ISSN 2729-8043

INTERNATIONAL JOURNAL OF

ORIGINAL MEDICINE

Original Medicine. Volume 1 Issue 1 2022
ISSN 2729-8043
Impact Factor Search 5
https://www.original-medicine.eu/

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Original Medicine.
ISSN 2729-8043 https://www.original-medicine.eu
Michalská 2, Bratislava, Slovakia, 81121
E-mail: info@original-medicine.eu

Original Medicine. Volume 1 Issue 1 2022
ISSN 2729-8043
Impact Factor Search 5
https://www.original-medicine.eu/

CLINICAL EFFICACY AND TOLERABILITY OF INFLIXIMAB IN PATIENTS WITH SEVERE ANKYLOSING SPONDYLITIS

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Abstract: This article is devoted to the effectiveness of the treatment of ankylosing spondylitis (AS), one of the chronic inflammatory disease of the musculoskeletal system. The study included 53 patients with active AS (BASDAI activity index >4) and failure of standard therapy, which included the TNF-a inhibitor infliximab (INF) at a dose of 3-5 mg/kg intravenously for 0, 2, 6 weeks and next every 8 weeks. In patients treated with INF, a positive clinical effect was achieved by indicators BASDAI and BASMI scores, as well as a remarkable positive result in dynamics vertebral mobility index and BASFI score. Tolerability of INF patients was satisfactory.

Keywords: ankylosing spondylitis, diagnosis, treatment, TNF-α inhibitors, infliximab.

Ankylosing spondyloarthritis (AS) is one of the common chronic inflammatory diseases of the human musculoskeletal system. The frequency of occurrence of AksC among the population reaches 0.9% [1]. In most patients with AS (81-97%), the first symptoms of the disease occur before the age of 40, and it is very rare in children under 10 years of age (2%), as well as in people over 50 years of age (5%). Men are 3 times more likely to suffer from AS than women [2,3].

The social importance of the problem stems from the fact that the main contingent of patients is young people, and the disease often leads to long-term and early disability. More than 20% of patients with AS become disabled in the first 5 years, 45% in those who have had the disease for more than 10 years, and 60-65% of patients with ankle injuries [4]

Currently, the principles of treatment of AS are undergoing significant changes due to the availability of detailed information about the course of the disease and its consequences, improvement of diagnostic methods, clarification of classification criteria, and a deeper approach to understanding the molecular mechanisms of chronic inflammatory diseases.

At the end of the 90s of the last century, genetically engineered biological drugs (GIBP) were introduced into clinical practice, blocking the activity of tumor necrosis factor-α (TNF-α), which is the most important mediator of the immune-inflammatory process in various human diseases [5, 6].

At present, infliximab (INF), an inhibitor of TNF-a, is registered for the treatment of AS in Uzbekistan. IFN is a chimeric monoclonal antibody of the IgG1 isotype to TNF-α.

The aim of our study was to evaluate the efficacy of INF medication in the treatment of AS patients.

Patients and methods. 53 AS patients (37 men, 16 women) who were treated from September 2020 to September 2022 in the rheumatology and arthrology outpatient department of the multidisciplinary clinic of the Tashkent Medical Academy were involved in the study. General characteristics of patients with AS are presented in Table 1. We included in the study patients who were ineffective and had an active stage of the disease (BASDAI activity index >4) for 4 weeks, despite receiving maximum doses of nonsteroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate, glucocorticoids (GC) for the last 3 months. 53 patients enrolled in the study received INF at a dose of 3-5 mg/kg/body weight intravenously at weeks 0, 2, 6 and every 8 weeks thereafter.

BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score), functional condition - BASFI (Bath Ankylosing Spondylitis Functional Index) and BASMI (Bath Ankylosing Spondylitis Metrology Index) were used to evaluate disease activity. The validated MASES (Maastricht Ankylosing Spondylitis Enthesitis Score) enthesitis index was used to calculate the number of enthesitis. Pain in the spine and joints during the last week was assessed using a visual analogue scale (VASh).

Erythrocyte sedimentation rate (EChT) was studied by the Westergren method. HLA-B27 antigen was determined in all patients and X-rays of the pelvis were performed. According to Kellgren-Lawrence (1987), symptoms of unilateral or bilateral sacroiliitis (SI) were identified in 41 patients. In 34 patients with inflammatory low back pain and other manifestations of spondyloarthritis, no radiographic signs of SI were detected; They underwent MRI to diagnose SI. To detect acute inflammation, STIR mode (with fat suppression) T1 and T2 modes were used (T2 fat saturation) or T2 STIR. SI was considered reliable in the presence of multiple inflammatory zones of bone marrow tumor in two consecutive sections or in one section. The study was performed on a SIGNAHDxt 3.0T device (USA).

The most common systemic manifestations are eye damage (uveitis, iridocyclitis) in 18 patients (20%), fever in 9 patients (10%), anemia with a decrease in hemoglobin to 120 g / l in 29 patients (33%) and aortitis it was found in 3 patients (3%) with aortic insufficiency.

Laboratory examinations were provided by clinical analyzes of blood and urine, biochemical blood tests, determination of the level of S-reactive protein (CRO), determination of HLA-B27.

Table 1

General characteristics of patients with AS

Parameters	Indicators (total number of patients 53)
Men/women	42/11
Age of patients, in years	35±9
Disease duration, years	13,9±7,5
Peripheral arthritis, n (%)	36 (67)
Systemic manifestations, n (%)	37 (69)

Sulfasalazine/methotrexate, n	27/18
GK ingesters, n	13
Activity according to ASDAS is moderate/severe, n	23/33
BASDAI index (0-10)	8,3±3,7
BASFI index (0-10)	6,2±2,5
BASMI index (0-10)	19,4±8,1

Side effects of therapy with O'NO-α inhibitors were noted based on the dynamics of clinical and laboratory analyses. The effectiveness of therapy was evaluated after 12, 24 and 48 weeks.

Criteria for partial remission of AS include assessment of the patient's general condition according to VASh (0-10), pain - VASh score (0-10) during the last 2 days, BASFI function of the musculoskeletal system (0-10), severity and duration of morning sickness (the average value of questions 5 and 6 of the BASDAI index). Partial remission - the values of all four indicators should not exceed 2 points on a 10-point scale.

Statistical processing of the results was performed using the Statistica 6.0 software package (StatSoft, USA), including commonly accepted parametric methods and non-parametric analysis. The Mann-Whitney test for two groups was used for parameters with non-normal distribution in the comparison, with results presented as median (Me) (25th; 75th percentile). Correlation analysis was carried out by the Spearman method. Differences were considered statistically significant at $r<0.05$.

Results. Of the 53 patients, 41 (77.3%) met criteria for AS (mean age 36.4 ± 0.9 years) and 12 (22.6%) met criteria for nonradiological axial spondyloarthritis (Nr-axSpA) (mean age 27, 0 ± 1.6 years). General characteristics of patients with AS and Nr-axSpA are presented in Table 1. As can be seen from the table, there are more men than women in both groups. There were no differences in age of disease onset between patients in both groups. In the Nr-axSpA group, female patients were slightly older at the time of the first symptoms of the disease, but these differences were not significant ($r>0.05$). There were no significant differences in the time of diagnosis, although female patients were diagnosed with AS later than men ($r>0.05$). HLA-B27 antigen was detected in 92% of patients in both groups.

Table 2

General characteristics of AS and Nr-axSpA patients

Indicators	**AC (n=41)**		**Hp-axCпA (n=12)**	
	men (n=28)	**women (n=13)**	**men (n=7)**	**women (n=5)**
Age, in years	36,6 ± 1,0	36,2 ± 1,2	25,9 ± 1,4	29,7 ± 2,4
Age at disease onset, in years	21,5 ± 0,6	21,6 ± 1,0	20,3 ± 1,4	25,2 ± 2,1
Disease duration, years	14,6 ± 0,6	15,1 ± 1,1	3,9 ± 1,8	4,4 ± 1,0
Time of diagnosis, in	11,5 ± 0,8	12,0 ± 1,2	2,9 ± 0,4	4,2 ± 1,0

years				
HLA-B27-antigen, n (%)	71 (86,6)	31 (91,7)	22 (91,6)	8 (80,0)

Selection of patients for treatment with INF was performed according to the International ASAS Study Group working recommendations, which suggest that patients should be based on persistently high disease activity despite adequate use of nonsteroidal anti-inflammatory drugs (NSAIDs). Ineffectiveness of sulfasalazine/methotrexate and local therapy with glucocorticoids (GC) was also noted in patients with peripheral arthritis/enthesitis.

Before starting INF therapy, all patients underwent a comprehensive clinical and laboratory examination; X-ray examination of the lungs and evaluation including intradermal tuberculin test. Patients with a history of tuberculosis, as well as patients with a positive tuberculin test, were not included in the study. In addition, the use of INF was also excluded in comorbid conditions with any active or frequently recurring, serious infections.

12 weeks after the start of INF therapy, clear clinical and laboratory dynamics were revealed: the concentration of EChT and CRO decreased by 2 times, the level of hemoglobin increased. During 24 and 48 weeks of therapy, significant laboratory changes were observed in patients receiving INF, and at the end of the 48th week of treatment, in this group, EChT decreased more than 3 times, CRO level - 6 times (Table 3).

Table 3

Dynamics of laboratory indicators against the background of treatment with infliximab

Indicators	Initial	12 weeks		24 weeks		48 weeks	
		n=53/33	P	n=42/24	P	n=37/15	P
EC, mm/h	39,6±15,8	19,8±12,4	<0,001	17,2±13,8	<0,001	18,6±10,3	<0,001
SRO, mg/l	36,8±17,3	13,2±10,6	<0,001	9,8±11,4	<0,001	7,9±14,6	<0,001
Hemoglobin, g/l	115,7±14,5	129,5±10,8	<0,001	133,8±12,3	<0,001	137,6±15,3	<0,001

After returning to the generally accepted conditions of taking drugs, a decrease in disease activity was noted. Analysis of the effectiveness of therapy according to the disease BASDAI index showed a significant decrease in the clinical activity of AS even after 12, 24 and 48 weeks after the start of treatment.

At the end of the 12th week of treatment in patients receiving INF, the average BASDAI value was 5.5 ± 2.5, after 24 weeks - 4.3 ± 2.0 and after 48 weeks - 3.8 ± 2.0 points; More specific dynamics were noted after 48 weeks of therapy. Partial remission (BASDAI <4 points) was achieved in 24 patients (64%) (Figure 1). By the end of the follow-up, the activity index was reduced by 2 times in patients treated with INF.

Original Medicine. Volume 1 Issue 1 2022
ISSN 2729-8043
Impact Factor Search 5
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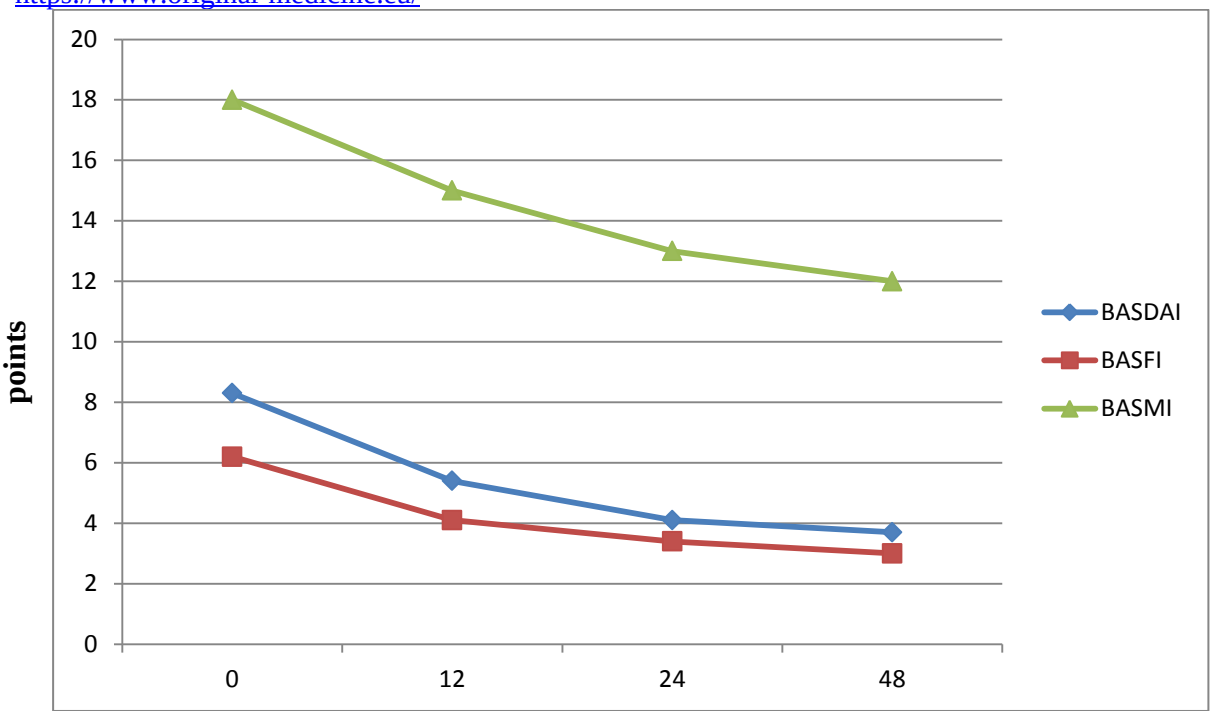

Figure 1. Dynamics of BASDAI, BASFI and BASMI indices against the background of treatment with INF in patients with AS.

According to the ASDAS index, initially high AS activity was detected in 33 (62%) patients. 12 weeks after the start of therapy, AS activity was significantly reduced in 69% (37 of 53) of INF-treated patients and minimal in 51% (19 of 37). After 24 weeks, high activity of the inflammatory process remained in 2 (4%) patients, moderate - in 21 (50%) and low - in 19 (45%) patients.

Assessment of the functional state of the musculoskeletal system using the BASFI index (Fig. 1). It showed significant changes after 12 weeks of treatment. The average value decreased by more than 2 times and was 4.2±2.2 points in the INF group, after 24 and 48 weeks of treatment, a stable improvement of functional ability was observed compared to the initial values. In patients receiving INF, a low level of BASFI was found in 25 (67%) patients, and in 9 (24%) patients no functional disorders were observed.

A positive trend was observed in the assessment of the functional state according to the BASMI index: after 12 weeks of treatment with INF, the index decreased to 16.1 ± 7.3, after 24 weeks - to 14.1 ± 5.3, after 48 **weeks** 6 ± 4, decreased to 8 (Fig. 1). Positive changes were also observed in spine indices (Table 4).

Table 4

Dynamics of spine indices against the background of treatment with INF in patients with AS

Indicators	Initial	12 weeks		24 weeks		48 weeks	
		n=53/33	P	n=42/24	P	n=37/15	P
U.p. neck rotation si, degrees	36,3±12,8	42,6±12,4	<0,001	41,3±10,4	<0,001	39,5±16,7	<0,06
Dakhan-tosh symptom, cm	1,4±0,8	1,1±1,7	<0,01	1,1±1,8	<0,01	1,0±1,6	<0,01
Tomayer's symptom, cm	36,3±25,9	20,3±27,6	<0,01	14,5±15,3	<0,002	10,6±16,3	<0,01
Chest excursion, cm	4,0±1,6	4,8±1,8	<0,001	4,6±1,1	<0,002	4,9±1,3	<0,002
Neck-wall distance, cm	3,8±4,8	2,9±3,9	<0,01	3,6±3,9	<0,001	3,4±4,0	<0,001
U.P. side bending, sm	12,4±7,1	16,2±6,5	<0,001	15,8±6,9	<0,001	16,6±7,4	<0,001
Shober test, cm.	2,6±1,5	3,7±1,3	<0,05	4,0±1,1	<0,05	3,9±0,8	<0,002

Explanation: U.P.- spine

At the initial stage of treatment with INF, a significant increase in spinal movements was observed. Statistically significantly improved average values were observed for rotation of cervical vertebrae (by 6°), chest excursion (by 1 cm), and side bends in the spine (by 5 cm). Such a positive dynamic confirms that the limitations in the movement of the spine in these patients are not caused by structural changes in the vertebrae, but by an active inflammatory process.

In our study, the evaluation of the effectiveness of INF treatment using the ASAS criteria showed that after 24 weeks of therapy, partial remission of AS was observed in most patients. Partial remission was achieved in 37 (69%) patients in the INF group.

Evaluation of tolerability and safety of infliximab. In our study, the overall incidence of adverse events (AEs) was 34%. Serious NT was detected in 2 patients in the INF group. In the 12th week of treatment, one of them had an allergic reaction: swelling of the left eyelid, sore throat, so the drug was canceled. In the second patient, the development of periodontitis after 24 weeks of treatment was the reason for the temporary withdrawal of INF until complete recovery.

After 12 and 24 weeks of therapy, 2 patients showed an increase in the number of leukocytes and platelets in clinical blood tests. In 9 patients, a transient increase in the level of liver enzymes more than 2 times compared to the upper limit of normal was noted. After a course of treatment with hepatoprotectors, these parameters returned to normal, INF treatment was continued. In 2 patients, 24 weeks after the start of therapy, the effectiveness of INF decreased and clinical and laboratory activity increased, so INF was changed to another drug (Table 5).

Thus, in our study, NT was observed in 20 (37%) patients, no deaths, malignancies, or tuberculosis were reported.

Table 5

Side effects observed against the background of treatment with infliximab (n)

Side effects	12 weeks	24 weeks	48 weeks
Hepatotoxic: ALT, AST, GGTP, IF	**3**	**3**	**-**
Hematological: leukocytosis, thrombocytosis	**1**	**-**	**-**
Increased creatinine level	**1**	**2**	**3**
Infectious complications: periodontitis, urinary tract infection	**-**	**3**	**-**
Skin: urticaria, allergic dermatitis, focal alopecia	**-**	**2**	**1**
Iridocyclitis relapse	**-**	**-**	**1**

Explanation: ALT - alanine aminotransferase, AST-aspartar aminotransferase, GGTP-g-glutaminetransferase, IF-alkaline phosphatase

Debate

The results of our study showed a high efficacy of IFN in most patients with AS. At the end of the 12th week of treatment with INF, normalization of EChT was achieved in 69% of patients. After 24 and 48 weeks, 67% of patients had persistently low EChT. CRO levels returned to normal in 64% of patients after 12 weeks of therapy, 78% after 24 weeks, and 72% after 48 weeks.

12 weeks after initiation of INF treatment, a 50% reduction in BASDAI disease activity was observed in 47% of patients ($r<0.05$); After 24 weeks - it was achieved in 66% of patients ($r<0.05$), after 48 weeks, the positive effect of therapy remained in 70%.

After 12 weeks of therapy, AS activity, according to the ASDAS index, significantly decreased in 69% of patients and was minimal in 51% of patients at the end of the study. Improvement of physical function (BASFI index) by 2 points after 12 weeks of treatment was found in 56% of patients ($r<0.05$), after 24 weeks - in 64% of patients.

Cervical spine rotation increased from 36.3±14.9° during INF therapy to 42.5±14.8° and 41.0±12.4° after 12 and 24 weeks, respectively ($r<0.001$); respiratory excursion of the chest (from 4.1±2.1 to 4.9±1.8 and 4.8±1.5 cm, 24 and 48 weeks, respectively; $r<0.003$); curvature of the lumbar spine (from 12.2±6.8 to 15.3±7.3 and 16.8±7.2 cm) at 12 and 48 weeks, respectively; $r<0.001$) was noted.

Patient acceptance of INF was generally satisfactory. The overall frequency of NTs we found was 37% (20 out of 53) patients, which was less than the reports of other authors. M. Breban et al. (2002) observed NT in 80% (40 out of 50), M. Schiff et al. (2008) - 52.1% (86 out of 165) and O.A. Rumyantseva (2010) - in 91% of patients (32 out of 35) [7, 8, 9]. Severe NT cases in INF therapy were less frequently detected in patients in our study compared to data from the BIOBADASER registry (Spain) (NT 5.8% (102 of 1915)) [10].

Most of the clinical studies of O'NO-α inhibitors focused on the development of infectious complications, including tuberculosis. According to the RATIO study, a risk factor for the development of tuberculosis was the age of patients during the first year of treatment with O'NO-α inhibitors [11]. Similar data are presented in the British register of biological products, in which reactivation of latent tuberculosis

during GIBP therapy and subsequent development of tuberculosis de novo were noted.

In our study, quantiferon test, diaskintest and chest X-ray were performed to rule out mycobacterial infection 24 weeks after the start of INF treatment. According to the results of the analysis, a positive test was not determined.

Summary:

1. In patients treated with INF, a clear clinical effect was achieved according to the BASDAI and BASMI indices, which in turn was associated with the initial high clinical and laboratory activity of the disease in patients.
2. A clear positive effect was also noted in the functional state of the locomotor system, which was confirmed by the dynamics of the spine mobility indices and the BASFI index.
3. Patient acceptance of INF was satisfactory. NT was noted with a frequency of 37% during the entire period of treatment. The results of our study were consistent with reports of good drug acceptance observed in patients with rheumatoid arthritis.

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