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REVIEW

Vaccines Against SARS-CoV-2 in Psoriasis Patients on Immunosuppressive Therapy: Implications of Vaccination Nationwide Campaign on Clinical Practice in Italy

Federico Diotallevi · Anna Campanati · Giulia Radi · Emanuela Martina · Giulio Rizzetto · Pamela Barbadoro · Marcello Mario D'Errico · Annamaria Offidani

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ABSTRACT

More than 12 months have passed since the World Health Organization (WHO) declared Coronavirus Disease 19 (COVID-19), caused by the SARS-CoV2 virus, to be a pandemic on 11 March 2020. The entire world scientific community agrees that at this time vaccine is the most promising weapon to combat the infection and the severity of the disease. According to the document "Draft landscape of COVID-19 candidate vaccines" by WHO, 272 vaccines against SARS-CoV-2 virus are in development, although only four of these, produced by Pfizer-BioNTech (Pfizer, Inc. and BioNTech), Moderna, AstraZeneca, and Janssen companies, respectively, have been approved by European Medicines Agency and Italian Medicines Agency and subsequently distributed nationwide for use. These vaccines are the result of highly innovative procedures and are quite different from each other in terms of composition. Even clinicians in various medical fields may be unfamiliar with the effects of these vaccines. There is the strong emerging need for dermatologists to understand the crucial role of vaccines, with a focus on the need to vaccinate patients suffering from immune-mediated skin diseases, such as psoriasis, while taking the ongoing treatment into consideration regarding the timing of vaccination. Similarly, psoriasis patients aware of having an immune-mediated and inflammatory disease are increasingly asking the dermatologist information about the efficacy and safety of vaccines against SARS-CoV-2 virus. In this narrative review of the literature and critical analysis of the recommendations of the Italian Ministry of Health, we analyze the implications of the vaccination campaign on dermatological patients with psoriasis undergoing immunosuppressive treatment.

Keywords: COVID-19; Pandemic; Dermatology; Vaccines; SARS-CoV-2; Psoriasis

Federico Diotallevi and Anna Campanati contributed equally to the manuscript.

F. Diotallevi · A. Campanati · G. Radi (✉) · E. Martina · G. Rizzetto · A. Offidani
Department of Clinical and Molecular Sciences, Dermatological Clinic, Polytechnic University of the Marche Region, Via Conca 71, 60020 Ancona, Italy
e-mail: radigiu1@gmail.com

P. Barbadoro · M. M. D'Errico
Department of Biomedical Sciences and Public Health, Section of Hygiene, Preventive Medicine and Public Health, Polytechnic University of the Marche Region, Ancona, Italy

Key Summary Points

Vaccines against the SARS-CoV2 virus are the most promising weapon to combat the infection and the severity of the disease.

Psoriasis patients are more susceptible to SARS-CoV2 infections than healthy individuals and the role of the dermatologist in recommending vaccination is of paramount importance in this patient group.

Psoriasis patients should be informed that SARS-CoV2 infection or COVID-19 vaccination can lead to an aggravation of psoriasis symptoms. However, this worsening is short-lived and can be easily resolved with temporary treatment.

In the Italian Ministry of Health's guidelines, psoriasis patients undergoing immunosuppressive therapy are considered to be "extremely frail," and it is recommended that they be vaccinated as soon as possible with the most effective vaccine.

INTRODUCTION

At the time of writing, vaccines are the most promising weapon to prevent, or mitigate the effects of SARS-CoV-2 infection [1]. According to the document "Draft landscape of COVID-19 candidate vaccines" by the World Health Organization (WHO), 272 vaccines against the virus are currently in development, although to date only four preparations have been authorized for use in the European Union and also in Italy by the European Medicines Agency (EMA) and the Italian Medicines Agency (AIFA), respectively: Comirnaty (Pfizer-BioNTech [Pfizer, Inc. and BioNTech]; authorized on 21 December 2020), COVID-19 Vaccine Moderna (authorized on 06 January 2021), Vaxzevria (AstraZeneca; authorized on 29 January 2021) and the Janssen COVID-19 vaccine (authorized on 11 March 2021) [2].

These vaccines are the result of highly innovative nanotechnology procedures and are quite different from each other in terms of composition. Even clinicians in various medical fields may be unfamiliar with the effects of these vaccines.

Among dermatologists, solid knowledge of vaccines against SARS-CoV-2 is of crucial importance, especially for those managing patients with psoriasis [3]. In this narrative review of scientific literature and critical analysis of the recommendations of the Italian Ministry of Health, we analyze the implications of the vaccination campaign on dermatological patients with plaque psoriasis undergoing immunosuppressive treatment.

METHODS

As a first step, we searched the PubMed and Web of Science databases using the following keywords: "COVID-19," "pandemic," "dermatology," "vaccines," "SARS-CoV-2" and "psoriasis." We also consulted the websites of the following organizations: WHO, EMA, AIFA and the Italian Ministry of Health, with updates as of 14 April 2021. The search was supplemented by manual searching of the reference lists of the articles identified by the searches of the databases and websites. We discarded studies not written in English and preferentially included randomized, double-blind, multicenter studies, followed by meta-analyses, observational studies, case series and case reports.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals.

The aim of this review is to provide a broad overview of the current use of vaccinations in psoriasis patients undergoing immunosuppressive therapies, integrating data from scientific literature with indications provided by the Italian Ministry of Health on procedures inherent to the current vaccination campaign against COVID-19.

SARS-COV-2 VACCINES APPROVED BY EMA AND AIFA

Four vaccines have authorized for emergency use from both the EMA and AIFA [4, 5].

The first vaccine licensed against SARS-CoV-2 was the mRNABNT162b2 (Comirnaty vaccine; BNT162) from Pfizer-BioNtech, authorized on 21 December 2020 by EMA and on 22 December 2020 by the AIFA. EMA and AIFA emergency authorization of the mRNA-1273 vaccine (Moderna) followed swiftly, with licensing by these agencies occurring on 6 January 2021 and 7 January 2021, respectively. Both vaccines consist of nucleic acids and messenger RNA (mRNA) that is able to induce human cells to use protein factories to make the antigen (viral spike protein) that will trigger a specific immune response. The mRNA administered through the vaccine penetrates the cytoplasm of the host cell and passes through ribosomes, part of the cellular translation machinery, for the synthesis of the viral spike protein. Once out of the cell, the newly produced viral spike protein activates the immune system for the production of specific antibodies [6, 7].

The main strength of these new alternatives to conventional vaccines is their efficacy and safety profile, combined with their relative low cost and ease of production. Since the antigen is strictly produced inside our own cells in large quantities, the immune reaction should be strong, involving both innate and acquired immunity.

According to data published by Pfizer-BioNtech and Moderna, the BNT162 and the mRNA-1273 vaccines showed 95 and 94.5% efficacy in preventing Covid-19, respectively [4, 6, 7]. In terms of their safety profile, phase III studies demonstrate an excellent safety profile for both the vaccines, as confirmed by AIFA pharmacovigilance report [5, 6, 8].

The most frequently observed adverse reactions seen with the BNT162b2 (Pfizer/BioNTech) vaccine are generally mild or moderate and generally resolve within few days after vaccination. They include pain and swelling at the injection site, fatigue, headache, pain in muscles and joints, chills and fever. Less common are redness and itching at the injection site and nausea. Rare adverse effects include limb pain, lymph node enlargement, difficulty falling asleep and a feeling of being unwell. These reactions are more pronounced in young subjects with a robust immune system and are considered to be signs of activation of the immune response; they also may be attenuated by taking nonsteroid anti-inflammatory drugs (NSAIDs) or acetaminophen. Mild-to-moderate pain at the injection site within 7 days after an injection was the most commonly reported local reaction with this vaccine, with $< 1\%$ of participants across all age groups reporting severe pain. The most commonly reported systemic events were fatigue and headache (59 and 52%, respectively).

Hypersensitivity reaction to vaccine components or anaphylactic reaction at the first administration are the only contraindications to vaccine administration. The latter is an exceptional reaction, and it can be treated with subcutaneous administration of adrenaline; no case of death due to anaphylaxis have been reported so far [9].

The mRNA-1273 Moderna vaccine pharmacovigilance data, in line with registration studies, include reports of vaccine-solicited adverse events at the injection site in 84.2% of patients after first dose and in 88.6% of patients at second dose. The most common injection-site adverse event is pain after injection (86.0%) and delayed injection-site reactions (in 0.8% of patients after the first dose and in 0.2% after the second dose). Solicited systemic adverse events occurred in 54.9% of patients after first dose and in 79.4% of patients after the second dose. The most common treatment-related adverse events are fatigue (1.5%) and headache (1.4%); other frequently reported adverse events include fever, widespread muscle and joint pain, headache, nausea and vomiting.

The main drawback of these mRNA vaccines is related to the required storage methods. They must be kept at ultra-low temperatures, which effectively complicates mass storage and administration procedures, making vaccination logistically impossible in countries with low socio-economic levels that do not have adequate systems for maintaining the “cold-chain”.

This is particularly true for Pfizer vaccine, which requires storage at − 70 °C; the Moderna vaccine requires a temperature of 2–8 °C in the first month and − 20 °C in the following months [6, 7].

In terms of administration modalities, Comirnaty® requires two doses of 0.3 ml with a 21-day interval while the Moderna vaccine requires two doses of 0.5 ml with a 28-day interval [6, 7].

On 29 and 30 January 2020, the EMA and AIFA, respectively, approved the distribution of a third vaccine, the Vaxzevria vaccine, developed by the University of Oxford and AstraZeneca for the prevention of COVID-19 in people aged ≥ 18 years [4, 5]. Compared with the Pfizer/BioNTech and Moderna vaccines, both of which are mRNA-based, the Vaxzevria vaccine is a viral vector vaccine using a modified, non-replicating variant of the chimpanzee adenovirus as a vector to provide the instructions to synthesize the SARS-CoV-2 spike protein. Once produced, the protein can stimulate a specific immune response, both antibody and cellular. Compared to the mRNA vaccines, it does not require excessively low temperatures for storage and transport [10].

Combined results from four clinical trials in the UK, Brazil and South Africa showed that Vaxzevria is safe and effective at preventing COVID-19 in people aged 18 years and older. These trials involved around 24,000 people, half of whom received the vaccine and half a control injection (either a dummy injection or another non-COVID vaccine). Those receiving the injections did not know if they had been given the test vaccine or the control injection [10]. The regulating agencies based their calculation of how well the vaccine worked on the results of two of these trials, COV002 (conducted in the UK) and COV003 (conducted in Brazil); the other two trials involved fewer than six COVID-19 cases in each trial, which was insufficient to measure the preventive effect of the vaccine. In addition, as the vaccine is to be given as two standard doses, and the second dose should be given between 4 and 12 weeks after the first, the agencies concentrated on results involving people who received this standard regimen [10]. These results showed a 59.5% reduction in the number of symptomatic COVID-19 cases in people given the vaccine (64 of 5258 got COVID-19 with symptoms) compared with people given control injections (154 of 5210 got COVID-19 with symptoms), translating to the vaccine having a 60% efficacy in clinical trials [4, 10].

The safety of Vaxzevria was demonstrated in all four of these trials. The most frequently observed adverse reactions, also confirmed by the pharmacovigilance reports of AIFA, are generally mild to moderate and resolve within few days of vaccination. The most common are pain and soreness at the injection site, headache, fatigue, muscle aches, general feeling of malaise, chills, fever, joint pain and nausea [4, 10]. Vaxzevria requires two doses, devlivered 12 weeks apart [10].

On 11 and 12 March 2021, the EMA and AIFA, respectively, approved the Johnson & Johnson vaccine [4, 5]. In Italy, procurement and distribution of this vaccine are expected in the second quarter of 2021 [5]. This vaccine contains an attenuated Ad26 adenovirus which itself contains the genetic information to produce the viral spike protein to stimulate antibody production by the immune system. Its efficacy is proven to be 72% for the standard variant, while it falls to 57% for the South African variant (the most feared variant) and the Brazilian one. Its main advantage is its extreme manageability, as it requires only one administration to guarantee that efficacy. Moreover, it can be kept at − 20° up to 2 years, while at 2–8° it survives up to 3 months, therefore guaranteeing easy management of a large number of doses, thanks to the possibility of using a standard refrigerator [11].

Side effects from the clinical trials are comparable to those of other vaccines and generally wear off within a couple of days [4, 5].

The main characteristics of the EMA-approved vaccines are reported in Table 1.

Multiple variants of SARS-CoV-2 have evolved since the beginning of the COVID-19 pandemic due to the large number of people infected, including prolonged infection in immunocompromised individuals [12]. Although new variants still continue to emerge, the most exhaustive information at present is

Table 1 List of SARS-CoV2 vaccines currently approved by the European Medicines Agency and the Italian Medicines Agency and their characteristics

Vaccine	Vaccine composition	Storage	Administration	Indication from data sheet
Pfizer	mRNA	− 90° to − 60 °C	2 doses at least 21 days apart	Individuals 16 years of age or older
Moderna®	mRNA	− 25° to − 15 °C	2 doses 28 days apart	Individuals 18 years of age or older
AstraZeneca®	Adenovirus vector	2–8 °C	2 doses 4–12 weeks apart	Individuals 18 years of age or older
Janssen	Adenovirus vector	2–8 °C	Single dose	Individuals 18 years of age or older

Information in table is from the European Medicines Agency website [4] and the Italian Medicines Agency website [5]

on four variants of concern (VOCs). A VOC is defined by the WHO as a virus with mutations compared with the reference genome found in multiple clusters with either increased transmission or virulence or decreased impact of vaccines and therapeutics [13]. The VOCs were recently renamed by the WHO as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2). These strains predominantly have changes in the *S* gene compared with the reference (Wuhan) strain.

A large number of studies have been carried out to assess the efficacy of vaccines against SARS-CoV2 and the virus variants [14–20]. What emerges is that across all of the VOCs known to date, there is an observed reduction of in vitro serum neutralization activity in highly sensitive assays. There has also been evidence of infection with VOCs in vaccinated populations, but that the severity of disease is nevertheless much reduced, indicating that the vaccines are still highly effective [21]. Prevention of severe disease, which could overwhelm hospitals and lead to death, is the most important goal of vaccination.

COVID-19 AS A SPECIFIC RISK IN PATIENTS WITH PSORIASIS

Few studies on the topic of the risk of COVID-19 in patients with psoriasis have been reported in literature, but the recent findings of Dadras et al. are very intriguing [22]. According to the authors, there would be a close connection between psoriasis and COVID-19 disease due to the role of angiotensi-converting enzyme (ACE). The SARS-CoV-2 spike protein has been shown to have a high similarity to the SARS-CoV spike protein that has a strong binding affinity to the human ACE2 receptor, which is is expressed in the lung, heart, kidney, endothelium and intestine. ACE2 immunoreactivity was also observed in the basal epidermal layer and sebaceous gland cells in normal skin [22]. These observations could mean that skin may be a possible specific target for the SARS-CoV-2, so much so that several cutaneous manifestations have been reported during the disease course of COVID-19; in some cases, SARS-CoV-2 has even been isolated from skin specimens [23–27].

In addition, the serum level of ACE tends to be higher among psoriasis patients, which correlates with higher rate of cardiovascular comorbidities, including subclinical atherosclerosis [28]. Moreover, tissue ACE activity seems to be higher among psoriasis subjects (especially in those with erythrodermic psoriasis) and to decrease after proper treatment, especially with UVB irradiation [29]. Moreover, it is well known that ACE inhibitors are associated with the induction or aggravation of psoriasis with either an allergic immune-dependent reaction or a pharmacologic dose-dependent response [22].

As mentioned above, the ACE2 receptor is a common site of action for SARS-CoV-2. It has been proved that the binding of coronavirus spike protein to the ACE2 receptor would result in ACE2 downregulation. This process would in turn lead to excessive production of angiotensin by the ACE enzyme, the opposing physiological homolog of ACE2 [30]. Taken together, the overactivity of ACE in COVID-19 patients may aggravate the psoriatic condition and—a reasonable possibility—favor a higher incidence of cardiovascular events in the subset of COVID-19 psoriasis patients. This could be particularly true for patients with severe psoriasis, as both higher ACE activity and cardiovascular comorbidities correlate with disease severity [18, 31]. Based on their results, Dadras et al. proposed that psoriasis patients may be at an increased risk of both deterioration in their condition and a higher incidence of cardiovascular events in case of COVID-19 infection [22].

An important study investigating the relationship between psoriasis and COVID-19 infection is that conducted by Patrick et al. [32]. These authors performed an epidemiological analysis of 435,019 patients managed in Michigan Medicine (formerly the University of Michigan Health System) who had at least one health system encounter between 1 January 2019, and 20 June 2020 and then compared gene expression across nine different inflammatory skin conditions, including psoriasis, and SARS-CoV2-infected bronchial epithelial cell lines. They performed a genome-wide association study trans-disease meta-analysis between COVID-19 susceptibility and two skin diseases (psoriasis and atopic dermatitis). The results of this study confirmed that having a skin condition or inflammatory skin disease increased the risk of being infected with SARS-CoV-2, but, in contrast to the conclusions of Dadras et al. [22], these authors reported that having a skin condition or inflammatory skin disease decreased the risk of requiring mechanical ventilation [22]. Skin conditions, such as psoriasis, atopic dermatitis and burn injuries, are associated with defective epidermal barrier, and the authors argued that because the immune system is already activated in lesional sites of the skin, it is possible these infected individual scans have different immunologic rates of viral response. Indeed, previous research has suggested that an early interferon response or decreased viral load can result in a mild form of the disease and thus could be associated with the lower rate of requiring ventilation among patients with COVID-19 with skin conditions [33–37].

Thus, there is a consensus in the literature that psoriasis patients are more susceptible to SARS-CoV2 infections and that recommending vaccination is of paramount importance in this patient group [38].

COVID-19 AND EXACERBATION OF PSORIASIS

The increasing prevalence of SARS-CoV-2 infection worldwide has made it possible to observe the consequences in people with skin diseases, such as psoriasis. Indeed, there are several reports in the literature describing exacerbation of the disease in patients with COVID-19 [39–46]. Kutlu and Metin reported a case of a patient with psoriasis and COVID-19, treated with hydroxychloroquine and oseltamivir, who developed exacerbation of psoriasis on the fourth day of treatment [39]. These authors suggested that the exacerbation of psoriasis was due to the use of hydroxychloroquine which promoted interleukin-17 (IL-17) production through p38-dependent IL-23 release, resulting in keratinocyte growth and differentiation, with a brief discussionn on the possibility that COVID-19 disease might trigger the exacerbation of psoriasis. The same authors also stated that the COVID-19 virus may have induced an exacerbation of the disease through the known production of inflammation-related cytokines, including IL-2, -7 and -10, granulocyte-colony stimulating factor, interferon-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha and tumor necrosis factor α (TNFα) [40], all molecules that are involved in the development of psoriatic disease.

Two similar cases were reported by Oncu et al. [41] and Ozaras et al. [42], but in the latter case, no therapy against COVID-19 was carried out before exacerbation of the disease as the

authors considered the pro-inflammatory state characteristic of COVID-19 as the main element of disease exacerbation.

There is also a case report of a 38-year-old-man with a history of chronic plaque psoriasis who suffered from guttate psoriasis secondary to COVID-19, which appeared on the sixth day after the onset of fever [43].

Cases of the development and exacerbation of pustular psoriasis (PP) during COVID-19 infection have also been described in the literature [44–46]. Mathieu et al. recently described a case report of a 62-year-old-woman with a positive family history for psoriasis that differed from that of the patient described in [43] as the described patient developed new-onset PP 2 weeks after the resolution of SARS-CoV-2 infection symptoms [44]. In November 2020, another case of PP exacerbation secondary to COVID-19 was published [45]. In this case, the described patient was also treated with hydroxychloroquine, albeit unlike the previously reported cases, she had a history of hydroxychloroquine use without exacerbation of psoriasis; therefore, the authors concluded that SARS-CoV-2 alone might have led to the PP flare-up [45]. Another similar case was described by Dadras et al. who treated a 60-year-old male patient with a childhood history of psoriasis who developed generalized PP (GPP) 26 days after the initial symptoms of COVID-19 had appeared [46]. Finally, Samotij et al. described the case of a 62-year-old patient with a history of Acrodermatitis Continua of Hallopeau who developed pustular psoriasis in the course of COVID-19 infection [47].

In summary, COVID-19 may aggravate already existing psoriasis, trigger psoriasis de novo or modify the phenotype of the disease.

COVID-19 VACCINES AND EXACERBATION OF PSORIASIS

Wide range of cutaneous side effects are being reported with different types of SARS- CoV-2 vaccines including early-onset or delayed-type local injection reactions, maculopapular rash, erythema multiforme, pernio and urticaria. [48] Exacerbation of chronic inflammatory skin disorders such as psoriasis has also been recently described [49–53].

Krajewski et al. [49] reported a case of plaque psoriasis flare-up five days after the application of the second dose of BNT162b2 mRNA SARS-CoV-2 vaccine. Before the event, the patient had achieved complete disease clearance due to deucravacitinib treatment in a clinical trial.

Lehhman et al. reported a new-onset guttate psoriasis after the BNT162b2 mRNA vaccine in a 79-year-old female, whose rash started 10 days after the first dose and flared up after the second dose [50]. Onsun et al. reported a case of generalized pustular psoriasis developed 4 days after the first dose of the inactivated SARS-CoV-2 vaccine in a 72-year old man who had plaque psoriasis treated only with topical treatments [51]. Bostan reported two cases exacerbation of Plaque Psoriasis After Inactivated and BNT162b2 mRNA COVID-19 Vaccines, the first one occurred 1 month after the second dose of the first vaccine (CoronaVac, Chine) and spread gradually, the second one initiated after the first dose of the second one (Pfizer/Biontech, German) and widespread extension of the plaques accelerated 2 weeks after the second dose of vaccine. Even in these cases, patients were not receiving systemic treatment for psoriasis [52].

Finally, Sotiriou et al. reported 14 cases of psoriasis exacerbation after COVID-19 vaccination. Of these, nine patients had had known mild psoriasis, which had been left without treatment for over a year. Five patients had only been receiving topical treatment (steroids, calcipotriol/betamethasone), with which they adequately controlled their disease [53]. Psoriasis flare was treated with topical calcipotriol/betamethasone (five cases) and systemic agents or phototherapy (nine cases). Almost all patients experienced an exacerbation of their psoriasis relatively soon (meantime, 10.36 days; standard deviation, 7.71) after the second vaccine dose. Notably, there was no difference between the types of the vaccine (50% mRNA technology vaccines and 50% adenovirus vaccine) used. Similarly, PASI was not statistically different in different vaccine groups ($P = 0.073$, 95% confidence interval − 0.36 to 6.96) [53].

The mechanism by which the SARS-CoV-2 vaccine causes exacerbation of psoriasis can be attributed to the immune response, both humoral and cell-mediated, that vaccines induce and it has been suggested that Th17 might play a key-role [54, 55].

Considering the risk of COVID-19 infection inpsoriasis patients, the comorbidities they have that could contribute to the disease course and the immunosuppressive therapies they undergo, the COVID-19 vaccination is strongly recommended for them. However, it should be kept in mind that vaccines against SARS-CoV-2 may exacerbate psoriasis and patients need to be followed-up closely. Further controlled studies based on larger cohort are needed to identify the exact relationship between SARS-CoV-2 vaccines and psoriasis exacerbation.

SPECIFIC RECOMMENDATIONS DRAWN FOR PSORIASIS PATIENTS RECEIVING VACCINE: ITALIAN MODEL

To date, specific data on the efficacy or safety of vaccines against SARS-CoV-2 in patients with cutaneous chronic inflammatory diseases on immunosuppressive therapy are not available, as these patients are naturally excluded from clinical trials. The only data regarding this type of population that can be extrapolated from the literature refer to other types of vaccines, such as the seasonal influenza vaccine, which differs by biomolecular profile from those directed against SARS-CoV-2 [56].

Corticosteroids and many disease-modifying anti-rheumatic drugs (DMARDs) negatively affect vaccine immunogenicity [56]. For example, treatment with prednisone-equivalent doses ≥ 10 mg/day diminishes humoral responses to influenza vaccines [57]. The use of DMARDS also affects cell-mediated immunity. Studies on the cell-mediated immune response in patients with systemic lupus erythematosus confirm a reduction in the humoral and cell-mediated immune response to influenza vaccination following the use of immunosuppressive therapies such as prednisone and azathioprine [58]. Similarly, the immunosuppressant methotrexate was found to suppress humoral responses to both influenza and pneumococcal vaccines [59, 60]. Papp et al. recommend, that treatment-naive patients affected by immune-mediated conditions should be immunized at least 2 weeks prior to initiation of immunosuppressive therapy, whenever possible, in order to optimize the immunogenicity of inactivated vaccines [56].

Regarding the relationship between vaccines and other immunosuppressive drugs, such as azathioprine and cyclosporine, results in the literature are conflicting, and none of them are strictly related to psoriasis [56, 61]. Cyclosporine is one of the most widely used DMARDs in the treatment of psoriasis due to its high efficacy and rapidity of action. Interesting findings come from the meta-analysis carried out by Karbasi-Afshar et al. that evaluated the efficacy of seroconversion following inactivated influenza vaccine related to one population of transplant patients [61]. The study shows that in transplant patients receiving cyclosporine therapy, there is no reduction in humoral immune response following injection of the influenza vaccine. The same conclusions have been drawn regarding azathioprine therapy [60]. Therefore, taking into account that the SARS-CoV-2 vaccine, although not strictly belonging to the category of inactivating vaccines, is still not a live vaccine, it should not be less effective in psoriasis patients undergoing treatment with cyclosporine or azathioprine, above all because dosages usually used to manage psoriasis are lower than those used in transplant patients.

To summarize, regarding traditional immunosuppressive DMARDs, it can be concluded that the interruption of treatment with these DMARDs before SARS-CoV-2 vaccination with currently available vaccines, is not recommended.

Biologic response modifiers, such as anti-TNFα, anti-IL12/23, anti-IL17 and anti-IL23, are monoclonal antibodies against proinflammatory cytokines or proteins that target cytokine receptors on lymphocytes [62]. These drugs are routinely used to treat several immune-mediated or autoinflammatory diseases, and

although usually used as monotherapy in psoriasis patients, they sometimes can be associated to other systemic immunosuppressive drugs, such as methotrexate or corticosteroids [63, 64]. The subset of psoriasis patients receiving treatment with biologics is at increased risk of infections, becoming highly susceptible to specific types of pathogens in relation to the mechanism of action of the drug: viral, bacterial, and/or opportunistic infections may be very common, and the majority of international guidelines agree that vaccination status should be assessed pretreatment and recommended vaccines should be administered [63]. Recommended vaccines include the inactivated influenza vaccine and either the pneumococcal polysaccharide vaccine (PPSV), provided according to the recommendations that the patients be aged $\geq$ 2 years and that pneumococcal conjugate vaccine (PCV13) doses were given according to the routine schedule, or PCV13 for patients aged $\geq$ 6 years who had never received PCV13. Inactivated vaccines are recommended during therapy according to the annual immunization schedule. Live virus vaccines are contraindicated during treatment with biologics and for weeks to months after discontinuation of treatment according to the half-life of the administered drug [65]. Regarding the currently available vaccines against SARS-CoV-2, both mRNA and non-replicating viral vector vaccines, no trials providing information on their use in psoriasis patients undergoing biological therapy have yet been conducted. However, given the nature of the vaccine and the results of studies on the efficacy of other types of inactivated vaccines in patients undergoing biological therapy, there are no obvious contraindications to the use of the available vaccines against SARS-CoV-2. Accordingly, major international scientific societies, as the National Psoriasis Foundation, recommend the use of SARS-CoV-2 vaccines even in patients undergoing biological therapy without the necessity to discontinue the on-going treatment [66].

Regarding the type of vaccine recommended for patients with psoriasis undergoing immunosuppressive therapy, the interim recommendations on target groups for SARS-CoV-

Table 2 List of diseases that characterize "extremely frail" patients who should be vaccinated with the most effective vaccine, according to the recommendations of the Italian Ministry of Health

Disease	Definition
Respiratory diseases	Idiopathic pulmonary fibrosis; other conditions requiring oxygen therapy
Cardiovascular diseases	Advanced heart failure (NYHA class IV); post cardiogenic shock patients
Neurological conditions and disability (physical, sensory, intellectual, mental)	Amyotrophic lateral sclerosis; multiple sclerosis; infantile cerebral palsy; patients treated with biological drugs or immunosuppressive therapies and cohabitants; myasthenia gravis; autoimmune neurological diseases
Diabetes/other severe endocinopathies (such as Addison's disease)	Subjects aged > 18 years with juvenile diabetes, type 2 diabetes and needing at least 2 oral hypoglycemic drugs and who need or have developed peripheral vasculopathy with a Fontaine index $\geq$ 3
Cystic fibrosis	Patients to be considered by definition as highly frail due to the respiratory implications of the underlying disease
Renal failure/renal pathology	Patients undergoing dialysis

Table 2 continued

Disease	Definition
Autoimmune diseases—primary immunodeficiencies	Patients with severe pulmonary impairment or marked immunodeficiency and cohabitants; immunodepression secondary to therapeutic treatment and cohabitants
Liver diseases	Patients diagnosed with hepatic cirrhosis
Cerebrovascular diseases	Cerebral ischemic hemorrhagic event that has compromised the neurological and cognitive autonomy of the affected patient. Patients who suffered a "stroke" in 2020 and for the previous years with a ranking ≥ 3
Oncological pathology and haemoglobinopathies	Onco-hematological patients undergoing treatment with immunosuppressive or myelosuppressive drugs or < 6 months after stopping treatment and cohabitants. Parents of patients aged < 16 years. Patients with thalassemia
Down's syndrome	All patients with Down's syndrome, due to their partial immunological competence and the very frequent presence of congenital heart disease, are considered frail
Solid organ transplantation: on waiting list and undergoing hemopoietic transplantation 3 months after transplantation and within 1 year of the procedure	Solid or hemopoietic organ transplantation outside the specified time frame, who have developed chronic anti-host disease on immunosuppressive therapy and are cohabiting
Severe obesity	Patients with body mass index > 35

2/COVID-19 vaccination drafted by the Italian Ministry of Health, published in the Gazzetta Ufficiale della Repubblica Italiana on 10 March 2021, have been reported. Based on collaboration with scientific societies, the category of "extremely frail" patients has been identified because of their increased risk, compared to the general population, of lethality to COVID-19, due to pre-existing organ damage or impaired capacity of the immune response to SARS-CoV-2 (Table 2) [67]. In addition, according to the document, "extremely frail" patients should be prioritized for vaccination with respect to the general population, using the most effective available vaccine [68]. According to efficacy data from phase III studies, mRNA vaccines have demonstrated superior efficacy compared with non-replicating viral vector vaccines, suggesting that the former category of vaccines are preferred for these "extremely frail" patients. As shown in Table 2, the category of "extremely frail" patients also includes patients with autoimmune disease undergoing immunosuppressive therapy.

CONCLUSIONS

Although further studies will be required to define the efficacy of the four main SARS-CoV-2 vaccines in patients with psoriasis undergoing immunosuppressive treatments, given current knowledge, we highly recommend vaccine

immunization against SARS-CoV-2 infection for this patient population. Considering also the potential intrinsic risk of psioriasis patients developing severe COVID-19, owing to the risk of co-existing multiple comorbidities and the on-going immunosuppressive therapies, it seems reasonable to adopt the recommendations of the Italian Ministry of Health and recommend the vaccination of these patients with mRNA vaccines. In our opinion, these recommendations should be extended to all patients with psoriasis, both those receiving treatment and those not currently being treated. Finally, possible exacerbations of psoriasis in patients undergoing treatment should not, in our opinion, be a reason to renounce vaccination, also because the cases that have occurred and are reported in the literature have all resolved without complications [49–53].

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