) damage to the posterior pole — 0.57 ± 0.15 ; 5) damage in the fovea zone — $0,62 \pm 0,12$; 6) damage to the optic nerve disc — 0.53 ± 0.12 . Interestingly, according to BOS24, an active inflammatory process was noted most often in the peripheral retina (94 eyes, 64.8 %) and in the vitreous (86 eyes, 59.3 %). Inflammatory changes in the anterior chamber of the eye were detected in 55 eyes (37.9 %), in the fovea zone — in 45 (31.0 %), in the posterior pole — in 36 (24.8 %), and in the optic nerve disc region — in 34 eyes (23.4 %). The maximum severity of inflammatory changes in BOS24 was revealed mainly in the peripheral retina (8 points in 67 eyes, 46.2 %), less often in the fovea zone (2 points in 46 eyes, 31.7 %), and in the optic nerve disc (2 points in 40 eyes, 27.6 %). The maximum score of inflammatory changes (4 points) in the anterior chamber of the eye and in the posterior pole of the retina was distinguished only in 7 eyes (4.8 %). The maximum possible inflammatory changes in the vitreous body (4 points) were detected in only one (2.7 %) eye (Figure 2). According to the BOS24 index, the inflammatory activity of uveitis positively correlated with the number of AU in the last year ($R = 0.81$), the number of parabulbar injections of GK for the last year ($R = 0.71$) and skin damage ($R = 0.44$). Additionally, the inflammatory activity of uveitis negatively correlated with the patient's age ($R = -0.22$), the total duration of BD therapy ($R = -0.31$), genital ulcer infections ($R = -0.22$) and the pathergy test ($R = -0.25$).

All patients with active uveitis during acute BD were treated with the anti-inflammatory therapy GK. GK is a pulse therapy with 6-methylprednisolone at an average

total dose of 1.53 ± 0.32 g (0.25 to 2.5 g), the average oral dose of 6-methylprednisolone was 14.8 ± 1.28 mg/day (from 8 to 24 mg/day). 53 % of patients received cyclosporine A as an immunosuppressant at an average dose of 150 mg/day, 47 % azathioprine in a dose of 100–150 mg/day.

After 9.43 ± 2.47 months (1 to 36 months), all patients were examined again. By this time, the BOS24 index significantly ($p < 0.001$) decreased and amounted to 1.86 ± 0.48 (from 0 to 9 points). The average score for each of the 6 parameters of BOS24 was as follows: 1) cells in the anterior chamber — 0.12 ± 0.07 ; 2) opacity of the vitreous humor — 0.48 ± 0.13 ; 3) damage to the peripheral retina — $0,36 \pm 0,15$; 4) damage to the rear pole — $0,18 \pm 0,10$; 5) damage in the fovea zone — $0,34 \pm 0,13$; 6) damage to the optic nerve disc — 0.37 ± 0.14 . The difference in values was significant for cells in the anterior

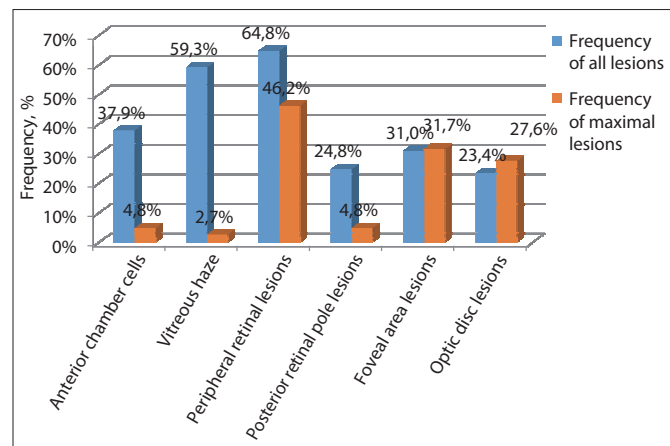


Fig. 2. Fig. 2. The frequency of the changes for each BOS24 parameters before the treatment.

chamber of the eye ($p < 0.001$), for opacity of the vitreous ($p = 0.002$), and for damage to the peripheral retina ($p < 0.001$) (Table 3). The number of AU in this year's group of patients after the initial examination and the immunosuppressive therapy, significantly decreased ($p = 0.002$) from 2.60 ± 0.49 to 0.17 ± 0.17 .

DISCUSSION

Uveitis with BD is described as a recurrent acute intraocular inflammation, often manifested as iridocyclitis with hypopyon, chorioretinitis, and occlusive angiitis. These inflammatory changes which are usually temporary can spontaneously disappear even without therapy. Evaluation of the activity of intraocular inflammation with BD is difficult since its form can vary greatly with time [5].

The evaluation of uveitis activity is based on defining the frequency of AU, the localization, and the severity of inflammatory changes [5, 7–9, 20]. The opinion of the doctor about the severity of uveitis is also considered [5]. The BDCAF index is used to evaluate the overall activity of BD [14, 15] and takes into account all the new clinical symptoms that have appeared in the patient 4 weeks prior to the medical examination. Determining the activity of uveitis with BDCAF depends on the patient's response to questions regarding the symptoms of uveitis (redness of the eyes, blurred vision, pain in the eyes) that have been present for the last 4 weeks. This assessment is partially subjective. The BOS24 index which was proposed by Japanese authors to assess the activity of uveitis in BD patients is free from these drawbacks.

BOS24 is the sum of scores for 6 parameters that characterize the main inflammatory changes occurring in BD patients with AU, and this score can be as high as 24 points. Since this index is composed only of objective data and does not take into account the patient's subjective opinion, it is preferable for scientific analysis. Therefore, BOS24 is proposed to be used in addition to BDCAF for assessing the activity of intraocular inflammation [5].

T. Kaburaki, et al. [5] proved the reliability of the BOS24 index and proposed it as an objective method for evaluating the activity of uveitis in BD patients. The authors first used BOS24 to evaluate the efficacy of infliximab therapy for uveitis activity and noted that this tool allows for objectively analyzing the beneficial effect of therapy.

In our work, we also demonstrated the possibility to objectify the intensity of intraocular inflammatory changes

that occur in patients with acutely developing BD with the help of the BOS24 index. Our studies showed that the areas that suffer most significantly from BD are the peripheral retina, the foveal zone, and the optic nerve disc. The degree of uveitis activity in BOS24 positively correlated with the frequency of AU, with the current total activity of BD according to BDCAF, and with skin damage, but not with the duration of BD treatment. Thus, AU in BD is associated with other symptoms of worsening BD that usually develop with inadequate immunosuppressive therapy. The results of our study which demonstrate that the activity of uveitis in BOS24 significantly decreased in patients undergoing therapy also allows us to consider BOS24 as a reliable tool for evaluating the effectiveness of uveitis therapy in BD patients.

It is important to note that this index does not only help evaluate the effectiveness of therapy with respect to the expression of intraocular inflammation in general; it can also be used to assess the detailed dynamics of inflammatory changes in specific areas of the eye. So, according to the data of T. Kaburaki, et al. [5], a more significant decrease in the expression of intraocular inflammation was noted in BD patients with infliximab therapy specifically in the vitreous, on the peripheral retina, and especially, in the posterior pole of the retina and in the foveal zone (i.e. in those areas where BD infection often leads to blindness). According to our data and the BOS24 index, the traditional therapy of GK and immunosuppressants results in a statistically more significant decrease of inflammation activity, in the anterior chamber of the eye, the vitreous, and at the periphery of the retina, than in the posterior pole. The dynamics of appearing inflammation in the posterior pole of the retina, the foveal zone, and on the optic nerve disc was also noted, but there were no significant differences (Table 3). Thus, taking into account the dynamics of BOS24, the effectiveness of TNF- α inhibitors, in particular infliximab, is shown to be more effective in preserving the visual acuity of patients compared to traditional immunosuppressants (cyclosporine and azathioprine) used in the treatment of AU in BD patients. In support of this conclusion, there are a number of studies demonstrating the benefits of TNF- α inhibitors over immunosuppressive drugs in the treatment of AU in BD patients [7–10].

It should be noted that the BOS24 index is fairly simple to use. It only considers new inflammatory changes such as, cells in the anterior chamber of the eye and in

Table 3. BOS24 parameters dynamics during treatment in BD patients, $M \pm m$

BOS24 parameters	Baseline BOS24, points	BOS24 after treatment, points	p
Anterior chamber cells	0.90 ± 0.14	0.12 ± 0.07	< 0.001
Vitreous haze	1.23 ± 0.14	0.48 ± 0.13	0.002
Peripheral retina lesions	3.19 ± 0.46	0.36 ± 0.15	< 0.001
Posterior pole lesions	0.57 ± 0.15	0.18 ± 0.10	n/s
Foveal lesions	0.62 ± 0.12	0.34 ± 0.13	n/s
Optic disc lesions	0.53 ± 0.12	0.37 ± 0.14	n/s

the vitreous, retinal hemorrhage, exudate, and retinal vasculitis which can usually be seen by any qualified ophthalmologist. In addition, it is possible to retrospectively calculate BOS24 from the ophthalmologist's examination records.

Despite the predominantly positive characteristics, BOS24 has a number of limitations. For example, the AU cannot be evaluated using BOS24 if the patient is unable to get to the ophthalmologist at the time in which the symptoms get worse. Moreover, it is difficult to assess the damage to the retina if the fundus is not ophthalmoscopically visible due to a pronounced turbidity of the vitreous, a vitreous hemorrhage, or because of cataracts. In such cases, to evaluate the activity of uveitis, it is necessary to use traditional methods which measure the frequency of AU and the visual acuity.

CONCLUSION

Based on the performed work, the BOS24 index should be widely introduced into the practice of ophthalmologists and rheumatologists involved in BD to make the assessment of the AU more objective, to prescribe adequate therapy, and to more efficiently evaluate the therapy's effectiveness.

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For contacts: Davydova Galina Anatol'evna
E-mail: 6298685@mail.ru