Immunosuppressive and immunomodulator therapy for rare or uncommon skin disorders in pandemic days

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Abstract

Immunosuppressive and immunomodulatory therapies are important in dermatology, but indications are influenced by SARS-CoV-2. We will focus on are skin disorders such as autoimmune connective tissue disorders, neutrophilic dermatoses and vasculitis. Immunomodulators such as colchicine and antimalarials can easily be preferred taking their beneficial effects on Covid-19 into consideration and also given their wide spectrum of action. Among the conventional therapies, methotrexate, azathioprine and mycophenolate mofetil increase the risk of infection, and thus their use is recommended only when necessary and at low doses. On the other hand, use of cyclosporine is also not recommended as it increases the risk of hypertension, which is susceptible to Covid-19. Anti-TNF agents from among the biological therapies appear to be slightly risky in terms of susceptibility to infection. However, there are ongoing studies which suggest that some biological treatments may reduce cytokine storm impeding the Covid-19 progression as a result, in spite of their susceptibilities to

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Covid-19. Patients, who will be started on immunosuppressive therapy, should be tested for Covid-19 prior to the therapy, and in the event that Covid-19 is suspected, the therapy should be discontinued.

Key Words: COVID-19, immunosuppressive drugs, immunomodulatory drugs, rare skin diseases.

Introduction

Covid-19 is an infection caused by a coronavirus called SARS-CoV-2, an enveloped RNA virus.[1] This infection, which first appeared in the Wuhan city of China in December 2019, has affected the world in months and gave rise to a pandemic.[2] Deaths and need for intensive care were more common in elderly and comorbid patients.[3,4] A suppressed immune system is one of the facilitating factors resulting in such adverse outcomes.[5]

Immunosuppressive medications are required in the therapies of many diseases, also including dermatological diseases. Some articles have been published on the management of the therapies of diseases we observe more frequently, such as psoriasis vulgaris and autoimmune bullous diseases. However, which method should be followed in dermatology patients suffering from the diseases that are less frequently observed in the society and who use these therapeutic modalities? This article will address the approach to immunosuppressive and immunomodulatory therapies in case of rare skin diseases.

Infection risk in immunomodulators and immunosuppressants used in dermatology and Covid-19

There are many immunomodulator and immunosuppressive medications used in dermatology. The most commonly used ones are systemic corticosteroids. Corticosteroids are used for a short period of time in case of some diseases, however, they are usually prescribed for long periods in case of chronic conditions. Many other such therapies include methotrexate, cyclosporin, azathioprine, mycophenolate mofetil, cyclophosphamide, and biological agents.

A- Non-biological conventional immunosuppressants

1- Corticosteroids

Systemic corticosteroids have strong anti-inflammatory, immunomodulatory and antineoplastic effects.[6] There is also an increased risk of infection with systemic corticosteroid use. In a published systemic review, secondary bacterial and fungal infection risk, need for intensive care and high mortality

rates were determined in people with influenza infection with the use of corticosteroids.[8] The risk of infection is higher when used for more than four weeks in doses equivalent to the dose of prednisone, that is minimum 20mg/day in adults and 10 mg/day in children.[9] Corticosteroids suppress the adrenal axis, when they are used at a dose of more than 15 mg/day and for a minimum of three weeks.[10] Therefore, their use should not be discontinued at once. Both of these conditions pose a risk in patients using corticosteroids in special conditions such as pandemic. Caution should be exercised if the patient's working environment is at risk for transmission of Covid-19, or if any of the individuals that the patient lives together has Covid-19 infection. If the underlying disease is under control, the dose may be gradually reduced and then discontinued. In cases where the dose needs to be discontinued at once, such as when infected with Covid-19, then the corticosteroids may be occasionally administered at a stress dose in order to prevent the suppression of the adrenal axis.[11] However, there are some who recommend increasing the dose of corticosteroids in case of physiological stress caused by Covid-19 infection, acute respiratory distress syndrome or another serious infection.[12] In cases, where their use may not be discontinued, the dose can be reduced to below 10mg/day instead.[13] If the patient uses more than one immunosuppressive agents, it would be appropriate to at least discontinue the medications other than corticosteroids.

2- Methotrexate

Methotrexate is prescribed mostly in case of psoriasis, but it is also used in diseases such as cutaneous lupus and scleroderma. It may cause particularly skin and respiratory infections as a side effect.[14] Considering that Covid-19 causes pneumonia in particular, the use of methotrexate in Covid-19 patients can pose a serious risk. The risk of pneumonia was found to be more frequent in those who use methotrexate due to rheumatoid arthritis.[15] The rate of developing a pneumonia in patients using psoriasis is 0.8%.[16]

In a study conducted on pediatric patients on the basis of the opinions of the specialists, it was found that 76% of doctors suggested their patients, who do not present any Covid-19 symptoms, to continue to use methotrexate during the pandemic period. On the other hand, it was found that 89% of the doctors suggested their patients, who tested positive for Covid-19, to temporarily discontinue to use methotrexate. Additionally, it was found that 76% of the doctors suggested their patients, whose close ones tested positive for Covid-19, to temporarily discontinue to use methotrexate; whereas 51% of the doctors suggested their patients, who only present symptoms of upper respiratory tract infection,

to temporarily discontinue to use methotrexate.[11] Considering that Covid-19 progresses more severely in adults, it would be wise to discontinue the medication, in cases that tested positive for Covid-19, in cases that present Covid-19 symptoms, or in cases, whose close ones tested positive for Covid-19. It is recommended to reduce the dose to less than 10 mg per week in cases where it needs to be reduced.[12]

3- Cyclosporine

Cyclosporine is often used in the treatment of diseases such as atopic dermatitis, psoriasis, pyoderma gangrenosum, chronic urticaria, and lichen planus.[17] Use of cyclosporine poses a slight risk of increasing the upper respiratory tract infections.[18] However, the risk of increased hypertension and renal dysfunction associated with the use of cyclosporine is more prominent than the risk of upper respiratory tract infections. Hypertension is an important comorbidity that increases the likelihood of death and intensive care in Covid-19.[4] It should not be overlooked that cyclosporine use may be risky in patients with hypertension.

As an interesting finding reported in 2013, cyclosporine has been shown to reduce in-vitro coronavirus replication.[19] However, cyclosporine should not be started in new patients based on this information, since the in-vivo effect of cyclosporine is unknown. The immunosuppressive effect of cyclosporine manifests very quickly.[20] Therefore, it may not be very wise to start its administration in new patients during this period. When cyclosporine use is deemed necessary, it is recommended to reduce its dose down to 1mg/kg/day and below.[13]

4- Azathioprine

Azathioprine is a premedication derived from thiopurine that turns into 6- mercaptopurine in the body.[21] It is used to spare the patient from corticosteroids and suppress the formation of autoantibodies against biological agents when it is used together with biological agents.[22] There is a moderate increase in the risk of serious infections associated with the use of azathioprine, especially with regards to herpes virus infections.[23] This risk is especially high in elderly patients that have been using corticosteroids for a long-term.[24] When azathioprine use is deemed necessary, it is recommended to reduce its dose to below 0.5mg/kg/day.[12]

5- Mycophenolate mofetil

Mycophenolate mofetil is a premedication that quickly turns into mycophenolic acid in the body and acts through purine metabolism.[25] It is safer in those who cannot tolerate other immunosuppressants, as it acts on the lymphocytes. It is also used as a corticosteroid sparing agent.[26]

There is an increased risk of upper respiratory infection, urinary tract infection and herpes virus infection associated with its use.[27] When mycophenolate mofetil use is deemed necessary, it is recommended to reduce its dose to below 1mg/kg/day.[13]

6- Cyclophosphamide

Cyclophosphamide is an alkylating agent with cytotoxic and immunosuppressive effects.[28] It is used in medicine to treat malignancies in general, whereas in dermatology, it is specifically used in cases of autoimmunity, such as in lupus, vasculitis, systemic sclerosis, and dermatomyositis.[29] It may cause leukopenia and increases susceptibility to infections, since it suppresses the bone marrow. Serious infections, such as pneumococcal pneumonia and herpes zoster infection have been reported in 9-15% of the cases.[30] This risk is greater in those undergoing concomitant corticosteroid therapy.[30] The risk of infection in patients with pemphigus was not found to be higher than those who use corticosteroids or receive other immunosuppressive therapies, but it still cannot be overlooked.[31] With respect to dermatological diseases during pandemic, it is not appropriate to start cyclophosphamide treatment in patients or to continue cyclophosphamide treatment if other treatment options are available.

B- Biological Agents and Small-Molecule Drugs

Biological agents are used in a wide range of cases in dermatology, including psoriasis, hidradenitis suppurativa, pemphigus, chronic idiopathic urticaria, connective tissue diseases, granulomatous diseases, and vasculitis. Studies on the use of biological agents in dermatology have been done mostly on patients with psoriasis. The most common side effects seen with the use of biological agents in general are upper respiratory tract infections and nasopharyngitis.[31]

We will address the biological agents in two categories in terms of infections in particular, as tumor necrosis factor alpha counterparts (Anti-TNF) and other biological agents.

1- Tumor Necrosis Factor Alpha Inhibitors (Anti-TNFs)

The use of anti-TNFs in dermatology is gradually increasing. Their efficacies are quite high, but it is known that they increase the risk of infection, and they thus require careful follow-up due to some important side effects.[20] Therefore, there are discussions as to whether they should be used during the pandemic period.

It is known that the risk of upper respiratory tract infection increases with the use of biological agents, and this also poses a risk for the pandemic period. However, because biological agents inhibit proinflammatory cytokines seen in the viral phase, they may also have protective effects against

cytokine storm in people using them for systemic diseases.[33] In this context, it is stated that the treatment of inflammation in the skin in psoriasis patients also removes inflammation in respiratory tracts.[34]

There are similar risks in terms of infections associated with the use of other biological treatments, and the risk of developing upper respiratory tract infections-nasopharyngitis is the most common side effect in respect of all treatments. In a study, in which the serious infection side effects of biological treatments were compared, the highest risk was found to be associated with the use of infliximab, followed by the use of adalimumab, etanercept and ustekinumab (2.49, 1.97, 1.47, and 0.83, respectively). It has been reported that etanercept and ustekinumab do not increase the risk of infection compared to conventional treatments.[35] In another study, no significant difference was found between the group that use biological treatments and the group that use nonbiological psoriasis treatments in terms of the risk of serious infection.[36]

It was observed that the probability of total infection and nasopharyngitis increased slightly (2.5%) in hidradenitis suppurativa, and The risk of upper respiratory tract infections increased 7% in psoriasis patients using adalimumab.[37,38,39] On the other hand, the risks of upper respiratory tract infection, total infection and nasopharyngitis were found to be high in patients using sertolizumab.[38]

2- Interleukin (IL) 12/23 Inhibitor (ustekinumab)

Studies conducted on patients with psoriatic arthritis and Crohn's disease who were received ustekinumab have not revealed an increased risk of infection.[40,41] The risk of upper respiratory tract infection and nasopharyngitis was found to be about the same in patients, who used ustekinumab at low doses and who used placebos, compared to the patients that did not use any medication or placebos; whereas the risk of upper respiratory tract infection and nasopharyngitis was found to be slightly increased in patients, who used the medication at high doses.[42] Listeria meningitis, esophageal candidiasis and disseminated cutaneous herpes zoster infections have been reported in patients, who use the medication for inflammatory bowel disease.[43] In the light of this information, if its use is absolutely required, it would be more appropriate to use the medication at the lowest possible dose during the pandemic period.

3- IL 17 Inhibitors

It is considered to be opportunistic, and to be protective of the IL-17F homodimers that are related to the upper respiratory infections. Use of secukinumab and ixekizumab is not thought to increase the risk of infection, as IL-17F is not targeted by secukinumab and ixekizumab.[44-46] However, there are also studies, where a slight increase in the risk of infection was reported with their use compared to placebo.[47]

It is considered that brodalumab would lead to more side effects than others, since it is not specific to IL-17A. However, no difference has been reported with its use in terms of infections, except suicidal ideation reported by the FDA as a side effect with its use.[48] This medication may pose a risk in terms of suicidal thoughts and suicide attempts during a depressed-prone period such as the pandemic period, in which an individual infected with Covid-19 remains isolated and alone, while experiencing severe effects of the Covid-19 infection that add up to his/her susceptibility to depression.

4- IL 23 Inhibitors

Risankizumab, guselkumab and tildrakizumab are IgG1 antibodies that inhibit the p19 subunit of IL-23.[49,50,51] In placebo-controlled studies conducted on the guselkumab, a slight increase in the risk of upper respiratory tract infection, nasopharyngitis and bronchitis was determined.[51] The risk of nasopharyngitis was found to have increased slightly with tildrakizumab, whereas the risk of upper respiratory tract infections was found to have increased slightly with risankizumab.[52,53]

5- IL-1 Receptor Antagonist

Anakinra is a recombinant IL-1 receptor antagonist.[54] IL-1 is an inflammatory mediator produced in response to many microbial and nonmicrobial stimuli.[55] It is used in case of in dermatological diseases such as systemic sclerosis, hidradenitis suppurativa, pustular psoriasis, adult still disease, pyoderma gangrenosum. The infections that can be seen in connection with the use of anakinra are urinary tract infections, soft tissue infections, upper respiratory tract infections.[56] However, the infections develop in the case of uses at doses higher than 100 mg/day.[57] Otherwise, its use at low doses is not too risky.

6- Janus Kinase (JAK) Inhibitors

Tofacitinib, ruxolitinib and baricitinib, which are JAK inhibitors, they may increase the risk of nasopharyngitis, upper respiratory tract infection, urinary tract infection, and varicella zoster infection.[58-59] However, since their half-lives are short, their use can be stopped immediately in case an infection develops as their immunomodulatory effects are also temporary. [60]

C- Immunomodulators

1- Intravenous immunoglobulin therapy

Use of IVIG obtained from people who have undergone the disease is on the agenda in patients with critical Covid-19 pneumonia.[61-63] The patient must apply to a hospital or a healthcare facility, where he/she can have had his/her infusion for IVIG use. It may not be for the best for the patient to apply to the hospital for this purpose during the period of a pandemic, especially if he/she has a disease resulting in his/her immunity to be suppressed. However, there is no evidence that IVIG treatment poses a risk in terms of getting infected with Covid-19.[64] If accessing the hospital is not a problem for the patient, IVIG treatment can be continued in patients, in whom IVIG is the main treatment option, but if it will be used in cases such as acute exacerbation then other treatment options should be considered. If the patient was already infected with Covid-19 and hospitalized, it may be more appropriate to discontinue or reduce corticosteroids and other treatments rather than stopping the IVIG treatment.

2- Dapsone

Dapsone is a drug from the sulfone group, which has an antimicrobial and anti-inflammatory effects.[65] Its side effects do not include risk of infections. It may lead to methemoglobinemia in people with glucose 6 phosphate dehydrogenase (G6FD) deficiency. Late-onset hypersensitivity reaction may develop in 0.5-3.6% of patients independent of the dose.[66] It is necessary to investigate the patient's G6FD deficiency before starting dapsone in a patients, and to keep the hypersensitivity issue that may be accompanied by eosinophilia and gastrointestinal symptoms in mind in patients that use it.[66] It should not be forgotten that people with Covid-19 may also have gastrointestinal symptoms and thus swab tests should be carried out when necessary.

Dapsone prevents neutrophil chemotaxis via IL8[67]; there are publications suggesting that increase of IL8 and increase of neutrophils can be controlled with dapsone in ARDS (acute respiratory distress syndrome) cases related to Covid-19.[68]

3- Colchicine

It is an anti-inflammatory drug, and its side effects are mostly related to the gastrointestinal tract.[70] Its side effects do not include risk of infections. There are publications indicating that colchicine can be used in Covid-19 pneumonia and ARDS, due to its role in the prevention of neutrophil chemotaxis and its anti-inflammatory role.[68,71] The fact that its effect manifests itself after a very short period of 24-72 hours from the time it is taken orally has also provided an advantage in its use in the treatment of

Covid-19 pneumonia and ARDS. It also has a cardioprotective effect. Pericarditis has been used for years to prevent atrial fibrillation and even in the acute stage of myocardial infarction.[72] It is known that Covid-19 causes death by involving myocardium even in individuals with no previous history of heart diseases. Studies suggest that colchicine may have a preventative effect with regards to the said aspect of Covid-19. [71,73]

4- Antimalarials

Antimalarial drugs have anti-inflammatory and antiviral effects.[74] Due to their antiviral effects, their use in Covid-19 treatment and prophylaxis has come to the fore, and dozens of clinical studies have been initiated in that regard.[75,76] It has been observed that the antimalarial drugs alleviate the pneumonia stage, improve the radiological images, negate the nucleic acid tests of the virus and shorten the duration of the disease.[77,78] In Turkey, 200 mg hydroxychloroquine is routinely given twice a day for five days to all patients diagnosed with Covid-19 on the basis of the Covid-19 swab test and/or computed tomography. Antimalarial drugs are also recommended prophylactically by the Indian Council of Medical Research for use in the healthcare professionals dealing with Covid-19 patients and to those, who have tested positive for Covid-19 on the basis of swab test performed at home.[79] On the contrary, Johns Hopkins group does not recommend their prophylactic use.[80] In the light of this information, if not feared of their cardiotoxic effects, treatments that include the use of chloroquine and hydroxychloroquine are the most convenient treatments that can be continued during the pandemic period compared to other treatment methods.

Use of immunosuppressants and immunomodulators during pandemic: Is it advantageous or disadvantageous?

It has been demonstrated that the incubation time of coronaviruses and carrying the viral asymptomatically have increased in patients with suppressed immune systems.[81] However, this result has not been validated specifically for Covid-19 yet.[12]

The increase in the risk of infection in immunomodulatory and immunosuppressive treatments depends on the medication used, the underlying disease and the dose of the medication.[12] In this case, it may seem reasonable to discontinue the biological agents in patients that use them at high doses. However, stopping the intake of biological agents may cause recurrence of the underlying disease. There is the risk of developing antibodies against some biological agents when the treatment is interrupted. [82] This risk is high in case of treatments that include biological agents such as ixekizumab,

infliximab and adalimumab, which are listed in the descending order in terms of the risk they carry. Antibody formation decreases the success of the treatment for some biological agents, but not for others. For example, interrupting the treatment may be a problem in treatments that include certain biological agents as in the case of infliximab, as restarting the treatment would cause antibody formation resulting in a loss of efficacy and an increase in the risk of infusion reaction. In the case of secukinumab and adalimumab however, it has been shown that the efficacy does not decrease and antibodies do not develop after the relevant treatments have been restarted.[83,84] It was reported that the antibodies developed as a result of interrupting the etanercept treatment do not reduce the efficacy of the treatment. Similarly, it was reported that the antibodies developed as a result of interrupting the ixekizumab treatment do not reduce the efficacy of the treatment, despite the fact that antibody development observed when ixekizumab treatment is discontinued is high. It would be beneficial to consider these different outcomes when making a decision to interrupt the treatments in patients. If there is no infection, reducing the dose of the medication may be a better option in treatments with high risk of developing antibodies.

Cytokine storm, which is an overstimulated immune response seen in Covid-19 patients, causes aggravation of the disease, an increased need for intensive care and an increased risk of death.[85] These cytokines are proinflammatory cytokines such as TNF- α, IL-1, IL-2, IL-6, IL-7, IL-8, IL-17 granulocyte macrophage colony stimulating factor (GM-CSF), and macrophage inflammatory protein 1-α.[86,87] Routine use of systemic corticosteroids to suppress these cytokines is currently not recommended.[85] However, it is known that drugs such as corticosteroids as well as anakinra that blocks IL-1, can suppress hyperinflammation in sepsis and septic shock and decrease mortality.[88,89] In a retrospective study, continuous intravenous (but not subcutaneous) anakinra infusion was found to treat the cytokine storm in five adult patients.[90] Another biological agent called tocilizumab, which blocks IL-6, suppresses the cytokine storm via IL-6 and GM-CSF, and its use is recommended for in patients with severe and critical Covid-19.[91] In addition, baricitinib, which is a JAK inhibitor, has been shown to inhibit the binding of the Covid-19 virus to the lung cells. [92] Furthermore, cyclosporine has been shown to reduce the replication of coronaviruses in-vitro, despite the fact that its in-vivo effect is not yet known.[19]

Biological agents intended to improve cytokine storm are being studied in China in two different studies registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn/abouten.aspx). In one of these studies adalimumab (ChiCTR2000030089), which is anti-TNF, is being studied, whereas in the

other, combination of ixekizumab (ChiCTR2000030703), which is an IL-17 inhibitor, with a conventional antiviral, is being studied. [87] In the light of this information, although use of biological agents does not seem very disadvantageous for Covid-19 pneumonia, it is still not clear.

Before starting treatment using biological agents, patients must definitely be screened for active tuberculosis, Hepatitis B and C, and for Human Immunodeficiency Virus infections.[20] It is best not to start a treatment including a biological agent during the pandemic period unless it is absolutely necessary. If it is absolutely necessary however, then it would be reasonable first to have a swab test for Covid-19 conducted on the patient and make sure that the patient is Covid-19 negative. Swab testing must definitely be performed whenever Covid-19 infection is suspected also in patients who continue to use the biological agents. Currently, stopping the treatment in case of patients that tested positive for Covid-19, and not restarting the treatment until the patient is recovered from the Covid-19 infection and the tests become negative seems to be the smartest option.

Individuals around each patient using biological agents and immunomodulators should protect themselves as if these patients are carrying the Covid-19 infection, and they should pay attention to their personal hygiene, minimize the use of common items, wash their hands frequently with water for at least 20 seconds rubbing with soap, or use a disinfectant, and always wear a mask when outside the house. It is most convenient for anyone that live together to show the same care.

Rare dermatological diseases requiring use of immunosuppressants during the Covid-19 period

These treatments are often prescribed in dermatology for diseases such as autoimmune bullous diseases, psoriasis vulgaris, and pustular psoriasis. However, they are also used in other dermatological diseases that are relatively rare but can cause mortality and morbidity. Connective tissue disorders, neutrophilic dermatoses and vasculitis from among these diseases will be discussed in this section.

A- Connective tissue disorders

Connective tissue disorders are a heterogeneous group of autoimmune diseases that impair the structure or functioning of the connective tissues such as collagen, elastin, and mucopolysaccharides.[93] Diseases such as systemic lupus erythematosus (SLE), dermatomyositis (DM), systemic sclerosis and morphea, rheumatoid arthritis, Sjogren's syndrome are included in this group.[94]

1- Dermatomyositis

Dermatomyositis, one of the idiopathic inflammatory myopathies, is a disease that goes along with skin involvement and symmetric proximal muscle weakness.[95] It may involve the heart, lungs, gastrointestinal tract, and may be accompanied by malignancies.[95] Hypertension and heart failure may occur due to the systemic corticosteroids used in the treatment of chronic patients.[96] These comorbidities can put the patients at risk for Covid-19, when the immunosuppressants being used is also taken into consideration. The response to corticosteroids, which are started at high doses, is achieved in 2-3 months, and the dose is gradually reduced to the lowest possible dose.[97] Dose reduction can be done a little faster in those at risk for Covid-19 infection. Azathioprine, methotrexate, IVIG, mycophenolate mofetil, cyclosporine, and cyclophosphamide can be used in patients, who are unresponsive to corticosteroids or in whom severe side effects of corticosteroids are seen.[95] In fast progressing cases, it might be that one of these drugs has been started in addition to corticosteroids. In such a case, it would be most appropriate to continue only with corticosteroids until the pandemic period is over. If the patient has tested positive for Covid-19, dose of the corticosteroids should be reduced to the smallest dose possible, and the use of a second agent, if any, and if this second agent is methotrexate in particular, should be interrupted if possible. In cases unresponsive to corticosteroids, use of IVIG, anakinra, cyclosporine, and adalimumab can be considered as the second option during the pandemic period. However, IVIG may pose another risk during the pandemic period, as it requires the patient to come to the hospital to receive the IVIG. The most common causes of death in dermatomyositis patients are cardiac, lung involvement and cancer, whereas 15% of the deaths are caused by infections.[98] These fatal infections are most commonly observed in the lungs and gastrointestinal tract.[98] It is important to regulate the medications patients receive and protect them from Covid-19, which can lead to fatal pneumonia, as the infections develop secondary to the frequently used drugs.

2- Systemic lupus erythematosus (SLE)

SLE is a chronic inflammatory disease involving many systems, including the immune system.[99] It is thought that the infections can cause SLE, and that SLE can increase the susceptibility to infections as well.[100] The susceptibility to bacterial infections, particularly to respiratory and urinary tract infections, is more pronounced than to viral infections.[101] Medications such as corticosteroids, biological agents, and JAK inhibitors used in treatment also increase the risk of this infection. Taking into

consideration that susceptibility to infection increases in SLE and that infections are among the primary causes of death, it is necessary to pay attention to the treatments during the pandemic period. In addition, infection may progress more severely in SLE patients with comorbidities such as heart and kidney involvement, in case of getting infected with Covid-19.[102] Additionally, the use of hydroxychloroquine used in the treatment in order to treat Covid-19 pneumonia is also on the agenda.[103] There is no need to interrupt the treatment in patients using hydroxychloroquine, even if he/she is diagnosed with Covid-19. However, it is necessary to follow the patient closely in case of use of corticosteroids and biological agents. In severe cases of Covid-19, it may be appropriate to discontinue these medications, reduce their dose, or switch to hydroxychloroquine. It seems to be best to start hydroxychloroquine in newly diagnosed SLE patients during this period. However, there is no data yet that long-term use of hydroxychloroquine protects SLE patients from developing Covid-19.[102]

It was reported in a letter published in May 2020 that in 31 (91%) of 35 patients with prolonged activated partial-thromboplastin time (aPTT), which is seen in Covid-19, the lupus anticoagulant (LA) test results were also positive. It is known that LA increases the risk of thrombosis in antiphospholipid syndrome or SLE. The authors think that testing positive for LA may be useful in demonstrating the tendency to thrombosis in Covid-19 patients. Therefore, they suggest that the length of aPTT should not prevent the use of anticoagulants.[104] This should be kept in mind when the SLE patients who are followed up get infected with Covid-19. Even if lengthy aPTT is detected In these patients that are already prone to thrombosis, low dose anticoagulants can be administered, provided that they are strictly followed up.

3- Localized scleroderma and Systemic sclerosis

Systemic sclerosis is an autoimmune disease that progresses through fibrosis and vasculopathy in the skin and internal organs and through dysregulation in the immune system.[105] Localized scleroderma is a relatively limited disease as it primarily holds the skin and the tissues underneath.[106] Systemic corticosteroid, pulsed IV methylprednisolone and methotrexate are frequently preferred options in localized scleroderma cases with generalized or resistant plaques. It may be appropriate to avoid pulsed steroid treatment during the pandemic period as it requires inpatient treatment. In severe forms such as pan sclerotic morphea, where corticosteroid and methotrexate therapy should be administered, or in drug-resistant patients, methotrexate should be preferred at doses below 10 mg/week. It may also be appropriate to reduce the dose of corticosteroid therapy. Interstitial lung

involvement is present in 80% of the patients in systemic sclerosis, and it is symptomatic in 1/3 of the patients.[107] This comorbidity is risky for Covid-19 pneumonia. Immunosuppressive treatments such as corticosteroids, methotrexate and mycophenolate mofetil can be used for skin findings.[108] Also, tocilizumab, rituximab, cyclophosphamide as well as abatacept, which is a T cell blocker, can be used especially in patients with advanced skin and lung involvement.[109] Tocilizumab treatment was discontinued in a systemic sclerosis patient, who has been using tocilizumab for four weeks and who has developed Covid-19 pneumonia, in Switzerland, and the patient got over the disease at home with mild symptoms. The treatment was started again four days after the result of the swab test became negative. The treatment was discontinued in the first place since the use of biological agents is contraindicated in active infection, but the authors considered whether this treatment had provided a benefit in Covid-19.[110] Since it is known that tocilizumab is also used in Covid-19 pneumonia, it may be thought that it could have been a factor in prevention of the cytokine storm enabling this patient to get over the disease with mild symptoms.

B- Neutrophilic dermatoses

Neutrophilic dermatoses are a heterogeneous group of diseases with histopathologically intense neutrophil infiltration in the skin, which is not accompanied by infection or vasculitis.[111] Sweet syndrome (SS) and pyoderma gangrenosum (PG) are the most commonly observed neutrophilic dermatoses. SS and PG respond very well to systemic corticosteroids. Treatments with lower doses during this pandemic period may be preferred. In SS cases that do not respond to systemic corticosteroids, dapsone, colchicine, potassium iodide, and anakinra can be used, in addition to anti-TNFs, which can be used in mandatory cases.[112] In cases of PG, corticosteroids, dapsone and IVIG can be preferred in the first place, whereas in cases that do not respond to these treatments cyclosporine, methotrexate and anti-TNFs can be preferred provided that the cases are closely followed up.[113] In patients resistant to corticosteroids, it may be plausible to start treatment of colchicine, which is thought to be effective in Covid-19, during the pandemic period.

C- Vasculitis

Cutaneous vasculitis are a group of diseases that progress with specific inflammation of the vascular walls, and which can also hold other organs in addition to the skin. [114] Treatment options in cutaneous vasculitis may vary depending on the diameter of the vein, density of lesions and involvement of internal organs. NSAID (nonsteroidal anti-inflammatory drug) drugs, dapsone, colchicine,

pentoxifylline and low-dose systemic corticosteroids can be tried in mild cases during the pandemic period, whereas in severe or unresponsive cases, primarily low-dose methotrexate, IVIG, and tocilizumab can be used.[115,116]

Conclusion

We do not yet have sufficient evidence in relation to Covid-19, however the infection risks posed by the treatments we use would be guiding for us. Treatment guidelines have been published for psoriasis, pemphigus and atopic dermatitis, however more evidence is needed in respect of rarely observed dermatomyositis, lupus erythematosus, scleroderma, neutrophilic dermatoses and vasculitis. Colchicine and antimalarials may have beneficial effects on Covid-19; these drugs can be easily preferred over others due to their wide spectrums of action. Methotrexate, azathioprine and mycophenolate mofetil from among the conventional treatments may increase the risk of infection. On the other hand, use of cyclosporine does not seem to be suitable as it may lead to hypertension, which predisposes the patients to Covid-19. Among the biological agents, anti-TNF agents seem a bit more risky in terms of susceptibility to infection, however they also seem to be more preferable over immunosuppressive conventional treatments in patients resistant to treatment. There are promising results in relation to the biological agents, as to whether they have beneficial effects against cytokine storm seen in Covid-19. Patients who will be started on immunosuppressive therapies, should be tested for Covid-19 before the treatment to ensure that they are not Covid-19 carriers, and the treatment should definitely be interrupted in case of suspicion of Covid-19 during the course of the treatment.

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