Clinical and laboratory evaluation of response to biological agents in Rheumatoid Arthritis and Ankylosing Spondylitis

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ARTICLE INFO

Article history:
Received 13 September 2018
Received in revised form 26 Sep. 2018
Accepted 23 October 2018

Keywords:
BASDAI
DAS28
Ankylosing spondylitis
Rheumatoid arthritis.

ABSTRACT

Our aim was to evaluate the anti-tumor necrosis factor (TNF) response to treatment, which has been in place in the treatment of Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) patients in recent years and has achieved successful results. In this regard, the follow-up of the disease is more predictable after the initiation of anti-TNF therapy; it is aimed to interpret the parameters used in follow-up more correctly. This cross-sectional, retrospective study was performed in a university hospital between 2010-2016. Files of 24 patients with AS and 53 patients with RA were retrospectively screened. Their clinical situations and laboratory levels were compared before and after the biological agent treatment. Treatment response with RA was evaluated by Disease Activity Score-28 (DAS28) scale and AS patients’ treatment response was evaluated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scale. A total of 77 patients were included in the study. Of the participants, 53 were diagnosed as RA and 24 were diagnosed as AS. After our study we have determined statistically reasonable decrease in C-Reactive protein (CRP), white blood cell (wbc), platelet, erythrocyte sedimentation rate (ESR) levels but an increase in blood urea nitrogen (BUN), haemoglobin (Hb), Albumin levels. The mean baseline score of BASDAI assessed before the treatment in 24 patients with AS was 6.08 and after the treatment was 3.42; DAS-28 assessed before the treatment was 5.77 and after the treatment was 3.58 and these differences were statistically significant. Patients treated with biological agents showed a significant improvement in clinical assessment evaluated by BASDAI in patients with AS and DAS28 in patients with RA. Significant decrease in CRP, ESR, wbc levels, improvement in chronic disease anemia, increase in albumin level as a negative acute phase reactant and decrease in thrombocyte levels were determined because of acute phase response and regression of inflammation.

1. Introduction

Ankylosing spondylitis (AS), usually arises around 20-30 years, is a disease that affects young people. Men are affected 2-3 times more frequently than women. First symptoms develop before the age of 30 in 80% of patients and over the age of 45 in less than 5% of patients (1).

AS is a chronic inflammatory disease associated with human leukocyte antigen (HLA)-B27 and its characteristic feature is that it affects sacroiliac joints in the early period and that the spinal cord is involved with the progressive disease. It can also keep the hip and shoulder joint. Peripheral joint involvement is generally asymmetrically. Non-skeletal findings may be associated with the disease. These include acute anterior uveitis, cardiac conduction disturbances, pulmonary disturbances especially fibrosis of apical lobe and renal involvement (secondary amyloidosis). AS is a disease that causes chronic pain and disability all over the world (2).

Tumor necrosis factor (TNF) alpha inhibitors are a turning point for AS therapy. Some of the most important studies on the role of TNF in AS pathogenesis are its relation to sacroiliitis, cartilage damage and erosion in transgenic mouse models, and reduction of these damages in animals given infliximab (3).

Rheumatoid arthritis (RA) is a chronic, autoimmune, multisystemic, inflammatory disease characterized by joint destruction of synovial cell proliferation and inflammation of unknown origin (4). It is the most common type of inflammatory arthritis with a frequency of 1% (5). Women are affected three times more common than men. Gender differences decrease with age. The disease most commonly occurs in the fourth and fifth decades (6). Interest in the use of biological agents has increased as RA copes with pathogenesis. In RA, cytokine balance is favored by
proinflammatory cytokines. Treatments to suppress cytokines have recently been among the treatment options. TNF is the most important proinflammatory cytokine.

Biological agents that block TNF alpha, as well as interleukin(IL)-1 and B cell inhibitors, are also used therapeutically. In addition, many new biological agents will be found as RA pathogenesis becomes evident (7).

Our aim in this study was to evaluate the anti-TNF response to treatment, which has been in place in the treatment of RA and AS patients in recent years and has achieved successful results. In this regard, the follow-up of the disease is more predictable after the initiation of anti-TNF therapy; it is aimed to interpret the parameters used in follow-up more correctly.

2. Material and Methods

The patients with RA and AS who were given anti-TNF treatment between 2010-2016 and followed by the immunology department of Karadeniz Technical University Farabi Research and Training Hospital, are this cross-sectional, retrospective study's universe. Ethics committee of Karadeniz Technical University Farabi Research and Training Hospital approved the study. The study conducted in accordance with the principles of the Declaration of Helsinki. The patients older than age of 18 years who were clinically and laboratory diagnosed with ankylosing spondylitis or rheumatoid arthritis, who had received at least six months of anti-TNF therapy, and volunteered to participate in the study were included. The patients were excluded from the study, who had anemia or thrombocytopenia associated with another reason, liver and renal dysfunction, a disease that caused immunodeficiency, who did not continue regularly with anti-TNF treatment for 6 months, did not volunteer to participate in the study, and under age of 18 years. Written obtained consent form was obtained from all the participants. The data were obtained retrospectively for 5 years between 2010 and 2016 by screening patients who applied to the immunology sciences and received anti-TNF therapy. During the sixth month follow up, obtained liver enzymes, renal function tests (blood urea nitrogen(BUN), creatinine), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti nuclear antibodies (ANA), immunoglobuline(IG)G, IGA, IGM, full urinalysis, complete blood count (CBC), rheumatoid factor (RF) and anti-cyclic citrated peptides (anti-CCP) values for rheumatoid arthritis patients and disease activity scores (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Disease Activity Score-28 (DAS28) were recorded.

2.1. Statistical Analysis

The data analysis was performed using the Statistical Package for the Social Sciences for Windows, version 22.0 (SPSS Inc, Chicago, IL, USA). The differences between groups were compared by using Mann-Whitney U-test and Kruskall Wallis H test where appropriate. Data were shown as mean±standard deviation or median (min-max), where applicable. A p value less than 0.05 was considered statistically significant.

3. Results

During the study period, a total of 134 patients were given anti-TNF therapy. Since 26 of these patients did not attend regularly for 6 months, since 4 of these had no communication address in hospital data system and since 27 of these did not have the necessary blood tests after the treatment, were excluded from the study. A total of 77 patients were included in the study. Of the participants, 53 (68.2%) were diagnosed as RA and 24 (31.2%) were diagnosed as AS.

The age range of the participants was 20-87 years (mean 47.4). The number of female patients was 50 (64.9%) and the number of male patients was 27 (35.1%). There was no statistically significant difference between the participants in terms of gender (p>0.05).

When laboratory values evaluated before and after anti-TNF therapy are examined: A statistically significant difference was detected in terms of White blood cell (wbc), haemoglobin (Hb), platelete (Pht), Bun, CRP, ESR and albumine (p<0.05) but not detected in terms of glucose, liver enzymes, renal function tests (BUN, creatinine), IgA, IgM, IgG, RF, Anti-CCP (p>0.05).

The mean baseline score of BASDAI assessed before the treatment in 24 patients with AS was 6.08 and this score was 3.42 after the treatment and this difference was statistically significant (p<0.001). Similarly, the mean baseline score of DAS-28 assessed before the treatment in 53 patients with RA was 5.77 and this mean score was identified as 3.58 after the treatment and this difference was statistically significant (p<0.001). Statistical analysis of laboratory data before and after treatment is shown in table 1 (Table 1).

4. Discussion

AS is a chronic inflammatory disease of unknown etiology, characterized by marked inflammation in the spinal joints and adjacent structures, leading to progressive bone fusion in the spine (8). Although CRP and ESR are the desired laboratory parameters in daily practice in the diagnosis and follow-up of ankylosing spondylitis, in recent studies, CRP and ESR have increased in only 30-40% of patients (9). RA is a chronic, inflammatory, systemic, autoimmune disease that has unknown origin, but rather involves synovial joints and progressive destruction around the joint. Erosive, symmetrical joint involvement is the most critical component of the clinical presentation, and extra articular findings may be accompanied by arthritis (10). American College of Rheumatology (ACR) criteria published in 1987 and ACR/European League Against Rheumatism
(EULAR) criteria published in 2010 are used in the diagnosis of RA (11).

Laboratory findings of RA are nonspecific. According to clinical signs and symptoms, diagnosis can be used to support or evaluate the course of the disease (12). In 85% of RA patients, RF is positive but not disease-specific. Recently, anti-CCP antibodies, which are more specific than RF in early RA, have been described. Anti-CCP is important not only to aid in diagnosis but also to point to a more severe and erosive disease (12).

Increase in CRP and ESR, anemia and thrombocytosis may indicate disease activity, too (13). There are many studies in the literature related to biochemically commonly used parameters and studies have focused specifically on CRP and ESR for evaluation of acute phase response. In a double-blind, placebo-controlled study that assessing 30 AS patients, Brandt et al (14) reported that there was a significant improvement in disease activity, pain, function, mobility, quality of life and CRP parameters at 6 weeks of treatment with etanercept. Kennedy et al. (15) defined that laboratory measurements except for active peripheral arthritis involvement are in normal range in patients with AS. In a study, patients who received 50 mg/week etanercept compared to the placebo group received a clinically meaningful response and improved CRP and sedimentation rate (16). There is also a study showing that adalimumab rapidly reduced CRP, ESR and serum cytokine levels (17).

Table 1. Statistical analysis of laboratory data before and after treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>8694 (N:77)</td>
<td>7699 (N:70)</td>
<td>0.009</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>12.52 (N:76)</td>
<td>13.27 (N:70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Platelet</td>
<td>320000 (N:76)</td>
<td>101000 (N:70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ALT (alanine aminotransferases)</td>
<td>21.39 (N:75)</td>
<td>22.83 (N:67)</td>
<td>0.213</td>
</tr>
<tr>
<td>AST (aspartate aminotransferases)</td>
<td>22.79 (N:58)</td>
<td>24.47 (N:58)</td>
<td>0.488</td>
</tr>
<tr>
<td>Glucose</td>
<td>99.14 (N:44)</td>
<td>93.87 (N:31)</td>
<td>0.101</td>
</tr>
<tr>
<td>Creatinin</td>
<td>0.70 (N:75)</td>
<td>0.72 (N:65)</td>
<td>0.170</td>
</tr>
<tr>
<td>BUN (blood urea nitrogen)</td>
<td>14.78 (N:25)</td>
<td>19.01 (N:30)</td>
<td>0.026</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>2.46 (N:76)</td>
<td>1.48 (N:69)</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR (Erythrocyte sedimentation rate)</td>
<td>49.09 (N:77)</td>
<td>30.55 (N:67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>proteinuria</td>
<td>9.76 (N:62)</td>
<td>6.45 (N:55)</td>
<td>0.461</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.07 (N:60)</td>
<td>4.17 (N:49)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

IG: immunoglobulin, anti-CCP: anti-cyclic citrated peptides, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, DAS 28: Disease Activity Score-28

On the other hand, Wang et al (18) in their studies with 35 patients with AS, ESH, CRP and platelet levels were found to be high. A study that is inconsistent with existing studies in the literature is also based on Mathieu et al. (19). In this study, patients with AS always had an elevated level of CRP with or without anti-TNF therapy, and no anti-TNF-treated CRP response was detected.

In our study, CRP levels were assessed in 76 patients before the treatment and in 69 patients after the treatment: mean CRP levels were 2.46 and 1.48 mg/dl, respectively and a statistically significant decline has been achieved. ESR, which is also an inflammatory marker, was evaluated in 77 patients before treatment and the mean ESR was 49.09 mm/h; in 67 patients after treatment and found to be 30.55 mm/h and this decline was statistically significant. The wbc values were evaluated in 77 patients before treatment and the mean wbc was 8694 U/mm3; in 70 patients after treatment and found to be 7699 U/mm3 and this decline was statistically significant, too. Our study showed that treatment of patients with biologic agents provided significant improvement in inflammatory markers and revealed data consistent with the literature. Hb levels increased after infliximab therapy in RA patients with anemia of chronic disease (ferritin> 60 ng / ml) without iron deficiency (20). Studies by Wolfe and Michaud (21) on patients with anemia and elevated CRP have shown that elevation of CRP is a strong predictor of anemia in patients with RA. There are new publications showing that anemia is resolved in RA patients after biological agent treatments (such as Tocilizumab and anti-TNF) (22). In our study, there was a significant increase in Hb levels after anti-TNF treatment. Hb values were evaluated in 76 patients before treatment and the mean Hb was 12.52 mg/dl and 70 patients were evaluated after treatment and found to be 13.27 mg/dl and this difference was statistically significant. We have clearly demonstrated that the anemia of chronic disease, which confronts RA and AS, is improved after anti-
TNF therapy. In our study clinical evaluation of treatment response was performed with DAS28 in RA patients and BASDAI scores in AS patients. Clinically, a significant clinical response to treatment was found in both groups of patients. The BASDAI score was assessed before and after treatment in 24 AS patients and the mean value before treatment was found to be 6.08, while it was found to be 3.42 after treatment and this difference was statistically significant. The DAS 28 score was evaluated in 53 patients before the treatment and the mean value was 5.77: in 46 patients after the treatment and the mean value was found to be 3.58. This difference was found to be statistically significant.

In a multicenter study conducted by Marte S. Heiberg et al. (23), patients with disease-modifying antirheumatic drug (DMARD)-resistant RA (n: 327) and AS (n: 71) were treated with etanercept or infliximab and disease activity and social function scores evaluated on third and sixth month of treatment. As a result, it was determined that the social function score was more improved in patients with AS than in patients with RA. Anti-TNF therapy in terms of response to disease activity was found to be similarly effective in both diseases. In another study conducted by J. Brandt et al. (24), 26 patients with AS were included in the study. The patient was administered 25mg etanercept subcutaneously twice a week. According to BASDAI and Bath AS Functional Index (BASFI) criteria, disease activity and treatment responses were evaluated. Treatment with etanercept at the end of the 54-week treatment was found to be effective and safe in patients without DMARD or steroid therapy. Baraliakos et al. (25) followed 26 AS patients for etanercept treatment for more than two years and their average BASDAI score was 6.3 before treatment and 2.6 after treatment. Comparable results were obtained in AS patients followed by etanercept treatment in another long-term study by Davis et al. (26). In another study, it was determined that Tolazumabum used in RA disease directly reduces acute phase reactants such as CRP and ESR. These acute phase reactants are significant components of the DAS28 scoring system and It is not surprising that significant changes are observed with treatment in the DAS28 scoring system (27). In another study, RA patients were followed up for up to 169 days with Abatasept treatment, and there was a significant decrease in the DAS28 scoring system and health assessment questionnaire disability index (28). In a study by Yang et al. (29), it has been shown that the level of BASDAI decreases after significant inhibition of TNF alpha. In a 24-week Adalimumab Trial Evaluating Long-Term Efficacy and Safety (ATLAS) study of Adalimumab (ADA)’s long-term efficacy compared with placebo in patients with AS studied by Van der Heijde D. et al. (30), BASDAI score regressed from 6.3 ± 1.7 to 3.6 ± 2.5 in 12 weeks and the ratio of patient’s have a regression of at least 50% in BASDAI was 45.2%. In another study in patients with AS, it is reported that a regression of -2.9 in BASDAI and -1.7 in BASFI at the end of 24 weeks with infliximab treatment (31).

Considering the studies in the literature, the therapeutic use of various biological agents in RA and AS patients resulted in a significant improvement in clinical as well as laboratory data. In our retrospective study, BASDAI was used for AS patients and DAS28 score was used for RA patients, and significant clinical improvement was observed, consistent with the literature.

5. Conclusion
As a result, patients treated with biological agents showed a significant improvement in clinical assessment evaluated by BASDAI in patients with AS and DAS28 in patients with RA. Significant decrease in CRP, ESH, Wbc levels, improvement in chronic disease anemia, increase in albumin level as a negative acute phase reactant and decrease in thrombocyte levels were determined because of acute phase response and regression of inflammation. Although there is no significant effect on transaminase levels, a more detailed assessment of liver function tests will be needed. The relationship between renal function tests and anti-TNF drugs is one of the issues that needs to be studied further in the coming years.

Funding and support: None.

Conflict of interest: Authors declare no competing interests.

Author Contributions: HD conceived the study and design the trial, supervised the conduct of the trial, data collection and drafted the manuscript, under took recruitment of participating patients and managed the data, including quality control. EKK drafted the manuscript and managed the data, including quality control and all authors contributed substantially to its revision.

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