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Immunosuppressive therapy in dermatology during COVID-19 pandemic: A review

[1]Dr. Sharmila Patil, Professor and Head of Department, Department of Dermatology Venerology Leprosy, Dr. D.Y. Patil Medical College and Hospital, Navi Mumbai.

[2]Dr. Krupa Ajmera, Dermatology, Kapadia Multispecialty Hospital and Arihant Sper-speciality Hospital

[3]Dr. Isheeta Manchanda, Dermatology

[4]Dr. Anant Patil, Dr. DY Patil Medical College, Navi Mumbai, Pharmacology

Corresponding Author: Dr. Isheeta Manchanda, Dermatology

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Abstract

In dermatology clinical patients most presenting with chronic inflammatory disorders have autoimmune disorders such as psoriasis or pemphigus vulgaris, where long term immunosuppressants are necessary for keeping them under remission. Immunosuppression, however is a double-edged sword. Nowadays, the most important concern with use of these drugs is risk of developing infection with Coronavirus disease (COVID-19). Immunosuppressive therapy decreases immunity, thereby allowing rapid viral replication and delay of viral clearance from the body. This is presumed to enhance the severity of COVID-19 infection. Therefore, certain guidelines and precautions are to be followed if we need to start immunosuppressants in dermatological disorders. Immunosuppressive drugs are initiated or continued after analyzing the risk benefit ratio. In this article, we discuss use of immunosuppressive agents for the management of chronic dermatological diseases, in light of ongoing COVID-19 pandemic.

Keywords: Immunosuppression, COVID-19, Viral Infection, Disease Severity

Introduction

Coronavirus are a large family of viruses, known to cause illness ranging from common cold to severe respiratory and other systemic complications. Coronavirus disease (COVID-19), after first being detected in December 2019 in Wuhan, China, was declared as pandemic by the World Health Organization on March, 11, 2020.Case fatality rate of 1.45% mild course of the disease in majority of the patients.

In addition to its classical presentation affecting respiratory system, a broad spectrum of skin manifestations are also reported in association with COVID -19. Need of all patients presenting with COVID-19 skin manifestations for dermatologic care has been debated, those with nonspecific skin reactions such as morbilliform eruptions or urticaria. Vesicular, urticarial, and maculopapular eruptions and livedo, necrosis, and other vasculitis forms have been reported

most frequently in association with severe acute respiratory syndrome (SARS)-CoV-2 infection.

In addition, for many dermatoses like other medical problems, any mental or physical stress, such as anxiety or infection, may exacerbate the disease course.

The ongoing COVID-19 has brought to the fore many concerns related to use of immunosuppressive agents (ISAs) in dermatology. While it is unclear whether the patients on ISAs for skin conditions are more prone to develop COVID-19, and what impact the ISA may have on the clinical outcome if a patient does get infected. Selecting an appropriate ISA based on the rationalization related to specific immune effects, and its existing literature on incidence of various infections is necessary.

Objective

The objective of this article is to discuss the use of immunosuppressive agents in patients with chronic dermatological diseases.

Method

We searched PubMed and Google Scholar to screen relevant literature published since the beginning of COVID-19 till February 2022. Search words included "immunosuppression", "COVID-19" and "dermatological diseases". Articles published in English literature were considered for review.

Results

Diseases requiring immunosuppressive drugs in dermatology are atopic dermatitis/eczema, psoriasis, pemphigus, Steven Johnson syndrome/ toxic epidermolysis necrolysis, Dress syndrome, dermatomyositis and erythroderma. Although, necessary, immunosuppression can be a double-edged sword in these patients. Suppression of immunity helps to control such chronic inflammatory cutaneous disorders; however, it also comes with potential risk of adverse effects. The most important concern with use of these drugs is the increased risk of various infections in patients receiving them.

Immunosuppressive therapy decreases immunity, thereby allowing rapid viral replication and delay of viral clearance from the body. This is presumed to enhance the severity of COVID-19 infection.

Coronavirus disease has a triphasic pattern. The first phase shows mild respiratory and systemic symptoms with clear evidence of lymphopenia. Mostly drugs inhibit the host immune response against the virus hence it is harmful in the earlier phase to administer them. However, adequate innate and adaptive immunity will eliminate the virus. The second phase is of viral multiplication and localized inflammation which manifests viral pneumonia. The third phase is critical and serious one in which a syndrome of systemic hyper inflammation, secondary hemophagocyte lymph histiocytosis and cytokine storm syndrome can be seen. In this phase, there is an abrupt increase in pro-inflammatory cytokines such as IL-2, IL-6, IL-7, TNF-alpha which leads to acute respiratory distress syndrome, multiorgan failure, and mortality. Immunosuppression prevents and treats the hyperinflammatory phase. [1]

Factors that increase the morbidity and mortality in COVID-19 patients include older age group, obesity, co morbidities like diabetes mellitus/hypertension/cardiovascular disease/severe respiratory disease or cancer. Whether to continue immunosuppressive drugs or not depends on these risk factors and the type of drug.

Based on the risks associated with immunosuppressive agents, they can be classified into three classes; low risk, intermediate risk and high-risk agents. [2]

Table 1: Classification of immunosuppressants based on the associated risk of adverse events.

Low risk agents	Intermediate risk agents	High risk agents
Sulfasalazine Apremilast Hydroxychloquine	Methotrexate Azathioprine	Cyclophosphamide Cyclosporine Leflunomide Mycophenolate mofetil Prednisolone Biologics

Biologics

TNF-α is a pro-inflammatory cytokine that engages neutrophils and monocytes to the area of inflammation and initiates intracellular signaling in various cells of the immune system [3] Examples of TNF-inhibitors includes adalimumab, etanercept, certolizumab, golimumab and infliximab. These agents target TNF-α. Their half-life varies from four to 14 days, and their duration of effect after stoppage ranged between one to six months approximately. However, other TNF-inhibitors i.e., mepolizumab, secukinumab, ixekizumab, usekinumab, and nemolizumab target of IL-5, IL-17A, IL-17A, IL-12, IL23, and IL-31RA with half-life of 12 to 28 days, and after stoppage their duration of immunosuppression ranges from three to 12 months, respectively.

For etanercept, the duration of immunosuppression after stoppage is 1 month. [3]

The cytokines targeted by biologics may have important role in an immune response against many bacteria, viruses, and fungi and potentially there may be high risk of respiratory tract infections with the use of these biologics. For example, IL-17 is important for mounting a mucosal immune response, and IL-17 targeting biologics could increase respiratory tract infections. A recent meta-estimate from phase 3 trials of secukinumab and ixekizumab revealed an increased risk of respiratory tract infections of any etiology in the IL-17 group versus placebo.[4] Ustekinumab may also have a slightly increased risk due to IL-12 blockade, as IL-12 has a vital role in mounting a protective immune response against viruses.[5]

Examples of B-cell inhibitor includes rituximab and belimumab. These agents aim to target CD20 and BAFF with half-life of 20.8 days and 12.5 to 19.4 days, respectively. Their duration of effect after stopping ranges between six to12 months for both. The profound and prolonged B- cell depletion induced by rituximab is especially a cause of concern. It may also reduce the immunological memory following SARS-CoV-2 infection, thereby making patients susceptible to reinfection. [6] Abtacept is a co-stimulatory modulator which acts on CD80 and CD86 with half-life of almost 17 days while duration of immunosuppression after termination is three to six months.

Non-biologic immunosuppressants

Many non-biologic medicines are used for immunosuppression. Methotrexate is a folate antagonist having 4- 12 weeks of duration after stoppage after dose of ≥0.4 mg/kg/week or ≥20 mg/week. Azathioprine is a purine analog with half-life of five hours. It has three months duration with >3.0mg/kg/day dose. Mycophenolate mofetil is inosine monophosphate dehydrogenase inhibitor with half-life of 17.9 hours, and duration of three months.

Other examples of non-biologic immunosuppressants include glucocorticoid (e.g. prednisolone), alkylating agent (e.g. cyclophosphamide), isoxazole derivative (e.g. leflunomide), and calcineurin inhibitor (e.g. cyclosporine). These drugs have half- life of some hours to days, and duration of immunosuppression after

stopping is one to three months, but for leflunomide it is two years.

Calcineurin inhibitors i.e. cyclosporine A (CsA) and tacrolimus (TAC)) prevent the phosphatase activity of calcineurin. Consequently, the dephosphorylation of the nuclear factor of activated T cells is reduced [7]

CsA significantly inhibits the viral replication and the cytopathic effect (CPE: the virus-induced changes in host cells that cause cell death). Similar to CsA, TAC inhibited viral replication.

Most current recommendations are for cautious initiation of cyclosporin, methotrexate, and TNFα inhibitors in patients from areas with high COVID-19 prevalence, and all immunosuppressives and biological therapy may be withheld if exposure to a confirmed COVID-19 case occurs. [8]

Mycophenolic acid (MPA) and its prodrugs, mycophenolate mofetil (MMF) and mycophenolate sodium, are used to prevent rejection in organ transplant recipients and in the treatment of autoimmune diseases. MPA inhibits inosine-5'-monophosphate dehydrogenase, which leads to depletion of intracellular guanosine and deoxyguanosine nucleotides. This suppresses DNA synthesis and thus the proliferation of T and B lymphocytes [9]. MPA inhibits viral replication in-vitro.[10] This is in contrast with COVID-19 guidelines for patients who are using immunosuppressive drugs for a pre-existing disease [11] These expert-opinion-based guidelines recommend discontinuing MPA or reducing the MPA dose in patients with COVID-19.

The results of some clinical studies suggest that corticosteroids are beneficial in patients with COVID-19, especially in alleviating the effects of the cytokine storm. An RCT found that dexamethasone use was associated with a lower 28-day mortality rate, a shorter length of hospital stays, and a lower prevalence of mechanical ventilation [12]

Thiopurine analogs (azathioprine (AZA) and 6-mercaptopurine (6MP)) are used as an anticancer treatment, to prevent rejection in organ transplant recipients and as treatment of several chronic autoimmune diseases. AZA is a prodrug of 6MP. In-vivo, 6MP is converted into 6-thioguanine (6TG) which is incorporated into cellular DNA. This prevents further DNA replication.

Use of immunosuppressants in different chronic dermatological diseases

Psoriasis

Patients with psoriasis who are already receiving immunosuppressants and residing in areas with high infection rates of COVID-19, need reassessment of their underlying condition. Consideration should be given to reduce the dose and duration of immunosuppressants. These patients should preferably be treated with topical therapy and low risk drugs. [13]

In a newly diagnosed case of psoriasis, with involvement of less than 10% body surface area, topical corticosteroid or topical calcitriol with emollient can be given. In patients with extensive skin involvement, i.e. more than 10% body surface area or those with disabling psoriatic arthritis, the risk-benefit ratio should be explained to the patient and home quarantine is advised. Apremilast with or without hydroxychloroquine can be initiated in these patients.

Old cases with involvement of less than 10% body surface area and receiving systemic immunosuppressive, therapy should be stopped. These patients should be maintained on topical medication with home quarantine for three months. In pustular and lupoid psoriasis, systemic acitretin and emollients can be given in this case. Patients of psoriatic erythroderma should be started

on acitretin or apremilast or both and if no response is shown - cyclosporine/methotrexate can be given. Among the small molecules, apremilast is more commonly used. Apremilast is indicated in chronic plaque psoriasis. This phosphodiesterase-4 (PDE4) inhibitor does not target specific cytokines, and has no increased risk of infection, or reactivation of latent infections. [14] A short half-life makes it easier to stop and resume within a few days. Limited immunosuppression makes it a safer therapeutic choice. [15]

In patients with comorbidities, switching to safer modalities such as systemic retinoids, apremilast, and home phototherapy is recommended. Those patients under treatment with biologics suffer from increased morbidity and mortality from COVID-19 rather than psoriatic patients treated only with topical drugs. [16]

Starting and continuing low-risk immunomodulating drugs, such as interleukin (IL)-17, IL-12/23, and IL-23 inhibitors, for treatment of poriasis during the COVID-19 era, are recommended. Immunosuppressive drugs should be withheld in psoriatic patients with the COVID-19 infection. [17]

According to pivotal trials and post marketing data, IL-17 and IL-23 blockers are safer than tumor necrosis factor alpha-blockers. Acitretin and apremilast have favorable safety data and may be safely administered and continued in uninfected patients. Without COVID-19 conclusive data, these recommendations may be helpful in guiding the treatment of psoriasis and atopic dermatitis patients during the COVID-19 pandemic. Azathioprine may increase susceptibility to infections, and if essential, exposure to COVID-19 should be minimized. [18]

Pemphigus vulgaris

In a newly diagnosed case of pemphigus vulgaris with severe disease, general measures with oral corticosteroid 1mg/kg/day or intravenous immunoglobulin (IVIG) is advised. If it is not available, mycophenolate mofetil (MMF) can be considered. Old cases without lesions on dexamethasone, cyclophosphamide pulse (DCP) therapy should be stopped. Oral cyclophosphamide stoppage leads to more immunosuppression. Prednisolone less than 20mg per day can be given.

For old relapsing pemphigus on daily steroid controlled/uncontrolled IVIG can be considered. If the disease is under control, prednisolone less than 20mg per day is advised. All pemphigus patients who have received rituximab treatment within the previous five years should be careful of the preventive measures against the COVID-19 infection regardless of the number of treatment courses or the number of years which has passed since the treatment. However, rituximab may be used in the treatment of pemphigus vulgaris during the COVID-19 pandemic if its use is urgent.

Atopic dermatitis

In atopic dermatitis/eczema with stable disease, topical calcineurin inhibitors (TCI)/ topical corticosteroids (TCS), emollient, and antihistamine can be considered.

If the disease is severe and not controlled on topical therapy, low dose corticosteroid (less than 20 mg per day) should be given for less than two weeks. Antihistamine and low dose methotrexate (less than 20 mg per week) can be also considered. For severe disease with acute flare, short-course oral corticosteroid up to two week and topical TCS/TCI + emollient and antihistamine can be given.

Other chronic inflammatory dermatoses

Dapsone, an aniline derivative is the recommended as first choice of treatment in chronic inflammatory dermatoses. Furthermore, it is effective in blocking inflammatory storms, and may be a favorable therapeutic option for severe COVID-19 cases. [19]

For emergency conditions like Steven Johnson syndrome/ toxic epidermal necrolysis: systemic steroid / oral cyclosporine and IVIG / plasmapheresis are options. For dermatomyositis, start IVIG and maintain on low dose immunosuppressive drug.

Dress syndrome: intravenous methylprednisolone 1mg/kg/day tapered off in 2-3 weeks.

For patients with erythroderma antibiotic coverage, acitretin, and if severe - consider starting cyclosporine and low dose prednisolone.

Discussion

After assessing the risk-benefit ratio, immunosuppressive drugs can be given in each disease during the COVID-19 pandemic. Discontinuing the treatment in the acute period of COVID-19 and the resume after recovery may prevent serious relapse and disturbing cytokine storms in these patients. [20]

In any case, the AAD guidelines generally advise patients to be considered /planning for systemic immunosuppressive agents to always think about the risk vs benefits on a case-by-case basis. In suspected or confirmed COVID-19 case, all immunomodulators used for treatment of skin diseases should be immediately withheld, with the possible exception of systemic corticosteroid therapy, which needs to be halt [21]

While patients requiring immunosuppressive therapy, should be tested for COVID-19 before the therapy, and if COVID-19 is suspected, the therapy should be given up. [22]

However, patients with serious health concerns and a history of infection after iatrogenic immuno- suppression could be replaced to less immunosuppressive regimens or given a drug holiday. A distinction must be made between patients with immunosuppressive treatments or biotherapies for inflammatory or autoimmune dermatoses and those treated for skin cancers with chemotherapy, immunotherapies, and targeted agents. [**Error! Reference source not found.**]

Data about the administration of steroid-sparing immunosuppressive drugs during COVID-19 are scarce and inconclusive. [24]

In an active COVID-19 case, immunosuppressive agents such as human interleukin1 receptor antagonist or anti interleukin 6, may be discontinued, however, some immunosuppressive agents may be useful in treating the exaggerated immune response associated with COVID-19. [25]

Withdrawal of immunosuppressive therapies leads to a significant deterioration of the disease course of COVID-19 which provides further evidence for the beneficial role of these therapies during COVID-19. This should be kept in mind by the rheumatologists, dermatologists, and gastroenterologists asked by their patients with IMIDs about the implications of COVID-19 for their immunosuppressive therapies.[26] Although there is limited data available to analyze if immunosuppression worsens outcomes in this population, patients with sarcoidosis are not necessarily at increased risk of COVID-19 [27]

In the age of precision medicine, our armamentarium now comprises such drugs that can target specific steps in the pathophysiology of SARS-CoV-2 infection without the widespread blunting of the protective host immune response. Calcineurin inhibitors, mycophenolate mofetil, and Tocilizumab indicate promising results in the covid-19 virus as well. Hence it should be used as an immunosuppressive drug wherever possible.

General guidance to patients with chronic skin diseases on immunosuppressant during COVID-19

All patients on immunosuppressive drugs should avoid useless travel, keep away from the crowd, stay home as much as possible, maintain six feet distance, get someone

else to pick up groceries and other supplies, use a face mask at all times when outside, not to touch eyes, nose and mouth, two to four weeks of supply of medicine should be kept at home to avoid unnecessary travel. The number of days/months a patient should be quarantined depends on how long it takes for the drug to wash out from the system.

Conclusion

Whether to start an immunosuppressive drug depends on if the patient is COVID-19 positive or suspected or comes in contact with a patient, washout period of the immunosuppressive drug, host factors, disease severity, and risk benefit ratio. According to recent data, a patient who is already on the immunosuppressive drug should not be stopped as it will increase the chance of a flare up, increase in the hospital visit, negative psychological stress, anti-drug antibody formation, which will increase the cost of treatment in future due to biologic switching. Sudden stoppage of a biologic can also lead to a higher pro-inflammatory state which will worsen the cytokine storm in COVID-19.

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