Psoriasis: Targets and Therapy

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REVIEW

Safety and Efficacy of Covid-19 Vaccination in Patients Undergoing Biological Treatments for Psoriasis

Luca Potestio*, Fabrizio Martora*, Gabriella Fabbrocini, Teresa Battista, Matteo Megna

Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

*These authors contributed equally to this work

Correspondence: Fabrizio Martora, Section of Dermatology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy, Tel +39 081 7462457, Fax +39 081 7462442, Email fabriziomartora92@libero.it

Abstract: The introduction of biologic drugs revolutionized the treatment of psoriasis, shifting treatment goals to higher treatment outcomes and less frequent safety issues. The outbreak of Coronavirus disease 2019 (COVID-19) represented a worldwide challenge, strongly affecting lifestyle, global economy, and overall health. Among the strategies adopted to contain the spreading of the infection, vaccination is the main one. In this context, the introduction of COVID-19 vaccines raised several doubts about their effectiveness and safety in patients undergoing therapy with biological for psoriasis. Even if molecular and cellular mechanisms by which COVID-19 vaccines lead to psoriasis development have not yet been fully elucidated, vaccination itself can trigger the release of interleukin (IL)-6, interferon (IFN) and tumor necrosis factor (TNF) α by T-helper (Th)1/Th17 cells. All these cytokines are involved in psoriasis pathogenesis. Thus, the aim of this manuscript is to review current literature on the safety and effectiveness of COVID-19 vaccination in psoriasis patients undergoing treatment with biologics, in order to clarify any concerns.

Keywords: psoriasis, COVID-19 vaccinations, biologic therapies, efficacy, safety

Introduction

Psoriasis is a common, chronic-recurrent, immune-mediated skin disease affecting up to 3% of worldwide population.[1,2] Clinically, it is usually characterized by erythemato-desquamative plaques that are well delineated from surrounding normal skin.[3] Several comorbidities (obesity, hypertension, anxiety/depression, hyperlipidemia, diabetes mellitus and inflammatory bowel disease) may be associated with psoriasis, impacting the psychological health of affected patients.[4–7] On consequence, early diagnosis and appropriate treatment play a key role.[8,9]

Even if mild forms of disease are usually treated with topicals, systemic treatments are often required for moderate-to-severe forms of the disease.[10,11] However, conventional systemic drugs (acitretin, cyclosporine, methotrexate, dimethyl fumarate) are often contraindicated or linked to adverse events.[10,11] Fortunately, the introduction of biologic drugs revolutionized the treatment of psoriasis, shifting treatment goals to higher treatment outcomes and less frequent safety issues. Indeed, biologics act against specific cytokines, receptors, or other cellular pathways that play a key role in psoriasis pathogenesis, allowing a directed and personalized treatment with generally fewer systemic adverse effects when compared to other systemic agents.[12–15] Several biologic drugs have been approved for psoriasis management [anti-Tumor Necrosis Factor (TNF) α, anti-interleukins (IL) 12/23, anti-IL17 and anti-IL23], showing excellent results in terms of effectiveness,[16,17] also in erythrodermic forms.[18] As regards the safety of biologic drugs, promising results have been reported, particularly for anti-IL17 and anti-IL23 classes.[19–22]

The outbreak of Coronavirus disease 2019 (COVID-19) represented a worldwide challenge, strongly affecting lifestyle, global economy, and overall health.[23,24] In this context, several measures have been adopted to reduce the spreading of the infection.[25–29] Among these, vaccination is the most important one to fight against the pandemic. Four

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vaccines have been approved by European Medicines Agency (EMA): 2 mRNA-based vaccines (Pfizer/BioNTech; BNT162b2 and Moderna; mRNA-1273) and 2 viral-vector-based vaccines (AstraZeneca; AZD1222 and Johnson & Johnson; Ad26.COV2.S).[30,31] Similar to other drugs, mild-to-moderate adverse events (AEs) following vaccination have been reported, including fatigue, diarrhea, headache, fever, muscle aches, pain or redness at the injection site, chills, etc. Fortunately, most of these AEs were mild and self-limited.[32,33] Moreover, several cutaneous reactions have been described following COVID-19 vaccination such as local injection reactions (erythema, swelling, tenderness, pain, induration, and pruritus), hypersensitivity reactions, rashes, etc.[34–37]

As regards the use of biologic treatments during the pandemic period, several concerns were raised on their safety.[38] However, several data confirmed that undergoing biologic treatment did not increase the risk of contracting COVID-19 neither worsening its natural course.[38] Similarly, the introduction of COVID-19 vaccines raised several doubt about their effectiveness and safety in patients undergoing therapy with biological for psoriasis.[39–41] Even if molecular and cellular mechanisms by which COVID-19 vaccines lead to psoriasis development have not yet been fully elucidated, vaccination itself can trigger the release of IL-6, interferon and TNF by T-helper (Th)1/Th17 cells.[42,43] All these cytokines are involved in psoriasis pathogenesis.[42,43] Thus, the aim of this manuscript is to review current literature on the safety and effectiveness of COVID-19 vaccination in psoriasis patients undergoing treatment with biologics, in order to clarify any concerns.

Materials and Methods

For the current review, literature research was performed on the PubMed, Cochrane Skin, Embase, EBSCO, MEDLINE and Google Scholar databases (until February 1, 2023). Studies were identified, screened and extracted for relevant data following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines using the following keywords: "COVID-19", "vaccine", "cutaneous", "vaccination", "side effects", "adverse events", "safety", "efficacy", "skin manifestations", "mRNA", "viral-vector, 'Pfizer/BioNTech', 'BNT162b2', 'Moderna', 'mRNA-1273', 'AstraZeneca', 'Johnson & Johnson', 'Ad26.COV2.S', 'AZD1222', 'psoriasis', biologic therapy, "biologics", "adalimumab", "etanercept", "certolizumab", "infliximab", "brodalumab", "ixekizumab", "secukinumab", "guselkumab", "risankizumab", "tildrakizumab". Analyzed manuscripts included reviews, metanalyses, letter to editor, real-life studies, case series. The most relevant manuscripts were considered. Studies were collected if they provided information on psoriasis worsening following COVID-19 vaccination with BNT162b2, mRNA-1273, AZD1222 and Ad26.COV2.S in patients undergoing biologic treatment for psoriasis. Articles regarding other skin reactions were not considered. Moreover, manuscripts where the type of vaccine leading to psoriasis exacerbation was not specified were excluded. Similarly, manuscripts assessing the effectiveness and safety of COVID-19 vaccines in patients undergoing biological treatment for psoriasis were considered. Thus, the research was refined by reviewing the texts and the abstracts of collected articles. The bibliography was also reviewed to include articles that could have been missed. Only English language manuscripts were considered. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Results

A total of 10 articles were included in this review. Even if several cases of psoriasis exacerbation or new-onset psoriasis have been reported in literature following COVID-19 vaccination,[44–53] few of these cases have been described in patients undergoing biologic treatment for psoriasis (Table 1). Interestingly, psoriasis flare during biologic treatment have been reported also in patients contracting COVID-19 infection.[54]

Sotiriou et al firstly highlighted the possibility of psoriasis exacerbation after vaccination reporting a case series of 14 patients who developed a flare of psoriasis following COVID-19 vaccination. However, none of these patients was treated with biologic at the moment of vaccine administration.[55] Subsequently, Megna et al reported 11 cases of patients developing psoriasis following vaccination. For the first time, they showed the possibility of psoriasis worsening also in patients receiving biologic therapies since 6 patients were receiving biologics at the moment of vaccination (secukinumab:2, adalimumab:1, ixekizumab:1, guselkumab:1, etanercept:1).[56] Of note, in two cases biologic switch was required.[56] Similarly, Koumaki et al reported 6 cases of psoriasis exacerbation following COVID-19 vaccination in

Table 1 Cases of Psoriasis Exacerbation Following COVID-19 Vaccination in Patients Undergoing Treatment with Biologics for Psoriasis

Authors	Patient	Sex	Vaccine/Dose	Days	Previous Treatment	New Treatment
Megna et al[56]	1	M	AZD1222 / 1	10	Secukinumab	Secukinumab*
	2	M	mRNABNT162b2 / 2	12	Adalimumab	Ixekizumab
	3	M	mRNABNT162b2 / 2	9	Ixekizumab	Ixekizumab*
	4	F	AZD1222 / 1	7	Guselkumab	Guselkumab*
	5	M	mRNABNT162b2 / 2	5	Secukinumab	Secukinumab*
	6	M	mRNABNT162b2 / 1	14	Etanercept	Ixekizumab
Koumaki et al[57]	1	F	mRNABNT162b2/2	10	Secukinumab	Secukinumab*
	2	F	mRNABNT162b2/2	2	Adalimumab	Adalimumab*
	3	F	mRNABNT162b2/1	20	Adalimumab	Oral Corticosteroids
	4	F	mRNABNT162b2/1,2	3	Secukinumab	Secukinumab
	5	F	mRNABNT162b2/1,2	7	Secukinumab	Secukinumab
	6	F	mRNABNT162b2/1	20	Ustekinumab	Ustekinumab*
Tsunoda et al[58]	1	M	mRNABNT162b2 / 2	3	Risankizumab	Risankizumab
Ruggiero et al[59]	1	M	mRNABNT162b2/2	16	Adalimumab	Brodalumab
	2	F	mRNABNT162b2/2	25	Secukinumab	Secukinumab*

Notes: AZD1222: AstraZeneca-Oxford AZD1222. mRNA-1273: Moderna mRNA-1273. mRNABNT162b2: Pfizer mRNABNT162b2. Dose: number of doses after which psoriasis flare occurred. *Biologic treatment associated with topical calcipotriol/betamethasone combination and/or phototherapy.
Abbreviations: M, male; F, female.

patients undergoing biological treatment for psoriasis (secukinumab:3, adalimumab:2, ustekinumab:1).[57] No biologic switch was required. However, one patient discontinued the treatment.[57] Finally, Tsunoda et al reported a case of psoriasis exacerbation in a patient undergoing treatment with risankizumab.[58]

Of interest, Ruggiero et al reported 2 cases of patients who developed nail psoriasis following vaccination during biologic treatment with adalimumab (n = 1) or secukinumab (n = 1).[59]

As regards the effectiveness and safety of COVID-19 vaccination, they have been poorly investigated. Talamonti et al reported their real-life experience including 369 patients with moderate-to-severe psoriasis undergoing therapy with anti-IL (ani-IL12/23: 192; anti-IL17: 93; anti-IL23: 84).[60] None of these patients discontinued treatment during the study period (5 months).[60] No serious AEs were reported as well as about one-third of patients reported mild AEs seen in the general population (injection site pain, fever, fatigue, etc).[60] The safety of COVID-19 vaccines in psoriatic patients treated with biologics has been also investigated by Musumeci et al on a cohort of 50 patients with stable plaque psoriasis treated with biologics (anti-TNFα: 24; anti-IL17: 14; anti-IL12/23: 7: anti-IL23: 5) for at least 2 months who received COVID-19 vaccination.[61] All patients discontinued their biological agents 10 days before and 10 days after each dose of vaccine. After the vaccines, all patients were assessed at day 2, 7, and 14.[61] None of them reported any side effects or a psoriatic flare except for one patient treated with infliximab biosimilar who referred an exacerbation of psoriasis after BNT162b2 vaccine.[61] Damiani et al reported a case series on 4 health-care workers with moderate-to-severe psoriasis undergoing treatment with biologics at the moment of COVID-19 vaccination (BNT162b2) to assess the immune response and safety to vaccines. No safety issues were collected as well as all patients developed IgG antibodies toward SAR-CoV-2.[62] Marovt et al conducted a prospective observational study to evaluate antibody response against SARS-CoV-2 following two doses of BNT162b2 vaccine in patients with psoriasis receiving biologics, and compare it with that

of healthy controls.[63] Blood samples were collected before the first vaccination and 4 weeks following the second one. Biologic treatment was not interrupted. Globally, 32 patients and 22 controls were enrolled.[63] All patients showed positive antibody response, statistically significant differences among the two groups. However, antibody titres were significantly lower in patients than healthy controls (1024.4 ± 870.3 vs 3055.8 ± 2450.9, $P < 0.001$).[63] Moreover, no significant difference in antibody titres in patients aged ≤55 years and patients aged >55 years (1150.7 ± 966.8 vs 898.1 ± 772.4, $P < 0.45$), or between different treatment groups ($P = 0.11$) were reported.[63] Similarly, Megna et al conducted a similar prospective study assessing blood samples 4 weeks (range 3–6 weeks) following the second dose of COVID-19 vaccination with mRNA vaccines on 44 patients with psoriasis under biologics (anti-TNFα: 19; anti-IL17: 18; anti-IL12/23: 2: anti-IL23: 5).[64] A total of 57 subjects were enrolled in the healthy control group.[64] A positive antibody response was detected in 43 (97.7%) patients and 56 (98.2%) healthy subjects, with no significant difference between the groups. Despite mean antibody titres being slightly higher in the healthy cohort (586.5 ± 408.3 BAU/mL vs 468.4 ± 420.3 BAU/mL), no statistically significant differences were found between the study groups.[64] Moreover, no statistically significant differences in antibody titres between patients >55 years (426.3 ± 403.5 BAU/mL) and those aged <55 years (497.5 ± 437.0 BAU/mL) and between the different treatment groups in the psoriasis cohort were observed.[64]

Finally, Cristaudo et al investigated the immunogenicity and safety of anti-SARS-CoV-2 BNT162b2 vaccine in psoriasis patients treated with biologic drugs on a cohort of 48 patients (anti-TNFα: 21; anti-IL17: 6; anti-IL12/23: 8: anti-IL23: 13) and 48 healthy controls.[65] Neutralizing IgG titers anti–SARS-CoV-2 were evaluated at baseline (day 0, first injection), after 3 weeks (day 21, second injection, TP1) and four weeks post booster (day 51, TP2).[65] Treatment suspension or dose modification of the biologic therapy was not planned.[65] A statistically significant increase of antibody titers on TP1 and TP2 was observed in both psoriatic patients and control group when compared to baseline, without statistically significant differences on the antibody response between psoriatic patients versus controls.[65] Moreover, older age resulted independently associated with a reduced antibody response to vaccine ($P = 0.004$). In line with other studies, biologics administration as well as the type of biological treatment minimally affect the immune response to the vaccine.[65] Moreover, the authors reported that the Body Mass Index did not affect the response to BNT162b2 as well. No significant AEs were collected, and no psoriasis flares were observed.[65] Finally, Mercuri et al reported a real-life, multicenter, case-control study on 160 patients undergoing biologic treatment for psoriasis or psoriatic arthritis showing that heterologous vs homologous primary and booster COVID-19 vaccination do not increase psoriasis flare rate.[66]

Discussion

Major knowledge on dermatological diseases led to the development of new drugs.[67–70] Biological drugs changed the treatment scenario of several diseases.[71–73] In particular, the introduction of biologic treatment revolutionized the management of psoriasis,[12,74,75] with a high profile in terms of efficacy and safety.[76–78] However, several concerns about their safety were raised at the beginning of COVID-19 pandemic period.[79–81] Fortunately, their safety was confirmed even during COVID-19 pandemic[82] which led to the adoption of several measures in order to contain the spreading of the infection allowing the continuity of biologic treatment, opening new era also after COVD-19 pandemic period.[25,83,84] However, the introduction of COVID-19 vaccination newly raised doubt on their efficacy and safety among psoriasis patients receiving biologics. Indeed, the immunologic reaction and immune system dysregulation caused by vaccination may lead to epidermal changes and onset or worsening of certain cutaneous diseases such as psoriasis[85] Moreover, the induction of neutralizing antibodies and T-cell responses by vaccines can lead to increased IFNγ and TNFα production.[86] In addition, vaccination may activate plasmacytoid and dermal myeloid dendritic cells might.[86] All of these conditions can be a trigger for psoriasis cascade.[87] Finally, vaccinations might induce IL-6 production. This cytokine may be a trigger for Th17 cells to produce IL-22, which itself stimulates keratinocyte proliferation.[88] On one hand, the worsening or new onset of several dermatological diseases cutaneous reactions (lichen planus, bullous disorders, pityriasis rosea, atopic dermatitis, hidradenitis suppurativa, etc.) have been reported following COVID-19 vaccination,[89–92] also after the third dose,[93,94] and, on the other hand, the mechanism of action of biologic drugs was suggested as a potential cause of vaccine inefficacy. Even if limited, current evidence indicates that the use of biologics in psoriatic patients does not seem to be associated with a reduced effect of COVID-19 vaccination and with an increased risk of COVID-19 severe disease. Moreover, biologic treatments seem to reduce the risk of psoriasis worsening following

vaccination. However, uncertainty remains due to the limitations of current studies which are often of short duration and limited sample sizes. Furthermore, a sub-analysis investigating on specific biologic classes is lacking.[95]

In our hypothesis, biologic drugs do not reduce the immune response to COVID-19 as they are immunomodulating and not immunosuppressive agents, unlike traditional systemic drug.[96] Moreover, the immunological protection caused by vaccines is not fully understood, as well as the utility of serological tests.

COVID-19 vaccination is the main weapon to overcome the pandemic period. Globally, worldwide vaccination campaign was a success, showing to be the most effective weapon to prevent and control COVID-19 epidemic, disease progression, hospitalization and mortality. Current guidelines strongly recommend vaccination in all subjects affected by chronic inflammatory skin diseases, also undergoing biological treatments.[97,98]

Strengths and Limitations

The use of PRISMA guidelines for reviewing the current literature is the main strength of our manuscript. Main limitation is the reduced number of studies investigating the effectiveness and safety of COVID-19 vaccination in patients undergoing biologic therapies for psoriasis.

Conclusion

Current data seem to confirm the safety and efficacy of COVID-19 vaccination in patients undergoing biological treatments for psoriasis. The risk of psoriasis worsening induced by COVID-19 vaccine seems to be very low. Certainly, vaccination should not be discouraged.

Data Sharing Statement

Data are reported in the current study and are on request by corresponding author.

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Disclosure

The authors report no conflicts of interest in this work.

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