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FORCED CHANGE IN RHEUMATOID ARTHRITIS TREATMENT DUE TO COVID-19 PANDEMIC: EFFECTS OF THE SWITCH FROM INTRAVENOUS TOCILIZUMAB TO SUBCUTANEOUS FORM

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Abstract

Aim: Rheumatoid arthritis (RA) is one of the most common chronic systemic autoimmune diseases that primarily affecting the synovial joints, causing progressive joint disability and involving extra-articular symptoms. The American College of Rheumatology (ACR) criteria published in 2010 were used for the diagnosis and classification of RA. The aim of RA treatment was to achieve remission or low disease activity. For this purpose, steroids, non-steroidal anti-inflammatory drugs, and conventional synthetic and biological disease-modifying antirheumatic drugs are used.

Material and Methods: Fifty-six patients with RA whose drug was switched from the intravenous (IV) tocilizumab form to the subcutaneous form in the Department of Internal Medicine Rheumatology-Immunology at Çukurova University Faculty of Medicine Research Hospital were included in the study. Patients with RA were diagnosed according to the criteria published by the 2010 ACR. The data were analyzed retrospectively.

Results: Forty-seven patients had initially received IV tocilizumab treatment. The baseline mean disease activity score (DAS-28) values were 7.65, and the mean treatment duration was 24.6 months. The mean DAS-28 values in the 3rd month of the patients who received IV tocilizumab treatment at baseline were 3.6. The decrease in DAS-28 from baseline was statistically significant ($p<0.0001$).

Conclusion: Consequently, subcutaneous tocilizumab therapy was effective and safe as IV therapy. The number of hospital admissions was less in the subcutan group, and Coronavirus disease-2019 (COVID-19) infection was less common. Subcutaneous therapy is a good alternative, especially during the pandemic period when patients can not easily access IV therapy and need to be isolated from the hospital.

Keywords: Rheumatoid arthritis, COVID-19 pandemic, tocilizumab, subcutaneous therapy

INTRODUCTION

Our aim in the study was to examine whether tocilizumab lost effectiveness in the transition to mandatory subcutaneous therapy in patients who received intravenous (IV) tocilizumab treatment during the Coronavirus disease-2019 (COVID-19) pandemic.

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases. It primarily affects the synovial joints and can cause progressive disability involves the joints, but should be

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considered a syndrome that includes extraarticular involvement, such as, pulmonary involvement, rheumatoid nodules, and vasculitis, and may be presenting with systemic comorbidities (1). The typical patient presents with swollen and tender small joints of recent onset, morning stiffness, and constitutional symptoms (fatigue and weakness). Abnormal laboratory tests may be found such as elevated C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), serologically rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP). This symtomps are not specific for RA (2). New classification criteria for RA were presented in 2010 [American College of Rheumatology (ACR) criteria], providing inclusion of features of chronicity and poor prognosis (3,4).

The disease activity score (DAS-28) score was used to determine the disease activation in RA. The DAS-28 is a composite score derived from 4 of these measures (swollen joints, tender joints, ESR or CRP tests, global assesment of health). Ranges of DAS-28 scores that correspond to high, moderate, and low disease activity have been proposed. The high disease activity related to DAS-28 >5.1, moderate to DAS-28 of >3.2 to 5.1, and low disease activity is regarded in the range of 2.6 to 3.2. A cut-off point for "remission" has also been proposed (DAS-28 <2.6) (5).

Management strategies for patients with RA are directed toward the control of synovitis and the prevention of joint injury. The aim of treatment is to achieve and maintain remission or low disease activity by using disease-modifying antirheumatic drug (DMARD) therapy that is initiated early in the disease course (6).

Therapies used in RA are conventional synthetic and biological DMARDs. Non-biologic (traditional or conventional) DMARDs include methotrexate (MTX), hydroxychloroquine, sulfasalazine and leflunomide (7). Biologic DMARDs, which are produced by recombinant DNA technology and generally target cytokines or their receptors or are directed against other cell surface molecules. Such as the tumor necrosis factor-alpha inhibitors (infliximab, adalimumab etanercept , golimumab and certolizumab pegol) and the interleukin (IL)-6 receptor antagonists (tocilizumab and sarilumab). Other biologic response modifiers are the T-cell costimulation blocker (abatacept) and the anti-CD20 B-cell monoclonal antibody (rituximab). Targeted synthetic DMARDs, including several janus kina (JAK) inhibitors, are also available for use in RA. These include tofacitinib, baricitinib, and upadacitinib, which are orally administered small -molecule DMARDs that inhibit cytokines and signaling through interference with JAKs (8).

There are two IL-6 inhibitors, tocilizumab and sarilumab, available for using with MTX or as monotherapy, which have shown efficacy in biologic naive patients or patients resistant to other bDMARDs. Tocilizumab is a humanized immunoglobulin G1 anti-human IL-6 receptor antibody, competes for both the membrane-bound and the soluble forms of human IL-6 receptor, thereby inhibiting the binding of the native cytokine to its receptor and reducing the cytokine's effects (9). Tocilizumab had 8 mg/kg/month IV and 162 mg/week subcutaneous therapy for RA treatment. Recent research has found similar efficacy and safety data for both forms (10). IL-6 inhibition therapy is also used in giant cell arteritis, systemic juvenile idiopathic arthritis, and multicentric Castleman's disease treatments resistant to conventional therapies (11-13).

COVID-19 caused by a novel coronavirus, severe acute respiratory syndrome-coronavirus 2, has spread globally since December 2019, and the World Health Organization declared COVID-19 to be a pandemic on March 11, 2020 (14). The clinical manifestations of COVID-19 range quite dramatically from no symptoms whatsoever, to mild cough and pneumonia, to acute respiratory distress syndrome and death. Because cytokine release syndrome with elevation of IL-6 is considered to be associated with severe cases of COVID-19, IL-6 inhibitors such as tocilizumab are expected to be effective for its treatment (15). The republic of Turkey The Ministry of Health has issued guidelines for the management of COVID-19 infection treatment in November 2020. In this guideline, IL-6 inhibitor therapy is included for treating patients with COVID-19 associated macrophage activation syndrome (MAS) (16). Therefore, patients with RA patients experienced difficulties in obtaining the IV form of tocilizumab. Many patients were switched from IV tocilizumab treatment to the subcutaneous form. In this study, we examined the data of 56 patients with RA patients whose drug was switched from the iv form to the subcutaneous form.

MATERIAL AND METHODS

Fifty-six patients with RA whose drug was switched from the iv tocilizumab form to the subcutaneous form in the Department of Internal Medicine Rheumatology-Immunology at Çukurova University Faculty of Medicine Research Hospital were included in the study. Ethics committee approval was not obtained because our study was conducted by a retrospective file scanning method. Patients with RA were diagnosed according to the criteria published by the 2010 ACR. The data were analyzed retrospectively. DAS-28 ESR was used to score the disease activity. The demographic characteristics of the cases, the swollen joint counts, the tender joint counts (out of 28 joints), the patient and the doctor's global evaluation of disease activity, ESR, and CRP

levels from laboratory data were recorded. The clinical scores were evaluated using the visual analogue scale and the Health Assessment Questionnaire. It was assessed with the DAS-28 calculator (17). RF and anti-CCP test were determined using the ELISA test. RF level >20 IU/mL and anti-CCP level >15.6 U/mL were accepted as positive.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) program version 20 software package (released 2011, IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY, USA). Demographic variables were analyzed using descriptive analyses. Te normality of the distribution of continuous variables was checked using the Shapiro-Wilk test. Continuous parameters were compared using the Mann-Whitney U test, and categorical variables were analyzed using the chi-square test. Results with p values less than 0.05 were regarded as statistically significant.

RESULTS

Fifty-six patients with RA who were followed up in our clinic were included in the study. Demographic and clinical data of the patients are given in Table 1. The mean age of 56 patients was 54.9 (21-70) years. Forty-nine were (87.5%) female and seven were (12.5%) male. Mean disease duration was 9.54 years. RF was negative in 15 (27%) patientsand positive in 41 (73%) patients. Anti-CCP was positive in 36 (64%) patients and negative in 20 (36%) patients. Nineteen patients (34%) were receiving tocilizumab therapy and DMARD therapy. Twenty patients (36%) were receiving concurrent steroid therapy. Before the treatment, the mean CRP and ESR values of the patients were 39 mg/L and 57 mm/hour. Mean laboratory values at the pre-treatment are given in Table 2.

Table 1. Demographic and laboratory characteristics of patients with RA

Gender	
Female	49 (87.5%)
Male	7 (12.5%)
Age (mean)	54.9 (21-70)
Disease age (mean) (year)	9.54 (2-19 year)
Rhematoid factor	
Negative	15 (27%)
Positive	41 (73%)
Anti-CCP	
Negative	20 (36%)
Positive	36 (64%)
Steroid therapy (≥4 mg methylprednisolone)	
Yes	20 (36%)
No	36 (64%)
DMARD therapy	
Yes	19 (34%)
No	37 (66%)

Anti-CCP: Cyclic citrullinated peptides, DMARD: Disease-modifying antirheumatic drug, RA: Rheumatoid arthritis

Forty-seven patients had initially received iv tocilizumab treatment. The baseline mean DAS-28 values were 7.65, and the mean treatment duration was 24.6 months. The mean DAS-28 values in the 3rd month of the patients who received IV tocilizumab treatment at baseline were 3.6. The decrease in DAS-28 from baseline was statistically significant ($p<0.0001$). All 47 patients who received iv therapy were switched to subcutaneous therapy after an average of 24.6 months. Nine patients were given direct subcutaneous treatment at the beginning. In a total of 56 patients, the mean DAS-28 value at the beginning of subcutaneous treatment was 4.2 and the mean therapy duration was 4.2 months. The mean DAS-28 value at 3 months was 3.47 and it was statistically significant in terms of treatment response ($p<0.0001$) (Table 3).

When subcutaneous treatment was evaluated in patients with RA; the DAS-28 value at the 3rd month was statistically significantly lower in patients on steroid therapy than patients who did not

Table 2. General laboratory characteristics

		Normal values
Beginning C-reactive protein (mg/L) (mean)	39 (±37.32)	0-9
Beginning eritrosit sedimantason rate (/hour) mean	57.43 (±22.68)	0-15
WBC/µL (mean)	8427.14	4800-10800
Neu/µL (neutrophil) (mean)	5261.61	1900-8000
Lymphosit/µL (mean)	2217.18	900-5200
Hemoglobin/µL (mean)	12.13	12-18
Mean corpusculer volume/µL (mean)	81.27	80-99
Platelets/µL (mean)	341.84	130-400
Creatinine (mg/dL) (mean)	0.75	0.3-0.8
Aspartate aminotransferase (U/L) (mean)	18.96	7-30
Alanine aminotransferase (U/L) (mean)	17.68	7-30

WBC: White blood cell

take steroid therapy. (p<0.0001). The DAS-28 value at the 3rd month was statistically significantly lower in patients on DMARD therapy than those without DMARD therapy (p<0.0001) (Table 4).

No statistically significant relationship was found between RF or anti-CCP positivity and response to treatment (Table 5). Drug-related adverse events and treatment-related infection rates were similar between both groups (p=0.07).

DISCUSSION

All the patients included in the study had received csDMARD treatments after the diagnosis of RA. Six patients were switched to tocilizumab treatment due to unresponsiveness to csDMARD treatment (DAS-28>3.2) and 47 patients due to unresponsiveness to other bDMARD treatment (DAS-28>3.2).

Markedly elevated pro-inflammatory cytokines (including IL-1 and IL-6) are associated with mortality at COVID-19 infection, and blocking the hyperinflammation may prevent disease progression (18). A few agents that target the IL-6 pathway have been evaluated in randomized trials for the treatment of COVID-19 infections; these include the IL-6 receptor blockers tocilizumab and sarilumab (19). Republic of Turkey Ministry of Health has issued guidelines for the management of COVID-19 infection treatment in November 2020. In this guideline, IL-6 inhibitor therapy is included for treating patients with MAS (16). Therefore, patients with RA patients experienced difficulties in obtaining the IV form of tocilizumab. Many patients were switched from IV tocilizumab treatment to subcutaneous form. Tocilizumab had 8 mg/kg/month IV and 162 mg/week subcutaneous therapy for RA treatment. Recent research has found similar efficacy and safety data for both forms (10).

In our study, the efficacy of treatment was successfully maintained in patients who were switched from IV tocilizumab therapy to subcutaneous therapy. When the mean DAS-28 values (mean DAS-28: 4.21) in the transition from IV to subcutaneous therapy were compared with the DAS-28 (mean DAS-28: 3.47) values in the 3rd month of subcutaneous therapy, the treatment efficacy was maintained (p<0001). When evaluated in terms of the number of hospital admissions, the subcutaneous therapy group was significantly less than that in the IV therapy group. For this reason, patients isolated themselves more from the hospital during the pandemic period. We did not find any COVID-19 infection in the follow-up of these patients. There were no treatment-related adverse events in either group. No treatment-related infection required hospitalization or antibiotherapy. There was no problem in compliance with the treatment in patients who switched from IV to subcutaneous therapy.

Table 3. General disease activation data for IV and SC treatment recipients

	IV therapy at the pre-treatment	Subcutaneous treatment
Patient number (n=56)	47 (84%)	56 (100%)
Duration of treatment (mounth) (mean)	24.6	4.2
Beginning DAS-28 value (mean)	7.65	4.21
3rd month DAS-28 value (mean)	3.66	3.47
Pre-treatment DAS-28 value and 3rd month DAS-28 value (p-value)	p<0.0001	p<0.0001

DAS-28: Disease activity score, IV: Intravenous, SC: Subcutaneous

Table 4. DAS-28 values according to treatment methods

	Pre-treatment DAS-28 value	IV therapy (3rd month DAS-28 value)	SC therapy (3rd month DAS-28 value)
DMARD therapy			
Yes	4.86	2.16	3.40
No	7.54	3.54	3.50
P-value	<0.0001	<0.0001	0.771
Steroid therapy			
Yes	5.81	2.60	2.70
No	7.09	3.33	3.89
P-value	0.079	0.840	<0.0001

DMARD: Disease-modifying antirheumatic drug, IV: Intravenous, SC: Subcutaneous, DAS-28: Disease activity score

Table 5. Effects of autoantibody presence on DAS-28 values according to treatment methods

	Pre-treatment DAS-28	IV therapy (3rd month DAS-28)	SC therapy (3rd month DAS-28)
RF positive (n=41)	6.84	3.10	3.47
RF negative (n=15)	6.06	2.99	3.47
P-value	p=0.327	p=0.804	p=0.999
Anti-CCP positive (n=36)	6.95	3.13	3.46
Anti-CCP negative (n=20)	6.06	2.96	3.4
P-value	p=0.228	p=0.702	p=0.926

RF: Rheumatoid factor, Anti-CCP: Cyclic citrullinated peptides, DAS-28: Disease activity score, IV: Intravenous, SC: Subcutaneous

Study Limitations

The limitation of our study was due to the small number of patients. Larger randomized controlled trials are needed in this area.

CONCLUSION

Consequently, subcutaneous tocilizumab therapy was effective and safe as IV therapy. The number of hospital admissions was less in the subcutan group, and COVID-19 infection was less common. Subcutaneous therapy is a good alternative, especially during the pandemic period when patients can not easily access IV therapy and need to be isolated from the hospital.

The clinical manifestations of COVID-19 range quite dramatically from no symptoms whatsoever, to mild cough and pneumonia, to acute respiratory distress syndrome, and death. For this reason, patients isolated themselves more from the hospital during the pandemic period. We did not find any COVID-19 infection in the follow-up of these patients. No treatment-related infection required hospitalization or antibiotherapy.

Ethics

Ethics Committee Approval: Ethics committee approval is not required as it is a retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.K., M.A.A., D.A.T., S.Ö., Design: E.K., M.A.A., D.A.T., S.Ö., Data Collection or Processing: E.K., M.A.A., D.A.T., S.Ö., Analysis or Interpretation: E.K., M.A.A., D.A.T., S.Ö., Literature Search: E.K., M.A.A., D.A.T., S.Ö., Writing: E.K., M.A.A., D.A.T., S.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

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