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Temporary withdrawal of immunosuppressive treatments in patients with hidradenitis suppurativa during COVID-19 pandemic: A retrospective cross-sectional study

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ABSTRACT

Aims: There is currently no evidence-based guideline to show how to manage immunosuppressive treatment in patients with hidradenitis suppurativa (HS) during the Coronavirus disease-2019 (COVID-19) pandemic. Therefore, we updated our routine clinical protocol to 1) inform patients with ongoing treatment about the potential risks of their medications in the case of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, 2) discuss opt out of treatment temporarily, and 3) perform a closer follow-up on a monthly basis. The aim of this study was to evaluate the clinical outcomes in patients with HS, who suspended and continued immunosuppressive therapy following COVID-19 outbreak.

Methods: This retrospective study included patients with HS, who had been receiving biologic/immunosuppressive treatment when the COVID-19 pandemic was announced. Those who withdrew treatment for any reason or continued were analyzed. The primary endpoint was physician-diagnosed disease exacerbation. The secondary outcomes were changes in visual analogue scale (VAS) and COVID-19 diagnosis.

Results: A total of 37 patients were included in the analysis. The majority of the patients were on adalimumab treatment (n=33). Fifteen (40.5%) patients withdrew the treatment for COVID-19 related concerns. During 83.2±0.6 days of follow-up following the withdrawal, all patients in this group had at least one exacerbation. Also, the mean VAS score increased from 5.7±0.56 to 8.6±0.57 (p=0.001). On the other hand, three patients (13.6%) who continued the treatment reported worsening in disease course, 12 patients (54.5%) remained stable and seven of them (31.9%) had clinical relief. We did not observe any confirmed SARS-CoV-2 infection in any of our 37 HS patients.

Conclusions: The present study suggests that even a temporary withdrawal of biologic/immunosuppressive treatments may have significant adverse consequences on disease course and quality of life in patients with HS. These individuals may safely continue the treatment provided that maximum measures are taken to avoid COVID-19 infection.

Introduction

Coronavirus disease-2019 (COVID-19), which is caused by the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, has quickly spread worldwide and become a global public health emergency with a wide spectrum of disease severity (1). After it was declared a pandemic by the World Health Organization on March 11th, 2020 (2), understandable concerns about patients with a chronic disease and/or under immunosuppressive therapy have arisen among clinicians and controversies about the follow-up and management of these patients to minimize the mortality and morbidity have been in question.

Hidradenitis suppurativa (HS) is a painful and destructive chronic skin disorder of which clinical control is difficult even under normal circumstances. Biological agents, especially tumor necrosis factor-alpha (TNF-α) inhibitors, are cornerstone of the treatment of moderate to severe HS (3).

Although HS itself is not considered as a major risk factor for COVID-19 (4), it should be noted that some of its frequent medical comorbidities including obesity, hypertension, diabetes mellitus, cardiovascular disease and smoking may increase susceptibility to COVID-19 or worsen its prognosis (5,6). More importantly, although a minimally increased risk in infections and nasopharyngitis was reported, there was not an increased rate of other upper respiratory infections in HS patients on adalimumab treatment in PIONEER 1 and 2 trials (7). Clinical outcomes of HS patients under immunosuppressive therapy are still a topic of debate and as of today, there is no clear guideline for the management of HS patients vis-à-vis RNA virus infections (8).

The first case of COVID-19 was announced on March 11th, 2020 in Turkey and several measures such as closure of schools, lockdowns at weekends and national holidays, and complete lockdown for young and elderly population were taken by the government to restrict case numbers. Also, the government provided patients to take chronically taken medications (e.g. biologics) from the pharmacy without any prescription with the aim of keeping patients with a higher risk of COVID-19 related death away from the hospital. As daily case numbers declined, almost all preventive measures were lifted by June the 1st, 2020. There were 163,942 confirmed cases in the country by this date. During this period, our outpatient and inpatient clinics were also restricted since a majority of our staff started working for the COVID-19 clinics. Therefore, all HS patients were contacted and followed up through telephone calls during the described "heavy" pandemic period between 15th March and 30th May 2020.

In this study, we aimed to investigate the effects of the COVID-19 pandemic on the continuation/cessation rates of immunosuppressive treatments in HS patients, clinical outcomes of these treatments as well as the extent to which patients were affected by the pandemic (whether they underwent COVID-19 and if they did, what the outcome was). Of the 198 HS patients currently being followed-up in our clinic, we mainly aimed to focus on clinical outcomes of HS patients under immunosuppressive medications whose medical management became more challenging during the pandemic. Since we would not consider interfering with the medications of a patient who benefited from biologic treatment, this pandemic gave us a unique opportunity to observe the clinical outcomes of discontinuation of immunosuppressive treatment in HS patients, which would not be possible under normal circumstances.

Methods

This retrospective cross-sectional study was carried out in accordance with the permission of Turkish Ministry of Health (issue number: 2020-08-18T17_00_38) and approved by Gülhane Local Ethics Committee (2021-21, 28.01.2021). Thirty-seven HS patients who were on immunosuppressive therapies before the announcement of the first COVID-19 case in Turkey were included in the study. Clinical [Hurley stage, 10-point visual analogue scale (VAS) score, current and past treatments] as well as demographic data were obtained from the HS patients' database of our clinic. Between March 15th and May 30th, 2020, all patients were contacted through telephone and were informed about the potential impact of HS treatment on their risk of getting COVID-19 and having severe disease, as well as preventive measures and symptoms of COVID-19. They were also explained that our clinic would not be able to perform dermatology outpatient clinic services for a then uncertain duration, since our staff had been appointed to the COVID-19 clinics. The decision to continue or to stop the treatment was taken by the joint consideration of the patient and physician, taking risk factors for each individual into account. Monthly follow-ups were performed through phone calls. In June 2020, after COVID-19 restrictions were ended, all 37 patients were invited for a clinical visit. Post-lockdown VAS score was calculated and compared to pre-lockdown VAS score for each patient. A short questionnaire involving COVID-19 history, change in smoking habits and weight during the lockdown period was applied for each patient.

Statistical Analysis

Statistical analyses were performed by using IBM SPSS (statistical package for social sciences) for Windows, version 22.0 package program. Numerical variables were shown as mean±standard deviation or median (minimum-maximum). Categorical variables were shown by number and percentage. Since pre- and post-lockdown VAS scores did not exhibit normal distribution, the Mann-Whitney U test was used to compare these variables. The chi-square test, where appropriate, was employed to compare these proportions in different groups. A p-value of less than 0.05 was considered to show a statistically significant result.

Results

A total of 37 patients (26 male/11 female) were included in the study. The mean age was 39.81±12.79 years. The median disease duration was eight years (minimum-maximum: 1-29). Most patients were at Hurley stage 3 (Table 1). Out of 37 patients, 33 (89.2%) were under treatment with adalimumab. Other treatments were secukinumab, ixekizumab, certolizumab pegol and methotrexate (Table 1). At least one comorbidity accompanied HS in 21 (56.7%) patients (Table 1).

Fifteen patients (14 adalimumab; 1 secukinumab) discontinued the treatment during the lockdown, for a mean period of 83.18±0.61 days. All patients in this interrupted treatment group reported aggravation in HS during this period. In the continued treatment group, seven patients had improved while three had worsened disease. Remaining patients

reported stable disease (Table 2). The interrupted treatment group exhibited significantly worsening disease compared to the continued treatment group (p=0.001). Post-lockdown VAS scores were significantly higher in the interrupted treatment group (p=0.001) (Table 2). After a detailed clinical examination throughout June, adalimumab treatment was reintroduced in 12 out of 15 patients in the interrupted treatment group while treatments of two patients under adalimumab and one patient under secukinumab were switched to certolizumab pegol due to decreased treatment response under adalimumab since pre-pandemic period. The mean VAS score of these 12 patients after the reintroduction of adalimumab was regressed from 8.6±0.57 to 7±4.6 at the end of two months and did not return to pre-lockdown VAS levels (p=0.072). None of the patients had had symptoms of COVID-19 or a confirmed SARS-CoV-2 infection. No hospitalization or deaths due to COVID-19 occurred in this cohort.

For smokers (27/37-72.9%), the number of cigarettes consumed daily increased by 10-50% during these two-and-a-half months. The mean body mass index was 28.82±4.64; nine (24.3%) and three (8.1%) of 37 patients reported a weight gain of 2-5 kilograms and more than 5 kilograms, respectively, throughout the lockdown. Two patients started using antidepressant medications due to uncontrolled anxiety of getting SARS-CoV-2 infection.

Table 1. Clinical characteristics of patients involved in the study

Clinical characteristics		n	%
Hurley stage	Stage 1	0	0
	Stage 2	5	13.5
	Stage 3	32	86.5
Treatment modality	Adalimumab	33	89.1
	Ixekizumab	1	2.7
	Secukinumab	1	2.7
	Certolizumab pegol	1	2.7
	Methotrexate	1	2.7
Comorbidities (n=21)	Diabetes mellitus	8	21.6
	Hyperlipidemia	8	21.6
	Hypertension	7	18.9
	Cardiovascular disease	6	16.2
	Psychiatric disease	5	13.5
	Spondyloarthropathy	2	5.4
	Inflammatory bowel disease	1	2.7
	Familial Mediterranean Fever	1	2.7

Discussion

There is currently no evidence-based management guideline for HS during the pandemic. However, it is generally not recommended to interrupt immunosuppressive medications, unless there are signs of active COVID-19 (5), due to the risk of HS exacerbation and possible loss of efficacy after the reintroduction of the same treatment (1,6,8). Although there are not many studies presenting the clinical outcomes of HS patients during the COVID-19 pandemic, recent publications have been summarized in Table 3. In a study by Galán Sánchez et al. (9), only 2 of 12 patients under adalimumab treatment, who were over 50 years old with several comorbidities, exhibited symptoms suggestive of SARS-CoV-2 infection, but the disease was not confirmed. In another study, 2 of 75 HS patients who were treated with adalimumab had a history of contact with confirmed COVID-19 positive individuals, but nasal and pharyngeal swab examinations were negative in both (10). In our study, none of our 37 HS patients presented any symptoms of SARS-CoV-2 infection. This may be because the patients were all contacted and informed about the ways to prevent the infection. Moreover, since the government took necessary measures to reduce spread of COVID-19 by giving the under-risk population (those over 65 years, and those having a chronic disorder or taking immunosuppressive medications) permission to stay home and not to work throughout the pandemic, our patients were probably very careful to stay home during the heavy pandemic period. Additionally, none of our patients admitted having a SARS-CoV-2 positive person in their close contact.

HS is characterized by increased levels of some proinflammatory cytokines and interleukins (IL) such as IL-6, IL-10, IL-12, IL-17, IL-23, IL-1β and TNF-α (12). TNF-α is also found to be higher in COVID-19 infection and increased levels of TNF-α showed a strong correlation with disease severity. Blockade of TNF-α has not only critical role in the management of HS, but it might also reduce the severity of COVID-19 and control the "cytokine storm" which is considered a poor prognostic factor

Table 2. Treatment status of 37 hidradenitis suppurativa (HS) patients on immunosuppressive agents during Coronavirus disease-2019 pandemic and HS outcome at the end of May 2020

		Disease status perceived by patient			VAS score	
Treatment status	**n**	**Worsened**	**Improved**	**Stable**	**Pre-lockdown**	**Post-lockdown**
Continued	22	3	7	12	5.32±0.58	5.18±0.53
Interrupted	15	15	0	0	5.7±0.56	8.6±0.57
		P value: **0.001***			P value: **0.001***	

N: number of patients, VAS: Visual analogue scale
*Analysis performed with the Mann-Whitney-test

Table 3. Summary of studies presenting clinical outcomes of hidradenitis suppurativa patients under immunosuppressive treatment

	n* of COVID-19 patients	Total number of patients under immunosuppressive treatment		Symptoms	Diagnostic confirmation
Galán Sánchez et al. (9)	2	12	Adalimumab	Respiratory infection, ageusia, anosmia and radiographic changes	Neither patients were tested.
Marasca et al. (10)	2	75	Adalimumab	Only recent contact risk without any symptom	Both patients were negative
Rozzo et al. (11)	0	46	Adalimumab	None	-
		11	Secukinumab		
		2	Apremilast		
Current study	0	33	Adalimumab	None	-
		1	Secukinumab		
		1	Certolizumab		
		1	Ixekizumab		
		1	Methotrexate		

COVID-19: Coronavirus disease-2019
*Number of patients who presented highly suggestive symptoms for COVID-19 infection under immunosuppressive therapy

in COVID-19 disease (1,6). Today, it is not possible to make a clear conclusion about whether TNF-α blockers are in effect as a protective or a facilitating factor for COVID-19 disease in HS, and large scaled observational studies are necessary to clarify this confusion.

In this study, all of 31 HS patients who were smokers were found to have increased the number of cigarettes consumed daily about by 10-50%, 12 of 37 patients admitted gaining weight, and 2 of them needed antidepressant medications during 2.5-month lockdown period. Therefore, we would like to underline that comorbidity screening including smoking, obesity, metabolic syndrome and depression may become even more important in situations of increased stress level such as lockdowns and social distancing in which daily physical activities are restricted. Clinicians should be aware of that exacerbated comorbidities will make treatment process of HS even more challenging.

It is already known that treatment success in HS decreases in 12 weeks after discontinuation or dose reduction of adalimumab (13). Sotiriou et al. (14) reported that the mean time to relapse was 11 weeks after the discontinuation of adalimumab. In the current study, we recorded exacerbations in all patients within 83 days -just about 11.85 weeks- and our results were very similar to those in previous studies. Although physical and psychological stress is one of the potential effects of pandemic and may accelerate flare-ups in HS, our results underlines that discontinuation of treatment is the most important factor that determines the duration of exacerbation.

In the current study, 15 of the 37 patients discontinued their immunosuppressive therapies and after a detailed clinical examination throughout June, all patients were put back on biologic therapies. Twelve out of 15 patients were reintroduced on adalimumab while three patients' treatments were switched to certolizumab pegol. Although follow-up period comprising June and July 2020 is not enough to make a proper inference after the reintroduction of the immunosuppressive therapies, we would like to underline that four patients reported lower treatment response with the reintroduction of adalimumab when compared to first treatment experience. In brief, our real life data results support the clinicians' concerns about lower efficacy due to anti-drug antibody formation after the cessation of treatment. Considering PIONEER trials (13,15), to minimize the risk of anti-drug antibody formation, it seems more rational to switch adalimumab every week treatment to every other week instead of cutting off completely, if the patient has a higher risk for COVID-19 and a treatment modification is absolutely required.

While this study comprises a small number of patients and lacks serological and molecular studies to confirm the presence or absence of SARS-CoV-2 infection as a limitation, we believe that it will provide important insights to achieve evidence-based management guidelines for the relevant issue. We are aware of that the evaluation of clinical response and disease severity solely by VAS without any objective scoring system (i.e. HISCAR, HS-PGA or Sartorius) is insufficient to make a realistic comparison. However, since face-to-face clinical visits could not be performed due to the pandemic period, VAS was a decent tool to understand the disease perception of patients.

Conclusion

Consequently, considering decreased efficacy after the reintroduction of immunosuppressive therapies as observed

in our study and the absence of any severe COVID-19 case reported under biologic treatments, HS patients should be recommended to continue their current treatment throughout the COVID-19 pandemic, unless they show signs and symptoms of infection. Another important point is that we currently do not know when the pandemic will be under control, and HS is a debilitating disease which thoroughly affects quality of life. Therefore, in our opinion, stopping the treatments of these patients would do more harm than benefit. However, patients under biologic or immunosuppressive therapies should be enlightened about the risks and benefits of withdrawing or continuing their treatments, and decisions should be made on a case-by-case basis considering HS disease severity, life conditions of the patients (whether they work or stay at home, and if they will be able to conform to the necessities of their treatment by maintaining social distancing etc.), medical comorbidities of the patients and also the COVID-19 burden of the country. It is also logical to follow-up patients closer until risks and outcomes about the COVID-19 become clearer.

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Ethics

Ethics Committee Approval: This retrospective cross-sectional study was carried out in accordance with the permission of Turkish Ministry of Health (issue number: 2020-08-18T17_00_38) and approved by Gülhane Local Ethics Committee (2021-21, 28.01.2021).

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Authorship Contributions

Surgical and Medical Practices: P.E., E.Ç., Concept: P.E., B.B., E.Ç., Design: P.E., B.B., E.Ç., Data Collection or Processing: P.E., E.Ç., Analysis or Interpretation: P.E., B.B., E.Ç., Literature Search: P.E., B.B., E.Ç., Writing: P.E., B.B., E.Ç.

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