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The Management of Autoimmune Bullous Skin Disorders in the Era of COVID-19 Pandemic: A Single Center, Retrospective, Cross-sectional Study

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19), a serious pulmonary illness caused by the highlycontagious novel coronavirus, is a global pandemic. In this retrospective study, we aimed to demonstrate the COVID-19 prevelance and treatment course of the patients with bullous skin disorders.

Materials and Methods: A total of 151 patients with bullous skin disorders who admitted toour department between the dates of October 2019-October 2020 were enrolled in this study. The statistical analysis was performed with the SPSS-21.

Results: One hundred twenty five patients were taking systemic steroid treatments and 113 patients were under the treatment of adjuvant treatment including azathioprine (AZA), mycophenolate mofetil (MMF) and dapsone. Eighteen patients received a minimum of a two-cure rituximab treatment, and 15 patients a minimum of a three-cure intravenous immunoglobulins (IVIG) treatment the year before the start of the pandemic. Only 4 of the 151 patients had a COVID-19 infection history where all of them experienced a mild disease without hospitalization.

Conclusion: As there is no consensus as to the immunosuppressive and biological treatments for autoimmune bullous diseases during the COVID-19 pandemic and we think that the maintenance of a systemic steroid treatment does not increase the incidence rate and the severity of the COVID-19 infection. The immunosuppressive agents including AZA and MMF should be discontinued for the COVID-19 infected patients since no data are showing their beneficial effect for the course of COVID-19 up until now. IVIG can be considered as a therapeutic option for the COVID-19-infected autoimmune bullous disease patients.

Keywords: Azathioprine, Bullous pemphigoid, Bullous skin disorders, Pemphigus vulgaris

Introduction

Coronavirus disease-2019 (COVID-19), is a worldwide pandemic that usually manifests itself as a respiratory tract infection. The most common symptoms are fever, dyspnea, cough, and myalgia. A sore throat, diarrhea, a loss of taste and smell are among the other symptoms [1]. Although most patients develop mild symptoms, pneumonia and a multi-organ failure can also be seen especially in high-risk patients. The studies have shown that the male gender as well as having diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and hypertension increase the risk of severe infections [2]. Bullous diseases are mucocutaneous blistering disorders in which systemic steroids and immunosuppressive drugs are used in the treatment. The most encountered bullous diseases are pemphigus vulgaris, pemphigus foliaceous, bullous

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pemphigoid, mucosal pemphigoid, dermatitis herpetiformis, epidermolysis bullosa acquisita, and linear immunoglobulin A (IgA) dermatosis. There are no clinical data that indicate whether the systemic steroids and immunosuppressive agents are safe during the COVID-19 pandemic. In this study, we aimed to demonstrate the COVID-19 prevalence among bullous patients in our clinic and the treatment process of those patients.

Materials and Method

This study was conducted between October 2019 and October 2020 and one hundred fifty one patients diagnosed with a bullous disease at our bullous diseases outpatient clinic were included. The bullous disease diagnosis was made based on histopathology, direct immunofluorescence and ELISA results. The demographical and clinical features of all patients were noted. The treatment courses and prevalence of COVID-19 infections were retrieved from the medical records. The information of the patients who did not visit the clinic in the last 6 months was obtained via telephone calls. The patients with positive polymerase chain reaction (PCR) tests or computerized tomographies suggesting COVID-19 infection were regarded as having a COVID-19 infection.

Statistical Analysis

The statistical analysis was performed with SPSS-21. The descriptive statistic method and frequency analysis were used for the data distribution.

Ethical Statement

Before commencement of the study, the approval was taken from Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (approval number: 151638, date: 17.11.2020).

Results

The demographical and clinical data of the patients who participated in the study are listed in Table 1. Of the patients 122 (80.8%) were diagnosed with pemphigus vulgaris, 13 (8.6%) with bullous pemphigoid, 4 (2.6%) with pemphigus foliaceus, 4 (2.6%) with dermatitis herpetiformis, 3 (2%) with mucous membrane pemphigoid, 1 (0.7%) with pemphigus vegetans, 1 (0.7%) with linear IgA bullous dermatosis, 1 (0.7%) with epidermolysis bullosa acquisita, 1 (0.7%) with subcorneal pustular dermatosis, and 1 (0.7%) with paraneoplastic pemphigus. The mean age of the patients was 53, with 84 (55.6%) of them being females and the remaining 67 (44.4%) males. The average duration of the bullous disease was 5.2±3.9 years. The number of patients visiting the clinic in the last 6 months was 94 (62.3%) while that of those not visiting 67 (37.7%). Of the 151 patients, 125 were taking systemic steroid treatments. Among the patients taking systemic steroid treatments, 43 were receiving methylprednisolone ≥16 mg/day. As for the treatment processes of the patients; of the 151 patients 26 did not receive any systemic steroid treatment, 104 patients who were on systemic steroid treatments were given a lower treatment dosage while 12 patients continued to receive the same dosage, 8 patients either started to receive steroid treatments or their treatment dosage was increased upon the occurrence of an active illness and one patient uncontrollably terminated the steroid treatment on his own. Moreover, of the 151 patients, 38 did not receive any adjuvant treatment, 93 were already receiving an adjuvant treatment and kept receiving it at the same dosage, and 10 terminated the treatment on their own. The adjuvant treatment dosage was reduced or discontinued for 9 patients, and one patient started to receive an adjuvant treatment due to active illness. Eighteen of the patients received a minimum of a two-cure rituximab treatment during last year, and another 15 patients a minimum of a three-cure intravenous immunoglobulins (IVIG) treatment in the last year. Of the 122 patients diagnosed with pemphigus vulgaris, 15 patients did not receive any systemic steroid treatment, 90 patients were given a treatment with a lower systemic

Table 1. Clinical characteristics of patients

Characteristics	No (%)
Number of patients	151
Average duration of disease, years, mean (min-max)	5.2 (0.5-19.0)
Age of patients, years, mean (min-max)	53 (21.0-87.0)
Sex	
Female	84 (55.6)
Male	67 (44.4)
Subgroup of patients	
Pemphigus vulgaris	122 (80.8)
Pemphigus foliaceus	4 (2.6)
Pemphigus vejetans	1 (0.7)
Bullous pemphigoid	13 (8.6)
Dermatitis herpetiformis	4 (2.6)
Lineer IgA bullous dermatosis	1 (0.7)
Mucosal membrane pemphigoid	3 (2)
Subcorneal pustuler dermatosis	1 (0.7)
Paraneoplastic pemphigus	1 (0.7)
Epidermolysis bullosa	1 (0.7)
Patients having COVID-19 infection	4 (0.02)
Patients receiving steroid treatment	125 (82.7)
Patients receiving adjuvant treatment	113 (74.8)
Patients having history of rituximab treatment over the last year	18 (11.9)
Patients having history of IVIG treatment over the last year	15 (0.1)

min-max: Minimum-maximum, IgA: Immunoglobulin A, COVID-19: Coronavirus disease-2019, IVIG: Intravenous immunoglobulins

steroid dosage and 10 continued to receive the same dosage while 6 patients were given a higher dosage, and finally, one patient terminated the treatment on his own. Only 4 of the 151 patients had a COVID-19 infection history where all of them experienced a mild disease with flu-like symptoms. The ages of COVID-19 infected patients were 38, 45, 49 and 52 respectively. All of the patients had pemphigus vulgaris and were taking methylprednisolone treatment greater than 16 mg/day when they were diagnosed with COVID-19. Three of those patients were taking azathioprine (AZA) 150 mg/day which was discontinued during COVID-19. Two of the patients had a history of 2-cure rituximab treatment in the last year and the other one received a 3-cure IVIG treatment in the last year. None of the patients required any hospitalization due to COVID-19.

Discussion

The COVID-19 infection has emerged as a pandemic infection by the World Health Organization in March 2020 and the number of patients infected with COVID-19 is still on the increase worldwide. The emergence of the COVID-19 infection affected the management of several diseases, also autoimmune bullous skin diseases have been affected during this pandemic. Autoimmune bullous disorders are potentially life-threatening disorders that require long-term immunosuppressive and immunomodulatory therapies. The immunosuppressive treatments used for autoimmune bullous diseases including systemic steroids and steroid-sparing agents [rituximab, AZA, mycophenolate mofetil (MMF)] may potentially increase the risk of viral infections [3,4,5,6,7,8]. However, there is no consensus as to the safety of these treatments during the COVID-19 pandemic for the autoimmune bullous disease patients who are already receiving immunosuppressive and/or biologic treatments or who require a new treatment to control their active diseases. Among the autoimmune bullous diseases, the treatment of pemphigus vulgaris is more challenging since the need for an immunosuppressive treatment is inevitable.

Systemic steroids are the first line treatment for many autoimmune bullous diseases, especially for pemphigus vulgaris [9]. It is known that systemic steroids increase the risk of infection in a dose-dependent manner. However, the current studies showed that the anti-inflammatory effects of systemic steroids may have a role in suppressing the cytokine storm in the COVID-19 infection via decreasing the pro-inflammatory cytokines [10,11,12,13]. These studies support that COVID-19 induced lung inflammation may benefit from systemic steroid treatment. As for autoimmune bullous disease treatment, Kasperkiewicz et al. [14] recommended that immunomodulatory therapy including systemic steroids should be continued if necessary. The patients should be informed about social distancing and hygiene rules. They also recommend that a prednisolone dosage of ≤10 mg/day can be continued for the autoimmune bullous patients infected with COVID-19. For the dosages of over 10 mg/day, they suggest that the dose be tapered following risk evaluations both for COVID-19 and autoimmune bullous diseases [14]. An abrupt cessation of systemic steroid treatments should be avoided due to the risk of adrenal insufficiency and the recurrence of an autoimmune bullous disease. In our clinic, one hundred twenty-five patients out of 151 autoimmune bullous disease patients were receiving systemic steroid treatments during the COVID-19 pandemic. The dose of the systemic steroid therapy was tapered for 104 patients properly. The dosage remained the same for twelve patients receiving less than 8 mg/day methylprednisolone. Three patients with the previous pemphigus vulgaris diagnosis were started a methylprednisolone dosage of over 16 mg/day due to the activation of their diseases. Three patients were diagnosed with pemphigus vulgaris during the pandemic and they started to receive a methylprednisolone dosage of over 24 mg/day. Two patients, one with a previous linear IgA dermatosis and one with an epidermolysis bullosa acquisita started to receive ≥16 mg/day methylprednisolone due to the widespread activation of the disease.

Four patients who had a previous history of pemphigus vulgaris experienced the COVID-19 infection and diagnosis was made either with a PCR test or a computerized tomography while they were receiving a methylprednisolone dosage of ≥16 mg/day. All experienced mild diseases with flu-like symptoms and the steroid therapy dose were tapered during and after the COVID-19 infection period without an abrupt cessation.

AZA and MMF are the first choices of a steroid-sparing treatment for the pemphigus vulgaris patients [9]. Although, there are limited data for the safety of AZA and MMF during the COVID-19 pandemic, Kasperkiewicz et al. [14] recommended the maintenance of these two agents unless patients were infected with COVID-19. The study performed by Russel et al. [11] showed that MMF may prove harmful during the COVID-19 infection. The study by Hormati et al. [15] showed that the AZA treatment did not decrease the severity of the COVID-19 infection. Similarly, Shakshouk et al. [16] suggested that the intake of these drugs be ceased in COVID-19-infected patients. The guidelines from the European Academy of Dermatology and Venereology states that AZA and MMF may increase the severity of the COVID-19 infection, and therefore the treatment with these two agents may be discontinued in patients with the diagnosis of COVID-19 [17]. In our clinic, we also discontinued the AZA therapy for the COVID-19-infected patients. Eighty-four patients who were already receiving adjuvant treatment with AZA or MMF remained at the same dosage.

Rituximab is a chimeric monoclonal IgG1 antibody targeting CD20 receptors on the mature B-cells. It is especially used for the recalcitrant pemphigus vulgaris cases when other treatments fail to control the disease and used for the patients who can not use systemic steroids due to their side effects or comorbidities [9]. Rituximab is associated with the activation of the hepatitis B virus, tuberculosis, and pneumocystis pneumonia [18]. It causes depletion in the B-cells in which the regeneration of B-cell immunity may take months. Therefore, Shakshouk et al. [16] pointed out that the generation of the COVID-19 specific plasma cells can be affected for the patients who were treated with rituximab especially in the last year. They recommended postponing the rituximab treatment as long as possible during the COVID-19 pandemic [16]. On the other hand, Schultz et al. [19] put forward the hypothesis that rituximab may decrease the severity of the COVID-19 infection via decreasing antiviral IgG which was shown to induce a lung injury. However, in an expert study, Kasperkiewicz et al. [14] recommended that the rituximab treatment be postponed during COVID-19 due to the risk of COVID-19-specific plasma cell suppression following rituximab. In our clinic, eighteen patients diagnosed with pemphigus vulgaris have received at least a two-cure rituximab treatment in the last year. Two of those patients were diagnosed with the COVID-19 infection after they received rituximab treatment. They had only mild symptoms, were treated with 5-day favipiravir, and did not require hospitalization [20].

Intravenous immunoglobulin (IVIG) is a biological agent that can be used for autoimmune bullous disease treatments. It is especially used for pemphigus vulgaris patients to maintain a long-term clinical remission [21]. Current studies showed that the IVIG treatment may have a place in the treatment of the COVID-19 infection via suppressing the cytokine storm [22,23,24]. Therefore, IVIG can be an option for patients with pemphigus vulgaris who necessitate treatment during the COVID-19 infection. The risk of thromboembolism should be kept in mind, non-etheless, since both IVIG and COVID-19 are associated with an increased risk of thromboembolism [25,26,27]. Fifteen patients received a minimum of a three-cure IVIG treatment in the last year in our clinic. One of the patients with pemphigus vulgaris had been treated with 3-cure IVIG treatment last year before having the COVID-19 infection. He had mild symptoms which improved following 5-day favipiravir treatment.

Dapsone, also known as diaminodiphenyl sulfone, is a drug that is widely used in autoimmune bullous diseases especially for bullous pemphigoid and mucosal membrane pemphigoid [28]. The current studies hypothesized that dapsone may have a role in the treatment of COVID-19 infection-induced cytokine storm via inhibiting neutrophil chemotaxis and signaling of certain interleukins including IL-1, IL-6, IL-8 [29,30]. Dapsone is not considered to increase the risk of infections, thus it may be continued or started in appropriate patients during the COVID-19 pandemic [14,15,16,17]. In our clinic, six patients with bullous pemphigoid and three patients with mucosal membrane pemphigoid were under treatment with dapsone 100 mg/day. One patient with bullous pemphigoid discontinued therapy on his own. None of the patients had documented COVID-19 infection.

Study Limitation

The limited sample size of COVID-19 infected patients are the main limitation of this study.

Conclusion

There is no consensus as to the immunosuppressive and biological treatments for autoimmune bullous diseases during the COVID-19 pandemic. Based on the results of our study, we think that the maintenance of a systemic steroid treatment does not increase the incidence rate and the severity of the COVID-19 infection. However, it should be noted that the number of the COVID-19 cases was limited. Although we did not observe any increment in the severity of the COVID-19 infection for patients who received the rituximab treatment in the last 1 year, we still recommend the rituximab treatment only for cases in which the benefit is greater than the risk of the COVID-19 infection. If possible, the treatment with AZA and MMF should be discontinued for the COVID-19 infected patients since the data showing their reliability during COVID-19 infection are limited. On the other hand, IVIG can be considered as a therapeutic option for the COVID-19-infected autoimmune bullous disease patients.

Ethics

Ethics Committee Approval: Before commencement of the study, the approval was taken from Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (approval number: 151638, date: 17.11.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.N.Y., T.K.Ü.U., Z.K., Concept: S.N.Y., T.K.Ü.U., Z.K., Design: S.N.Y., T.K.Ü.U., Z.K., Data Collection or Processing: S.N.Y., T.K.Ü.U., Z.K., Analysis or Interpretation: S.N.Y., T.K.Ü.U., Z.K., Literature Search: S.N.Y., T.K.Ü.U., Z.K., Writing: S.N.Y., T.K.Ü.U., Z.K.

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