SHORT
COMMUNICATION

Predictors of Ophthalmic Manifestations in Patients with Ankylosing Spondylitis

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Abstract

The aim of this study was to conduct a clinical and statistical analysis of ophthalmological manifestations in patients with Ankylosing Spondylitis (AS) using biologic disease-modifying antirheumatic drugs (bDMARDs) as a basic therapy.

The study included 58 patients (19[32.7%] women and 39[67.3%] men) with AS receiving bDMARDs. The median age of patients was 41.81(25;60) years. The average age of the disease onset was 25.23(9;47) years. The patients were divided into two groups: Group 1 included 24 patients with ophthalmic manifestations; Group 2 included 34 patients without ophthalmic manifestations. All patients in Group 1 took TNF-α inhibitors, (infliximab, adalimumab, golimumab, etarnacept, and cetrolizumab-pegol). In Group 2, TNF-α inhibitors (infliximab, adalimumab, golimumab, etarnacept) were received by 32(92.4%) patients and interleukin-17 inhibitor (secukinumab) by 2(5.8%) patients. Group 1 was characterized by a greater age and average duration of the disease, as well as the presence of metabolic instability (blood glucose and creatinine levels in the borderline range). The effectiveness of bDMARD in AS is characterized by the normalization and stabilization of clinical and biochemical parameters, including blood cholesterol and creatinine levels, which prevents the occurrence of vascular lesions, including uveitis. (**International Journal of Biomedicine. 2022;12(3):470-473.**).

Keywords: ankylosing spondylitis • ophthalmopathy • uveitis • TNF-α inhibitors

Abbreviations

AS, ankylosing spondylitis; **NSAIDs**, non-steroidal anti-inflammatory drugs; **bDMARDs**, biologic disease-modifying antirheumatic drugs.

Introduction

Ankylosing spondylitis (AS) is a chronic, immune-mediated, inflammatory disease of the axial spine, which can manifest with various clinical signs and symptoms.[1] AS is characterized by damage to the spine, sacroiliac joints, peripheral joints and extra-articular manifestations such as inflammatory bowel disease, acute anterior uveitis and psoriasis.[2,3] AS is the most common form of the seronegative spondyloarthropathies with a prevalence of 0.03–1.8%, which varies depending on the frequency of HLA-B27 in the population.[4] Uveitis affects up to 50% of patients with AS, while it occurs in approximately 2%-5% of patients with inflammatory bowel disease and approximately 7% of patients with psoriatic arthritis.[4] The clinical presentation of the typical AS patient is that of a young male who gradually develops low back pain and morning stiffness. The disease begins earlier in patients with HLA-B27. It usually occurs in the second decade of life and rarely occurs after age 45. Men are more susceptible to the disease and are more likely to develop anterior uveitis.[4] Uveitis is most often characterized by recurrent, asymmetric, and bilateral iridocyclitis that affects only one eye per episode of exacerbation and is unrelated to

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the severity and course of joint damage.[4] This may be the first manifestation of AS, preceding other joint symptoms. AS is diagnosed in approximately 24.3% of patients with idiopathic acute anterior uveitis.[5] As a result, such patients first turn to an ophthalmologist, so early diagnosis, additional examination by a rheumatologist and treatment of the disease play an important role, which can lead to a more favorable prognosis. Non-steroidal anti-inflammatory drugs (NSAIDs) are used as the first line of treatment for patients with AS.[6,7] However, NSAIDs are ineffective in some patients with AS. According to the modern clinical guidelines, biologic disease-modifying antirheumatic drugs (bDMARDs) can be prescribed to patients with AS for any duration of the disease and functional status.[7,8] In the absence of contraindications, all patients with AS with recurrent or chronic uveitis, regardless of the activity of the disease, are recommended to be prescribed TNF-α inhibitors.[7,8] The determining factors in the choice of therapy are its effectiveness and safety for a particular patient.[6,8]

In this study, we investigated the ophthalmic manifestations of AS, since timely and correctly prescribed treatment directly affects the prognosis for visual functions and the prevention of long-term complications in this group of patients. The aim of our study was to conduct a clinical and statistical analysis of ophthalmological manifestations in patients with AS using bDMARDs as a basic therapy.

Materials and Methods

A non-randomized prospective study was conducted on the basis of the rheumatology department of the Regional Clinical Hospital No. 1. The study included 58 patients (19[32.7%] women and 39[67.3%] men) with AS receiving bDMARDs. The median age of patients was 41.81(25;60) years. The average age of the disease onset was 25.23(9;47) years. The debut of the disease was inflammatory back pain (51.7%), peripheral arthritis (41.4%), and anterior uveitis (6.9%). Extra-articular manifestations in the general group were represented by ophthalmic manifestations (41.4%), inflammatory bowel diseases (8.6%) and psoriasis (6.9%). The patients were divided into two groups: Group 1 included 24 patients with ophthalmic manifestations; Group 2 included 34 patients without ophthalmic manifestations. Ophthalmological examination included visometry, tonometry using non-contact pneumotonometer (Reichert Technologies), perimetry using PNR-2-01, biomicroscopy of the anterior segment of the eye and vitreous body on an SL-140 slit lamp (Carl Zeiss Meditec AG, Germany), and fundus ophthalmoscopy using a non-contact Ocular MaxField High Mag 78D Lens.

Statistical analysis was performed using STATISTICA 7 (Stat-Soft Inc., USA). Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean±SEM for continuous variables. Inter-group comparisons were performed using Student's t-test. The frequencies of categorical variables were compared using Fisher's exact test (2-tailed), Differences were considered statistically significant at $P<0.05$.

The study was conducted in accordance with ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the Tyumen State Medical University Ethics Committee. Written informed consent was obtained from each patient.

Results

Comparative analysis in the study groups (Table 1) showed the presence of significant differences depending on the age of patients and the average duration of the disease, which were higher in Group 1. At the same time, we did not reveal significant differences in gender and age of onset of the disease, which could be due to an insufficient number of observations. The level of total cholesterol and cretianine in the blood was significantly higher in Group 1 than in Group 2; the groups did not differ in terms of blood glucose levels. Hypercholesterolemia is the most important factor in the formation of endothelial dysfunction, leading to vascular damage, including the eyeball (uveitis). Thus, Group 1 was characterized by a greater age and average duration of the disease, as well as the presence of metabolic instability (blood glucose and creatinine levels in the borderline range).

Table 1.

Clinical and laboratory parameters in the study groups

Parameter	Group 1 (n=24)	Group 2 (n=34)	*P*-value
Gender (F/M)	9/15	10/24	0.5179
Age, yrs	45.87±1.92	38.94±1.79	0.0108
Average duration of the disease, yrs	19.83±2.01	14.35±1.52	0.0340
Age of onset of the disease, yrs	25.58±1.68	24.88±1.66	0.7680
Cholesterol, mmol/L	5.40±0.24	4.80±0.15	0.0385
Glucose, mmol/l	4.98±0.22	5.25±0.22	0.3893
Creatinine, μmol/l	91.90±6.21	78.07±2.69	0.0458

The structure of comorbidities in the study groups is presented in Table 2. No comorbidities were detected in 10(41.6%) patients in Group 1 and 18(52.9%) patients in Group 2, a result that was associated with a greater age in Group 1. The most common pathology in both groups was diseases of the cardiovascular system: 20.8% in Group 1 and 20.6% in Group 2. There was a tendency for the development of ophthalmological manifestations in patients with pathologies of the cardiovascular system, kidneys, gastrointestinal-intestinal tract, and anemia. It should be noted that diabetes mellitus and gout, which were detected only in Group 2 (in 5.8% of cases), were not accompanied by changes in blood parameters due to therapy to compensate for characteristic disorders. At the same time, metabolic disorders found in patients of Group 1 were associated with uveitis.

An analysis of bDMARDs used for the treatment (Table 3) showed that all patients in Group 1 took TNF-α inhibitors, (infliximab, adalimumab, golimumab, etarnacept, and cetrolizumab-pegol). In Group 2, TNF-α inhibitors

(infliximab, adalimumab, golimumab, etarnacept) were received by 32(92.4%) patients and interleukin-17 inhibitor (secukinumab) by 2(5.8%) patients. It is important to note that the patients who participated in the study were regularly observed by a rheumatologist and took basic therapy for the underlying disease, in connection with which there was a remission of the inflammatory process in the choroid, and only in one patient (1.7%) at the time of the examination did we find the exacerbation of chronic iridocyclitis in both eyes.

Table 2.
The structure of comorbidities in the study groups

Comorbidities	Group 1 (n=24)	Group 2 (n=34)	*P*-value
Cardiovascular diseases:	5 (20.8%)	7 (20.6%)	1
- arterial hypertension	3 (12.5%)	7 (20.6%)	0.499
- aortic valve disease	2 (8.3%)	0	0.167
Kidney diseases:	2 (8.4%)	2 (5.8%)	1
- chronic kidney disease	0	1 (2.9%)	1
- chronic tubulointerstitial nephritis	2 (8.4%)	0	0.167
- urolithiasis disease	0	1 (2.9%)	1
Gastrointestinal diseases:	2 (8.4%)	2 (5.8%)	1
- ulcerative colitis	1 (4.2%)	1 (2.9%)	1
-gastroduodenitis	1 (4.2%)	0	0,414
- Crohn's disease	0	1 (2.9%)	1
Metabolic disorders:	0	4 (11.6%)	0.134
- diabetes	0	2 (5.8%)	0.506
- gout	0	2 (5.8%)	0.506
Psoriasis	1 (4.2%)	2 (5.8%)	1
Mild anemia	2 (8.4%)	0	0.167
No comorbidities (according to the medical record)	10 (41.6%)	18 (52.9%)	0.435

Table 3.
The bDMARDs used for the AS treatment in the study groups

bDMARD	Group 1 (n=24)	Group 2 (n=34)	*P*-value
Infliximab	5 (20,8%)	11 (32,4%)	0.385
Adalimumab	7 (29,2%)	10 (29,4%)	1
Golimumab	7 (29,2%)	5 (14,7%)	0.205
Etarnacept	3 (12,5%)	6 (17,7%)	0.722
Cetrolizumab-pegol	2 (8,3%)	0	0.167
Secukinumab	0	2 (5,8%)	0.506

Case Presentation 1

A 49-year-old man with a debut of the disease at the age of 25. First symptoms of the disease: pain and stiffness in the spine. The patient sought medical help, but the diagnosis remained unknown for a long time. In 2015, after another examination based on complaints, anamnesis, and physiological examination, revealed HLA-B27, signs of sacroiliitis according to MRI data, the patient was diagnosed with "AS, advanced stage (2-sided sacroiliitis, Stage 3, according to Dale), moderate activity, HLA-B27 associated,

FC-1." Basic therapy included NSAID (Voltaren) and methotrexate 10 mg per week. The patient took the medicines regularly, but did not feel any obvious improvement. In 2016, for the first time, iridocyclitis in the right eye was diagnosed.

Biochemical blood test (01/13/2016): glucose - 4.77 mmol/l, total cholesterol - 5.9 mmol/l, creatinine – 108 µmol/l. Since 2017, the patient, under the supervision of a rheumatologist, has taken NSAID (nimesulide). During the period from 2016 to 2017, there were three exacerbations of chronic iridocyclitis in the right eye. Taking into account recurrent iridocyclitis of the right eye, moderate activity (BASDAI 2.8), working age, indications for the initiation of bDMARDs with TNF-alpha inhibitor golimumab (50mg subcutaneously once a month) were determined. However, there were episodes of recurrent iridocyclitis in January 2018, October 2018, and November 2019. The patient is currently taking bDMARD. Biochemical blood test (01/16/2021): glucose - 5.15 mmol/l, total cholesterol - 4.88 mmol/l, creatinine - 85.9 µmol/l. The data obtained show the stabilization of the blood cholesterol and creatinine levels. Since November 2019, no exacerbations of iridocyclitis have been determined.

Case Presentation 2

A 49-year-old man with a debut of the disease at the age of 35. First symptoms of the disease: pain in the spine and peripheral joints. The patient was long observed and treated for osteochondrosis, reactive arthritis. AS was diagnosed the first time in 2007. As a basic therapy, the patient took sulfasalazine for several years. In January 2016, he was hospitalized in the rheumatology department with a diagnosis of "AS, advanced stage, HLA-B27-associated, peripheral arthritis, high degree of activity (BASDAI 5.4), FC-2." Therapy: NSAIDs, vascular therapy, ½ pulse glucocorticoid therapy; a short-term positive effect was noted. Since March 2016, methotrexate has been prescribed at a dose of 10mg, after which the patient noted short-term dyspepsia. There was no clear positive dynamics from inpatient and outpatient treatment. Taking into account the diagnosis of AS, high inflammatory activity, ineffectiveness of the therapy, including methotrexate, and the short-term and incomplete effect of a program of treatment with corticosteroids, the patient was prescribed a course of infliximab therapy from July 2016 (300 mg once every 8 weeks), against which positive clinical and laboratory dynamics were noted. Biochemical blood test (06/06/2016): glucose - 4.94 mmol/l, total cholesterol - 4.44 mmol/l, creatinine – 70 µmol/l; 03/02/2021: glucose - 5.18 mmol/l, total cholesterol - 4.21 mmol/l, creatinine – 79 µmol/l. In the period from June 2016 to February 2021, no ophthalmological manifestations were detected.

Thus, the analysis of clinical and laboratory parameters revealed characteristic features that can be considered as biological markers of ophthalmic manifestations in AS (age, duration of the disease, and blood cholesterol and creatinine). The effectiveness of bDMARD in AS is characterized by the normalization and stabilization of clinical and biochemical parameters, including blood cholesterol and creatinine levels,

which prevents the occurrence of vascular lesions, including uveitis.

Competing Interests

The authors declare that they have no competing interests.

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