Evaluation of the frequency and intensity of COVID-19 in patients with ankylosing spondylitis under anti-TNF therapy

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Dear Editor,

After the coronavirus disease 2019 (COVID-19) pandemic affected the whole world, rheumatologists began to think about how COVID-19 will progress in patients with inflammatory conditions. High cytokine levels play a role in the pathophysiology of COVID-19 infection.

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine known to have a key role in the pathogenesis of chronic immune-mediated diseases. Anti-TNF therapy may cause increase in active tuberculosis, other granulomatous diseases and serious infections [1]. According to many studies, rheumatological diseases have not been identified as a risk factor for severe COVID-19 infection [2]. Should significantly increased cytokine levels during COVID-19 infection make us think about anti-cytokine therapies that may be used in the treatment of patients with COVID-19 rather than a risk?

We aimed to explore whether the frequency of COVID-19 infection increased, the effect of comorbidities on the frequency of infection, whether the severity of the disease and need for intensive care support increased in patients who used anti-TNF agents. We performed a retrospective case-control study between March and December 2020 in Sakarya University Training and Research Hospital. Retrospectively, we evaluated whether there was a difference in the frequency and severity of COVID-19 in our patients diagnosed with ankylosing spondylitis (AS), 77 of whom were using anti-TNF and 49 of whom didn’t use anti-TNF. Hospitalization and intensive care unit (ICU) requirements were evaluated as endpoints. In the anti-TNF group, patients used adalimumab, etanercept, certolizumab, infliximab and golimumab. Patients were questioned at outpatient clinic visits or by phone.

77 patients with AS using anti-TNF agents (58 males, 19 females) and 49 patients with AS (38 males, 11 females) not using anti-TNF agents were included in the study (p=0.943). Mean age of patients using anti-TNF agents was 41.53±10.38 and mean age of patients not using anti-TNF agents was 42.94±10.86 (p=0.468). 33 (42.9%) patients smoked in the anti-TNF group and 23 (46.9%) patients smoked without using TNFi (p=0.791). There was 12 pack-year smoking in the anti-TNF group, and 14 pack-year smoking in not using TNFi (p=0.623). The frequency of diabetes mellitus (DM), Hypertension (HT), Amiloidosis, Familial Mediterranean Fever (FMF), Coronary Artery Disease (CAD), Chronic Obstructive Pulmonary Disease (COPD) was similar in both groups (p=0.403, p=0.999, p=0.521, p=0.999, p=0.999, respectively). 6 patients using TNFi and 3 patients not using recovered from COVID-19 infection. However, this result was not statistically significant (p =0.999). One patient using anti-TNF was hospitalized but no need for admission to the ICU (p = 0.999). All 9 patients recovering from COVID-19 were male (p=0.113). There were 2 (22.2%) smokers in the SARS-CoV-2 positive group and 54 (46.2%) smokers in SARS-CoV-2 negative group (p=0.297). There was 37.5 pack year smoking in SARS-CoV-2 positive group, and 12 pack year smoking in SARS-CoV-2 negative group (p=0.151). Nobody has comorbidities (DM, HT, Amiloidosis, FMF, CAD, COPD) in SARS-CoV-2 positive group. There were patients with DM (5.1%), HT (15.4%), Amiloidosis (1.7%), FMF (1.7%), CAD (0.9%) and COPD (0.9%) in SARS-CoV-2 negative group (p=0.999, p=0.356, p=0.999, p=0.999, p=0.999, p=0.999, respectively). Having comorbidities was not detected to be associated with frequency of COVID-19. 31 (40.3%) patients adalimumab, 25 (32.5%) patients etanercept, 13 patients (16.9%) certolizumab, 6 (7.8%) patients golimumab and 2 patients (2.6%) was using infliximab in TNF group. 6 patients using anti-TNF (2 adalimumab, 1

etanercept, 1 golimumab,2 infliximab) and 3 patients of non user recovered from COVID-19 (p=0.999). No statistically significant difference was found between SARS-CoV-2 positive and negative patients in terms of the types of anti TNF they used.

Patients were called in March 2020, when the COVID-19 pandemic began, and they were advised to discontinue their anti-TNF therapy. Among those who used anti-TNF, 2 (33.3%) people who had COVID-19 and 38 (53.5%) people who did not have COVID-19 interrupted treatment (p=0.419). Anti-TNF users who did not have COVID-19 interrupted treatment for an average of 3 months (min 2-max 4 months) starting from March 2020, and 1.5 months (min 1-max 2 months) who had COVID-19 (p=0.102). Duration of interrupting TNFi was not significant for the risk of COVID-19.

Comorbidities, older age, and the presence of active disease have been associated with worse outcomes in previous studies [3]. In our study, the group using anti-TNF and non user group were similar according to age, gender and comorbidities. Although comorbidities in COVID-19 are associated with severe disease in the literature, we did not find a significant difference in our study. This result is probably related to our insufficient number of patients. As a result, we found that the use of anti-TNF did not increase the frequency and severity of COVID-19. In a recently published multicenter study, it was stated that the use of biological DMARDs in patients with inflammatory rheumatic diseases were not significantly associated with a worse outcome of COVID-19. But unlike our study, having no comorbidities was associated with a decreased risk of a worse outcome [4].

There are currently studies investigating the therapeutic utility of infliximab and adalimumab in hospitalized COVID-19 patients [5]. The results of these studies are very

important. The usability of TNFi in treatment and at which stage of the disease anti-TNF agents can be used are wondered. We will see the course of the disease all over the world after the administration of the COVID-19 vaccines, but we still need more information about effective and safe treatment.

Conflict of interest

The authors declare that there is no conflict of interest.

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References

1. Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Soluble immune effector molecules: anti-tumor necrosis factor-α agents). Clinical Microbiology and Infection. 2018; 24: 10–20. doi:10.1016/j.cmi.2017.12.025

2. Ouédraogo D-D, Tiendrébéogo WJS, Kaboré F, Ntsiba H. COVID-19, chronic inflammatory rheumatic disease and anti-rheumatic treatments. Clinical Rheumatology. 2020; 39: 2069–2075

3. Haberman R, Axelrad J, Chen A, Castillo R, Yan D et al. Covid-19 in Immune-Mediated Inflammatory Diseases-Case Series from New York. New England Journal of Medicine. 2020; 383(1): 85-88. doi: 10.1056/NEJMc2009567

4. Esatoglu SN, Tascilar K, Babaoğlu H, Bes C, Yurttas B et al. COVID-19 Among Patients With Inflammatory Rheumatic Diseases. Frontiers in Immunology. 2021; 12: 651715. doi: 10.3389/fimmu.2021.651715

5. Robinson PC, Liew DFL, Liew JW, Monaco C, Richards D et al. The Potential for Repurposing Anti-TNF as a Therapy for the Treatment of COVID-19. Med (New York). 2020; 1: 90–102. doi: 10.1016/j.medj.2020.11.005