Anti-interleukin-6 (tocilizumab) therapy in Takayasu’s arteritis: real-life experience

Abstract

Background/aim: Tumor necrosis factor inhibitors (TNFi) and anti-interleukin 6 (anti-IL-6) therapies are increasingly being used in Takayasu’s Arteritis (TA) patients unresponsive to corticosteroids ± conventional immunosuppressive agents. The aim of this study was to assess the efficacy and safety of anti-IL-6 (tocilizumab) therapy in refractory TA patients in real life.

Materials and methods: Fifteen (86.7% female) TA patients who received at least three cycles of tocilizumab therapy were retrospectively assessed using clinical, laboratory and radiological evaluation before and after tocilizumab therapy.

Results: The median (min-max) age of the patients at evaluation was 35 (20-58) years and the median disease duration from diagnosis was 24 (12-168) months. The median (min-max) duration of follow-up after tocilizumab was 15 (3-42) months. There was a significant decrease in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and visual analog scales (VAS)-patient-global of patients after tocilizumab therapy; median (min.-max.) ESR [26 (5-119) vs. 3 (2-49) mm/h, p = 0.02], CRP [39.8 (2.4-149.0) vs. 7.9 (0-92,9) mg/L, p = 0.017], VAS-patient-global [50 (0-90) vs. 30 (0-60), p = 0.027], respectively. In 8 patients ERS and CRP levels were in the normal range at last control. Imaging modalities after tocilizumab were available in 9 patients; 8 patients were radiologically stable and regression was seen in one patient. Comparable imaging modalities before and after tocilizumab were available in 5 patients; 4 patients were radiologically stable and regression was seen in one patient. Radiologic findings were...
consistent with laboratory response. Glucocorticoids dosage decreased from a mean dosage of 16.2 (9.1) mg/day at baseline to 7.1 (3.8) mg/day (p=0.001) at last follow-up visit. There was no increase in steroid dosage in any patient. All patients tolerated Tocilizumab well.

**Conclusion:** Based on retrospective real-life data, anti-IL-6 (tocilizumab) appears to be an effective and tolerable treatment option in refractory TA patients.

**Key Words:** Anti-Interleukin 6 (Anti-IL-6), Tocilizumab, Takayasu’s arteritis

**Key Point:** Anti-IL-6 (tocilizumab) therapy appears to be effective and tolerable in refractory TA patients.

1. **Introduction**

Takayasu’s arteritis (TA) is a rare chronic, inflammatory and granulomatous type of large vessel vasculitis that affects predominantly the aorta and its main branches [1]. Although high-dose glucocorticoids are the cornerstone of the medical therapy, almost half of patients need immunosuppressive agents due to relapses or resistance to glucocorticoids. Combinations of glucocorticoids with conventional immunosuppressives (methotrexate, azathioprine, mycophenolate mofetil and leflunomide) agents may lead to a better response and disease control. However, clinical relapses and progression of vascular involvement remain frequent [2]. Biologic therapies like TNF inhibitors (TNF-i) and anti-IL-6 therapies may be effective in TA patients with uncontrolled disease [3]. IL-6, which is shown to be expressed in TA arterial lesions, influences function of many cell types and have a role in vascular inflammation [4-6]. Preliminary studies and case reports suggested that tocilizumab, a humanized anti-IL6 receptor antibody, may be an option for refractory TA patients [7-15]. The aim of this
A retrospective, observational study was to assess the efficacy and safety of tocilizumab in refractory TA patients in real life.

2. Material and Methods:

2.1. Study population:

In the prospective database of the Hacettepe University Vasculitis Center (HUVAC), 105 TA patients meeting the 1990 modified American College of Rheumatology (ACR) criteria were registered by the end of July 2017. Totally, 28 (26.7%) patients received biologic therapies and 22 (21.0%) of them were treated with tocilizumab. After reviewing the charts of these patients, 7 were excluded (2 patients had less than 3 cycles of tocilizumab infusion, 3 patients had no follow-up data and 2 patients were referred to our center after the initiation of tocilizumab). Overall, 15 TA patients who had received at least three doses of monthly tocilizumab infusions and had available follow-up data were included. All included patients were treated with tocilizumab 8 mg/kg intravenously every 4 weeks.

2.2. Demographic and Clinical Features:

Demographic and clinical characteristics of the patients, acute phase reactants (erythrocyte sedimentation rate (ESR), c-reactive protein (CRP)) and visual analog scales (VAS) for pain, fatigue, patient global assessment were recorded at the initiation of tocilizumab therapy and last follow-up visit. Raised acute phase reactants was defined as; ESR > 25 mm in the first hour by Westergren method and/or CRP > 8 mg/L. Likert 0-100 mm scale was used for assessing VAS (pain, fatigue, patient global assessment). Data regarding prior and current immunosuppressive agents and concomitant glucocorticoids accompanying tocilizumab therapy were also recorded. In our cohort, some patients
received alternate day prednisone (or its equivalent). Therefore, glucocorticoid dosages of patients were calculated according to daily dosage of prednisone (or its equivalent).

Available computed tomography angiography (CTA) and/or magnetic resonance angiography (MRA) results of the patients within the 3 months prior to tocilizumab initiation and during follow-up were obtained from the hospital data system. According to the angiographic findings, TA patients were classified into five categories [16].

2.3. Laboratory and radiologic evaluations:

Patients’ clinical, laboratory and radiological data and treatments were analyzed at baseline (at initiation of tocilizumab) and last follow-up visit. Radiological evidence of new areas of vessel involvement or worsened vascular lesions was considered as ‘active’ disease. Radiological disease activity was classified as stable disease (absence of any change in lesions), progression (development of a new lesion: vessel wall thickening / irregularity, stenosis, occlusion, aneurysm and dilatation) and regression (decline in existing lesions). Patients were considered to have ‘clinically active’ disease if they had persistence or exacerbation of clinical symptoms and elevated inflammatory laboratory markers despite unchanged angiographic findings. The adverse events attributable to tocilizumab, such as infusion reactions, infections requiring hospitalization, elevated liver enzymes, hypertriglyceridemia and leukopenia were checked for safety assessment.

2.4. Ethical Considerations:

The Turkish Ministry of Health granted the compassionate use of anti-IL-6 for TA patients and every patient planned to use this treatment signed an informed consent form. Therefore, this study was performed after the approval of both the local ethical committee (approval number: GO 18/266-01) and the Turkish Medicines and Medical
2.5. Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 21.0; IBM Corporation, Armonk, NY, USA). Values are expressed as mean ± SD, median (minimum-maximum), unless indicated otherwise. Wilcoxon signed rank test used to compare parameters whenever appropriate. A P-value of less than 0.05 was considered as statistically significant.

3. Results

Fifteen (86.7% female) patients who had received at least three doses of monthly tocilizumab infusions and had available follow-up data were included in the analysis. The median (min-max) age of the patients was 35 (20-58) years and the median disease duration from diagnosis was 24 (12-168) months. The median (min-max) follow-up for tocilizumab therapy was 15 (3-42) months. Clinical and demographic characteristics of the patients were shown in Table-1. Before tocilizumab therapy, all patients received corticosteroids and at least one conventional immunosuppressives agent [12 (80%) patients received methotrexate, 7 (46.7%) patients received intravenous cyclophosphamide, 4 patients received azathioprine, leflunomide or mycophenolate mofetil]. Also, 5 (33.3%) patients received TNF-i before tocilizumab (Table-2).

Indications for tocilizumab therapy was as follows; radiologically active disease in 6 patients (acute phase reactants were normal in one of them) and clinically active disease in 9 patients (5 of them were radiologically stable, the other 4 patients had no radiologic imaging).
Tocilizumab was combined with methotrexate in 8 patients and in one patient with leflunomide. There was a significant decrease in median (min-max) ESR [26 (5-119) mm/h vs. 3 (2-49) mm/h, p = 0.02], CRP [39.8 (2.4-149.0) mg/L vs. 7.9 (0-92.9) mg/L, p = 0.017], and VAS-patient-global assessment [50 (0-90) vs. 30 (0-60), p = 0.027] after tocilizumab. In 8 patients, ESR and CRP levels were in the normal range at last follow-up visit. During follow up, tocilizumab was ceased in 2 patients; due to ineffectiveness in one patient (P5) and activation of accompanying ankylosing spondylitis in the other one (P6). Control vascular imaging studies after tocilizumab therapy were available in 9 patients; 8 patients were radiologically stable and regression was seen in one patient in comparison with the last imaging before tocilizumab. However, radiologically stable 4 patients had CRP levels above the upper limit of normal (another patient (P2) who has radiologically stable but increased acute reactants had concomitant active AS). The mean daily dose of prednisone (or its equivalent) at the first tocilizumab administration was 16.2 (9.1) mg/day while the mean dosage at last follow-up was 7.1 (3.8) mg/day, there was significant decrease in glucocorticoid dosage after tocilizumab (p=0.001). During follow-up, no serious adverse events such as severe infections, gastrointestinal perforation or infusion-related reactions occurred. We did not observe leukopenia or neutropenia in any of the patients. There were minor non-specific side effects in 3 patients, (malaise in one patient, leg swelling in one patient and dizziness in one patient) without causing drug cessation.

4. Discussion:

This study is one of the largest series evaluating the effect of tocilizumab therapy in refractory TA patients in real life. Our findings supported the effectiveness of tocilizumab in the treatment of refractory TA without major adverse events. In most
patients, acute phase reactants levels were decreased and follow-up imaging findings were stable.

Previously, several case reports and observational studies with small group of patients reported the efficacy and safety of tocilizumab in refractory TA, including the patients unresponsive to TNF-i [7-15]. Recently, Decker et al. published four cases and an updated literature review on the tocilizumab efficacy and safety in patients with TA [17]. In this literature review, among 105 patients most of them are refractory cases, 90 patients (85.7%) had an initial clinical meaningful response within three months. Among these patients, 17 (77%) of 22 patients who were previously treated with TNF-i had clinical improvement with tocilizumab. Corticosteroid dose reduction was achieved in 75/83 patients (90.4%). CRP and ESR levels at the end of follow-up were reduced when compared to the initiation of tocilizumab treatment. Radiological improvement was noted in 43/66 patients (65.2%). In that study, only 7 patients were considered to have relapse in a median treatment duration of 12 months [17]. Recently, the efficacy and safety of tocilizumab (162 mg/week subcutan) was investigated in a randomized, double-blind, placebo-controlled, phase-3 trial (the TAKT study) from Japan [18]. For inclusion, patients had to be receiving a stable GC dose at ≥ twice the dose at relapse and to be in remission for 1 week. Thirty-six patients with TA were randomized into 1:1 to receive weekly tocilizumab (162 mg/week subcutaneously) or its placebo. In both groups, prednisone was tapered by 10% / week from week 4. The primary endpoint was time to relapse based on the signs and symptoms of TA without imaging evaluation. The primary endpoint was not met in this study; however, a treatment difference suggesting favor for tocilizumab was observed in the per-protocol set sensitivity analysis and secondary endpoints. However, the results of this study should be interpreted keeping in mind that
it includes only refractory TA patients and low number of patients [18]. The responses to
tocilizumab therapy in our study are consistent with the previous reports in literature.
There was a significant decrease in glucocorticoid dosage, ESR and CRP levels, and most
of the patient’s radiological findings were stable after tocilizumab therapy.

In the review of Decker et al., they reported that in 18 (18%) of 101 patients, had
adverse events with tocilizumab therapy (Ten infections, five cytopenia, six hepatitis, one
pancreatitis, one cutaneous rash and one breast cancer) and in 7 (7%) patients’ therapy
was stopped due to adverse events [17]. In our study, tocilizumab was well tolerated by
all patients. Minor side effects which were non-specific and did not cause drug cessation
were observed in 3 patients. Tocilizumab therapy was switched due to ineffectiveness in
one patient and in the other due to the activation of accompanying ankylosing spondylitis.

Our result should be evaluated with caution, although we reported a good clinical
and radiologic response in refractory TA patients with tocilizumab. Firstly, this was a
retrospective study with limited number of patients. Secondly, we used the clinical and
laboratory parameters to define the disease activity. Evaluating the disease activity of
TA is still challenging. Previous studies showed progression of vascular lesions and
presence of histologically active disease in half of patients despite clinical and laboratory
remission [19,20]. Thirdly, TA is generally slowly progressive disease and progression
rate of radiologic findings are variable [1,19]. Therefore, although we did not document
radiologic progression any patients, treatment duration in our study may not be sufficient
to make a final conclusion.

Increasing evidence about the importance of IL-6 in the pathogenesis of TA
promise the use of tocilizumab in refractory TA. Our results support the clinical
effectiveness of tocilizumab in this patients’ group. However, long standing studies with
sufficient number of patients are needed to document the effectiveness and safety of tocilizumab.

Acknowledgement and/or disclaimers: None

References:


Table 1: Clinical and demographic characteristics of the TA patients

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age/ Sex</th>
<th>Age at diagnosis</th>
<th>Disease Duration (months)</th>
<th>Type of Vascular Involvement*</th>
<th>Co-morbidity</th>
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<tbody>
<tr>
<td>1</td>
<td>57/F</td>
<td>53</td>
<td>48</td>
<td>2a</td>
<td>hypothyroidism</td>
</tr>
<tr>
<td>2</td>
<td>40/M</td>
<td>31</td>
<td>72</td>
<td>2a, P (+)</td>
<td>IBD, EpA</td>
</tr>
<tr>
<td>3</td>
<td>47/F</td>
<td>37</td>
<td>96</td>
<td>2b</td>
<td>AS, OP</td>
</tr>
<tr>
<td>4</td>
<td>25/F</td>
<td>20</td>
<td>36</td>
<td>5, P (+)</td>
<td>HT</td>
</tr>
<tr>
<td>5</td>
<td>55/F</td>
<td>53</td>
<td>12</td>
<td>5</td>
<td>HT, RA</td>
</tr>
<tr>
<td>6</td>
<td>40/F</td>
<td>36</td>
<td>12</td>
<td>5</td>
<td>HT, AS</td>
</tr>
<tr>
<td>7</td>
<td>30/F</td>
<td>27</td>
<td>12</td>
<td>2b</td>
<td>HT</td>
</tr>
<tr>
<td>8</td>
<td>28/F</td>
<td>23</td>
<td>48</td>
<td>2b, C (+)</td>
<td>AVR</td>
</tr>
<tr>
<td>9</td>
<td>52/F</td>
<td>35</td>
<td>168</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>43/F</td>
<td>40</td>
<td>24</td>
<td>5, P (+)</td>
<td>HT</td>
</tr>
<tr>
<td>11</td>
<td>31/F</td>
<td>23</td>
<td>84</td>
<td>5, P (+)</td>
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</tr>
<tr>
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<td>31/F</td>
<td>29</td>
<td>24</td>
<td>5</td>
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</tr>
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<td>59/F</td>
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<td>5</td>
<td>OP</td>
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<td>HT</td>
</tr>
<tr>
<td>15</td>
<td>24/M</td>
<td>20</td>
<td>24</td>
<td>2a, P (+)</td>
<td>-</td>
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</tbody>
</table>


*According to the angiographic findings, TA patients were classified into five categories16.
Table-2: Parameters of disease activity before and after Tocilizumab therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Previous Treatments</th>
<th>Steroid dosage</th>
<th>ESR mm/s</th>
<th>CRP mg/L</th>
<th>VAS (0-100) (Pain/Fatigue/Pt. Global)</th>
<th>Imaging</th>
<th>Follow-up duration (months)</th>
<th>ESR mm/h</th>
<th>CRP mg/L</th>
<th>Steroid dosage</th>
<th>VAS (0-100) (Pain/Fatigue/Pt. Global)</th>
<th>Imaging</th>
<th>Outcome/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MTX</td>
<td>Pred. 15mg/ad</td>
<td>34</td>
<td>42.80</td>
<td>0/20/20</td>
<td>MRA: Stable</td>
<td>3.00</td>
<td>3.00</td>
<td>2.00</td>
<td>Pred. 15mg/ad</td>
<td>Pred. 15mg/ad</td>
<td>MRA: Stable</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CYC, MTX, SSZ, IFX, ADA</td>
<td>Pred. 10mg/day</td>
<td>75</td>
<td>81.70</td>
<td>-</td>
<td>MRA: Stable</td>
<td>34.00</td>
<td>49.00</td>
<td>92.90</td>
<td>Pred. 5mg/day</td>
<td>Pred. 5mg/day</td>
<td>MRA: Stable</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CYC, SSZ, MTX, PS, ETN</td>
<td>MPZ 32 mg/ad</td>
<td>24</td>
<td>19.6</td>
<td>50/70/30</td>
<td>MRA: Progression</td>
<td>18.00</td>
<td>12.00</td>
<td>18.10</td>
<td>Pred. 12mg/ad</td>
<td>Pred. 12mg/ad</td>
<td>MRA: Stable</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CYC, MTX, LEF, IFX, ADA</td>
<td>Pred. 30mg/ad</td>
<td>11</td>
<td>42.7</td>
<td>80/70/60</td>
<td></td>
<td>20.00</td>
<td>20.00</td>
<td>16.50</td>
<td>Pred. 20mg/ad</td>
<td>Pred. 20mg/ad</td>
<td>CTA: Stable</td>
<td></td>
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<tr>
<td>5</td>
<td>MMF</td>
<td>MPZ 16 mg/day</td>
<td>68</td>
<td>76.1</td>
<td>-</td>
<td>MRA: Stable</td>
<td>5.00</td>
<td>30.00</td>
<td>80.00</td>
<td>MPZ 4mg/day</td>
<td>Pred. 4mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MTX, PS, IFX</td>
<td>Pred. 40 mg/ad</td>
<td>26</td>
<td>28.1</td>
<td>-</td>
<td></td>
<td>28.00</td>
<td>2.00</td>
<td>1.70</td>
<td>Pred. 30mg/ad</td>
<td>Pred. 30mg/ad</td>
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<tr>
<td>7</td>
<td>MTX, PS, IFX</td>
<td>Pred. 40 mg/ad</td>
<td>119</td>
<td>149.0</td>
<td>70/50/70</td>
<td>BTA: Progression</td>
<td>21.00</td>
<td>2.00</td>
<td>1.70</td>
<td>Pred. 30mg/ad</td>
<td>Pred. 30mg/ad</td>
<td>MRA: Stable</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MTX, PS</td>
<td>PS 500 mg/month</td>
<td>103</td>
<td>85.1</td>
<td>0/0/0</td>
<td></td>
<td>15.00</td>
<td>12.00</td>
<td>37.50</td>
<td>PS 500 mg/month</td>
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<td>CTA: Stable</td>
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</tr>
<tr>
<td>9</td>
<td>CYC, MTX</td>
<td>Pred. 40 mg/ad</td>
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<td>63.7</td>
<td>10/30/40</td>
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<td>42.00</td>
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<td>16.20</td>
<td>Pred. 5mg/ad</td>
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<tr>
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<td>-</td>
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<td>16.7</td>
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<td>10.00</td>
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<td>Pred. 20 mg/ad</td>
<td>6</td>
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<td>2.00</td>
<td>1.90</td>
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<td>Pred. 15mg/ad</td>
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<tr>
<td>12</td>
<td>AZT, MTX</td>
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<td>7.00</td>
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<td>2.00</td>
<td>5.10</td>
<td>Pred. 15mg/ad</td>
<td>Pred. 15mg/ad</td>
<td>MRA: Stable</td>
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<tr>
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<td>39.8</td>
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<td>BTA: Stable</td>
<td>3.00</td>
<td>3.00</td>
<td>1.00</td>
<td>-</td>
<td></td>
<td></td>
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<tr>
<td>14</td>
<td>MMF</td>
<td>MPZ 6mg/day</td>
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<td>8.6</td>
<td>50/80/80</td>
<td>MRA: Progression</td>
<td>7.00</td>
<td>10.50</td>
<td>50/50</td>
<td>MPZ 4mg/day</td>
<td>Pred. 4mg/day</td>
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<tr>
<td>15</td>
<td>CYC, MTX</td>
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<td>0/0/10</td>
<td>BTA: Progression</td>
<td>27.00</td>
<td>2.00</td>
<td>7.90</td>
<td>D/C 12.5/day</td>
<td>Pred. 12.5/day</td>
<td>MRA: Stable</td>
<td></td>
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*Tocilizumab was switched to adalimumab in 2 patients; due to ineffectiveness in P5 and activation of accompanying ankylosing spondylitis in P6