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Expert Opinion on Biological Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iebt20

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To cite this article: Paolo Gisondi, Davide Geat, Francesco Bellinato & Giampiero Girolomoni (2022) Use of biologics during the COVID-19 pandemic: lessons learned from psoriasis, Expert Opinion on Biological Therapy, 22:12, 1521-1529, DOI: 10.1080/14712598.2022.2110467

To link to this article: https://doi.org/10.1080/14712598.2022.2110467

Published online: 08 Aug 2022.

EXPERT OPINION ON BIOLOGICAL THERAPY
2022, VOL. 22, NO. 12, 1521–1529
https://doi.org/10.1080/14712598.2022.2110467

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REVIEW

Use of biologics during the COVID-19 pandemic: lessons learned from psoriasis

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ABSTRACT

Introduction: Given the increased infectious risk associated with biologics, particularly with TNFα inhibitors, concerns were raised over the safety of these agents in relation to SARS-CoV-2 infection. Furthermore, the impact of biologics on SARS-CoV-2 vaccination was questioned.

Areas covered: In this review, studies conducted on patients with moderate to severe plaque psoriasis treated with biologics during the COVID-19 pandemic have been analyzed, including 1) the safety of biologics in psoriatic patients in terms of increased risk and/or worse outcome of SARS-CoV-2 infection; and 2) whether biologic agents could affect the safety and response to SARS-CoV-2 vaccines in psoriatic patients.

Expert opinion: Current evidence indicates that the use of biologics in psoriatic patients does not seem to be associated with an increased COVID-19 infection risk or worse outcome, with TNFα inhibitors being even protective of severe COVID-19 relative to other treatments or no treatment at all. Furthermore, biologic treatment does not seem to have a significant impact on the response and safety of vaccines in patients with psoriasis treated with biologics. However, uncertainty remains given the limitations of current studies which are often of short duration, limited sample sizes and do not stratify on specific biologic classes.

ARTICLE HISTORY
Received 7 June 2022
Accepted 3 August 2022

KEYWORDS
Biologics; psoriasis; pandemic; COVID-19; SARS-CoV-2; vaccination

1. Introduction

More than two years have passed since the first case of COVID-19 was reported, and yet despite the herculean efforts of the vaccination program, COVID-19 still remains a top health concern and continues to pose significant challenges to patients and physicians all over the world. Moreover, the use of biologics during the COVID-19 pandemic has arguably represented a particularly daunting challenge considering the high number of patients treated with biologics agents and the ever-growing indications to their use. Plaque psoriasis represents a key indication to the use of biologics, with eleven biologics already approved and more in the pipeline [1]. While uncertainty on the safety of these agents during the first COVID-19 lockdown led to a marked decrease in their initiation [2] and many patients discontinued them [3,4], a growing number of studies has provided reassurance about their use [5]. More recently, the impact of biologic agents on SARS-CoV-2 vaccination in terms of safety and serological response has been questioned and represents an important field of research. In this review, the lessons learned from the use of biologics in psoriasis in relation to COVID-19 and its vaccines is summarized. In the following paragraphs, studies conducted on patients treated with different classes of biologics which did not differentiate COVID-19 outcomes based on the biologic class will be reviewed first. Then, studies investigating the COVID-19 outcomes for each biologic class will be summarized. Finally, studies evaluating the safety and immunogenicity of SARS-CoV-2 vaccines in psoriatic patients treated with biologics will be presented.

2. Biologics and COVID-19

The COVID-19 outbreak was understandably met with apprehension by psoriatic patients treated with biologics and their physicians. Indeed, some biologic agents, particularly TNFα inhibitors, have long been known to be associated with an increased risk of serious infection, i.e. an infection that required intravenous antibiotics or resulted in hospitalization or death. In the Psoriasis Longitudinal Assessment and Registry (PSOLAR) registry which included data from 11,466 psoriatic patients, adalimumab and infliximab had a higher risk of serious infections compared with nonbiologic agents unlike ustekinumab and etanercept [6]. More recently, an American cohort study including 123,838 biologic-exposed psoriasis and/or psoriatic arthritis (PsA) patients found that, compared to ustekinumab, all other biologics were associated with 1.4- to 3-times higher risk of hospitalized serious infections [7]. Despite this, several studies allowed for reassurance on the safety of biologics in relation to COVID-19.

A consistent amount of research showed no increased risk of COVID-19 infection or worse outcome in psoriatic patients treated with biologics (Table 1). In particular, an Italian study on 1,830 psoriatic patients on biologics (55.3% TNFα inhibitors) found neither increased risk of COVID-19 nor COVID-19-related respiratory or life-threatening complications [8]. The incidence rate difference between psoriatic patients on biologics and the general population was −3.1 (95%CI − 7.5–6.0) for COVID-19 hospitalization and −1.2 (95%CI −2.6–3.7) for COVID-19-related death [8]. Similarly, no increased risk of COVID-19 infection in psoriatic patients

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Article highlights

- A consistent amount of research showed no increased risk of COVID-19 infection or worse outcome in psoriatic patients treated with biologics, particularly with TNFα inhibitors.
- No serious safety concerns were raised in psoriatic patients on biologics vaccinated with SARS-CoV-2 vaccines.
- Psoriasis flare-ups following SARS-CoV-2 vaccination have been described, but they should not discourage vaccination as they appear to be rare, and a causal relationship is not established as it is based on sporadic spontaneous case reports whereas billions of doses of COVID-19 vaccines have been administered globally.
- Psoriatic patients on biologics were shown to have a similar antibody response to controls after SARS-CoV-2 vaccination, unlike those on nonbiologic agents such as methotrexate.
- However, uncertainty remains given the limitations of current studies which are often of short duration, limited sample sizes and do not stratify on specific biologic classes.

on biologics compared to those treated with topical treatment was found in a smaller single-center study conducted on 180 patients (80 on biologics, 100 on topicals; OR 1.22, 95% CI 0.58–2.58, P = .699) [9]. Furthermore, another Italian study which conducted serological analyses for SARS-CoV-2 on 93 psoriatic patients treated with either biologics or apremilast found an incidence rate (13%) which was similar to that of the reference general population (7.7%–19.7%) during the first wave of the pandemic [10].This is also in line with the findings of a Spanish study conducted on 239 psoriatic patients treated with biologics which reported an incidence of COVID-19 of 3.1% (95%CI 1.0%–5.2%), similar to that of the general population (3.35%), while there were no cases of COVID-19-related hospitalization or death [11]. Ultimately, in the Italian PSO-BIO-COVID study which included 12,807 psoriatic patients on biologics the incidence of swab-confirmed SARS-CoV-2 infection was similar to that of the general population (0.2% vs 0.31%) [12]. Partly conflicting results were reported by an Italian study conducted during the first COVID-19 outbreak on 1,193 psoriatic patients treated with biologics and small molecules. In that study, patients on biologics were at higher risk of testing positive for COVID-19 (OR 3.43, 95% CI 2.25-5.73, P < .0001) and being hospitalized (OR 3.59, 95% CI 1.49-8.63, P = .0044), although not of being admitted to the Intensive Care Unit or dying [13]. However, the generalization of these findings may be limited by the relatively short study

Table 1. Studies evaluating the safety of biologics in relation to COVID-19 in psoriatic patients.

Size of study population (n)	Treatment(s)	Relevant findings	Reference
1,830 PsO, 4,905,854 general population	Biologics	No increased risk of COVID-19 nor COVID-19-related respiratory or life-threatening complications vs general population	[8]
180 PsO	Biologics, topicals	No increased risk of COVID-19 in psoriatic patients on biologic vs topical agents	[9]
93 PsO	Biologics, apremilast	COVID-19 incidence rate similar to that of the general population	[10]
239 PsO	Biologics	COVID-19 incidence rate similar to that of the general population; no COVID-19-related hospitalizations or deaths	[11]
12,807 PsO	Biologics	COVID-19 incidence rate similar to that of the general population	[12]
1,193 PsO, 10,060,574 general population	Biologics, small molecules	Higher risk of testing positive for COVID-19 and being hospitalized vs general population but not of ICU admission or death due to COVID-19	[13]
980 PsO, 257,353 general population	Biologics	No cases of COVID-19-related hospitalization or death	[14]
6,501 PsO	Biologics	Standardized incidence ratio of hospitalization and death similar to those of the general population.	[15]
61 PsO	Biologics	No cases of severe COVID-19 observed.	[16]
1,322 PsO	Biologics, conventional systemics, topicals, phototherapy	No differences in COVID-19-related hospitalization between patients on biologics vs nonbiologics.	[17]
1,418 PsO	Biologics, conventional systemics	No increased incidence of severe COVID-19.	[18]
1,326,312 PsO	Biologics, nonbiologics, topicals	No increased risk of COVID-19-related in-hospital mortality for systemic agents (including biologics).	[19]
1,163,438 IMID, 16,508,627 general population	Biologics, conventional systemics	No increased risk of COVID-19-related death in patients on most targeted agents (except rituximab) vs conventional systemics	[20]
374 PsO	Biologics, conventional systemics	COVID-19-related hospitalization more frequent for non-biologics vs biologics	[21]
1,943 PsO	TNFi, ustekinumab, MTX, acitretin	Similar COVID-19 infection and mortality risk for TNFi vs other agents; lower hospitalization risk for TNFi vs MTX and ustekinumab.	[26]
7,361 IMID, 74,910 controls	Biologics	Lower COVID-19 infection risk for TNFi vs controls	[27]
843 cutaneous IMID	Biologics, conventional systemics, antihistamines, phototherapy	No impact on COVID-19 severity or duration of TNFi, anti-IL or MTX in psoriatic patients.	[28]
214 IMID, 31,862 nontreatment group	TNFi, MTX	No increased hospitalization or mortality for TNFi or MTX vs the nontreatment group.	[29]
6,077 IMID	TNFi, small molecules, conventional systemics	Lower risk of adverse COVID-19 outcomes for TNFi monotherapy vs other agents or combination therapy	[30]
3,538 IMID, 311,563 comparator cohort	Biologics, small molecules, conventional systemics	Lower COVID-19-related hospitalization risk in RA patients on TNFi vs non-TNFi biologics and the comparator cohort.	[31]
141,583 PsO	IL-17i, MTX, non-systemic/non-immunomodulatory agents	No increased COVID-19 infection, hospitalization or mortality risk for IL-17i vs other agents.	[40]
57 PsO	Risankizumab	No COVID-19 cases observed during the study period.	[48]
66 PsO	Risankizumab	No cases of COVID-19-related hospitalization or death during the study period	[53]

PsO psoriasis; IMID immune mediated inflammatory diseases; MTX methotrexate; TNFi TNF inhibitors; IL-17i IL-17 inhibitors.

time frame (48 days) and the low number of outcome events observed among psoriatic patients (17 quarantined, 5 hospitalized).

Regarding the risk of hospitalization and death due to COVID-19 in psoriatic patients, other studies have provided evidence on the safety of these agents. A retrospective observational study conducted in Italy early in the pandemic that assessed the timeframe from 02/20/2020 to 04/10/2020 found no cases of hospitalization or death among 980 psoriatic patients on biologics [14]. Furthermore, a Northern Italian study on 6,501 psoriatic patients on biologics, the standardized incidence ratio of hospitalization and death in patients with psoriasis vs the general population were 0.94 (95%CI 0.57–1.45, P = .82) and 0.42 (95%CI 0.07–1.38, P = .19), respectively [15]. Other studies from other countries yielded similar results [16–18]. A French study conducted on 1,326,312 psoriatic patients found that biologics (as well as other systemic agents for psoriasis) were not associated with an increased risk of in-hospital mortality due to COVID-19 [19]. Furthermore, a study which included 1,163,438 patients with immune-mediated inflammatory diseases (of whom 54,593 with PsA and 693,178 with psoriasis) found no increased risk of COVID-19-related death in patients on most targeted agents (with the exception of rituximab) compared with standard systemic agents [20]. Ultimately, in a registry-based study that included 374 psoriatic patients from 25 countries (71% treated with biologics, 18% with non-biologics, 10% not treated with systemic agents), hospitalization due to COVID-19 was more frequent in patients on non-biologics than in those treated with biologics (OR 2.84, 95%CI 1.31–6.18) [21]. In that study, increased COVID-19 hospitalization risk was also associated with older age, male sex, nonwhite ethnicity and comorbid chronic lung disease [21].

Other studies including, among others, psoriatic patients and evaluating the differential safety of each different class of biologics in relation to COVID-19 are discussed below.

2.1. TNFα inhibitors

Currently approved TNFα inhibitors for psoriasis include etanercept, infliximab, adalimumab and certolizumab pegol [22]. A fifth anti-TNFα agent, golimumab, is only approved for PsA but not psoriasis. These agents are associated with an increased risk of serious infections, particularly herpes zoster [6], and an increased risk of tuberculosis acquisition or reactivation [23]. In addition, TNFα is known to contribute to the defense against viral infection by recruiting and activating macrophages, natural killer cells, T cells and antigen-presenting cells [24]. Regarding respiratory tract infections (RTI), however, a meta-estimate of pivotal phase 3 trials in psoriasis found no increased risk of RTI in patients treated with TNFα inhibitors compared to placebo (OR 1.08, 95%CI 0.84–1.38, P = .55) [25].

As to COVID-19, a population-based cohort study by Kridin et al. compared COVID-19 outcomes of 1,943 psoriatic patients on TNFα inhibitors to those of psoriatic patients on methotrexate, ustekinumab or acitretin [26]. Compared to patients on methotrexate, ustekinumab and acitretin, patients with psoriasis treated with TNFα inhibitors had a comparable risk of COVID-19 infection (adjusted HR 1.07, 95%CI 0.67–1.71 vs methotrexate; 1.07, 95%CI, 0.48–2.40 vs ustekinumab; 0.98, 95%CI 0.61–1.57 vs acitretin) and comparable risk of mortality [26]. Of note, the risk of SARS-CoV-2 infection was found to be even lower in patients treated with TNFα inhibitors than in controls (OR, 0.69; 95% CI, 0.48–0.98; P = .04) in another large study conducted on 7,361 patients with immune-mediated inflammatory diseases (27.3% of whom with psoriasis) treated with biologics [27].

Regarding the risk of hospitalization, Kridin et al. found that patients on TNFα inhibitors had a decreased risk of hospitalization compared to methotrexate and ustekinumab (adjusted HR 0.10, 95%CI 0.01–0.82 and 0.04, 95% CI 0.00–0.64) but not to acitretin (adjusted HR 1.00, 95%CI 0.16–6.16) [26]. Partly different results were reported by a Brazilian survey which reported no impact of anti-TNFα treatment on COVID-19 severity (OR for COVID-19 severity 1.1, 95%CI 0.2–5.8, P = 0.88), however the sample size was much smaller (229 psoriatic patients) [28]. Furthermore, similar hospitalization risk for TNFα inhibitors versus the nontreatment group (RR 0.73, 95%CI 0.47–1.14, P .1594) was found in a subgroup analysis of a study which included 214 COVID-19 patients treated with TNFα inhibitors or methotrexate, but again the study population was relatively small [29].

As to the safety of TNFα inhibitors compared to other immunosuppressants, the findings of Kridin et al. are consistent with a pooled analysis from three international COVID-19 registries that included patients with psoriasis, rheumatic diseases and inflammatory bowel diseases (6,077 patients) and found a lower risk of adverse COVID-19 outcomes in patients on TNFα inhibitor monotherapy than in those treated with other immunosuppressants [30]. For example, compared with patients on TNFα inhibitor monotherapy, higher odds of hospitalization or death were observed in those who received with azathioprine/6-mercaptopurine monotherapy (OR 1.84, 95%CI 1.30–2.61, P = .001), methotrexate monotherapy (OR 2.00, 95%CI 1.57–2.56, P < .001) or JAK inhibitor monotherapy (OR 1.82, 95%CI 1.21–2.73, P = .004) [30]. Furthermore, a cohort study on 3,538 COVID-19 patients with either rheumatoid arthritis, PsA or ulcerative colitis found that the hospitalization risk was lower in COVID-19 patients with rheumatoid arthritis on TNFα inhibitors vs non-TNFα inhibitor biologics (OR 0.32, 95% CI 0.20–0.53) [31]. Ultimately, in a metanalysis that included 35 studies (conducted on patients with psoriasis, rheumatic diseases and inflammatory bowel diseases), COVID-19 cases receiving anti-TNFα agents had a lower probability of hospitalization (pooled OR 0.53, 95%CI 0.42–0.67) and severe disease (pooled OR 0.63, 95%CI: 0.41–0.96) compared to patients treated with non-anti-TNFα agents (i.e. biologics and conventional immunosuppressants) [32].

A hypothesis which could explain the favorable COVID-19 outcome in patients with psoriasis treated with TNFα inhibitors may be related to the role of TNFα in the pathogenesis of severe SARS-CoV-2 infection. Indeed, serum levels of TNFα were reported to be higher in patients with severe COVID-19 than in those with mild disease [33] and to be an independent risk factor for death in patients with severe COVID-19 [34]. Of note, TNFα is one of the mediators of the cytokine storm syndrome, a systemic inflammatory syndrome in which

pathologically activated monocytes and macrophages release large amounts of IL-6, IL-1β and TNFα that drive the progression to a severe SARS-CoV-2 infection [35–37].

2.2. Interleukin (IL)-17 inhibitors

Currently FDA approved anti-IL-17 agents for psoriasis include secukinumab, ixekizumab and brodalumab [1]. These agents are associated with an increased risk of fungal infections [38] and, according to a meta-estimate of phase 3 pivotal trials, of RTI (OR 1.56, 95%CI 1.04–2.33, P = 0.03) [39]. In regard to COVID-19, however, real world data appear reassuring on the safety profile of these agents. A population-based cohort study which included 680 psoriatic patients treated with IL-17 inhibitors and compared them with patients treated with methotrexate or non-systemic/non-immunomodulatory treatments found that was the use of anti-IL-17 agents was not associated with an increased risk of COVID-19 (adjusted HR 0.91, 95%CI 0.48–1.72 vs methotrexate; 0.92, 95%CI 0.54–1.59 vs non-systemic/non-immunomodulatory treatments) [40]. There was also neither increased risk of hospitalization compared to methotrexate and non-systemic/non-immunomodulatory treatments (adjusted HR 0.42, 95%CI 0.05–3.39 and 0.65, 95%CI 0.09–4.59, respectively), nor of COVID-19-associated mortality (adjusted HR 7.57, 95%CI 0.36–157.36 and 7.05, 95%CI 0.96–51.98 respectively) [40]. Similarly, a survey that included 229 psoriatic patients with confirmed COVID-19 diagnosis found that anti-IL-17 agents did not influence COVID-19 severity (OR 1.4, 95%CI 0.1–13.0, P = 0.79) [28]. Interestingly, a possible role of IL-17 in the COVID-19 cytokine storm and disease severity has also been suggested. Indeed, IL-17 levels were shown to be elevated in COVID-19 patients, and to be associated with lung injury [41,42]. A certain degree of uncertainty still remains, however, as a case of severe interstitial COVID-19 pneumonia has been reported in a psoriatic patient treated with ixekizumab [43].

2.3. IL-23 and IL-12/23 inhibitors

IL-23 inhibitors approved by FDA for psoriasis are guselkumab, tildrakizumab and risankizumab whereas the only approved IL-12/23 inhibitor is ustekinumab [1]. The safety profile of this class of biologics in regards to infections appears also reassuring, as shown by a meta-estimate of phase 3 pivotal trials in psoriasis which found no significant increased risk of RTI (OR 1.24, 95%CI 0.98–1.56, P = .07) [44]. Of note, in a meta-analysis of randomized controlled trials in immune-mediated inflammatory diseases (including psoriasis), anti-IL-23 or anti–IL-12/IL-23 agents did significantly increase the risk of RTIs (Mantel-Haenszel risk difference, MH RD 0.019, 95%CI 0.005–0.033, P = .007), however this was attributed to upper RTIs but not viral upper RTIs (MH RD 0.001, 95%CI −0.002–0.003, P = .60) and lower RTIs (MH RD 0, 95% CI, −0.002–0.002, P = .71) [45]. This is not surprising, given that IL-23 is not a major contributor to antiviral responses [46,47]. Regarding COVID-19, in a multicenter study conducted in Italy on 57 psoriatic patients treated with risankizumab during the first months of the COVID-19 outbreak there were no COVID-19 cases even though three patients had contact with SARS-CoV-2-infected patients [48]. Clinical case reports of COVID-19 in psoriatic patients on IL-23 inhibitors confirm the safety of these agents in regard to COVID-19 outcome [49–52]. In addition, a retrospective 40-week real-life study conducted during the COVID-19 pandemic on 66 psoriatic psoriatic patients treated with risankizumab reported no cases of COVID-19-related hospitalization or death during the whole study period [53].

3. Biologics and SARS-CoV-2 vaccines

While SARS-CoV-2 vaccines have dramatically changed the course of the COVID-19 pandemic, they also raised concerns over the safety and response in patients treated with biologics. Again, studies conducted on psoriatic patients have offered several useful insights into both aspects.

3.1. Safety

Regarding the safety of SARS-CoV-2 vaccination in psoriatic patients on biologics, adverse effects were shown to be comparable to those observed in healthy individuals (Table 2) [54]. A study on 436 psoriatic patients treated with biologics (78 of whom underwent SARS-CoV-2 vaccination) reported no vaccination-related adverse effects, and a similar reduction in PASI from baseline in those who were vaccinated vs those who were not (73.4% vs 74.13%) [55]. Furthermore, in a study on 369 psoriatic patients treated with anti-IL agents who underwent SARS-CoV-2 vaccination, no serious vaccination-related adverse events were reported, while about a third developed mild adverse events (such as injection site pain, fever, fatigue, and muscle pain) that resolved within 48 hours [56]. Similarly, in another study that enrolled 50 psoriatic patients on biologics who underwent SARS-CoV-2 vaccination (mRNABNT162b2 or Moderna mRNA 1273) no vaccine-related adverse effects were reported except for a case of psoriasis exacerbation following the vaccination in a patient on infliximab [57]. Of note, several other cases of psoriasis flares have been reported following SARS-CoV-2 vaccination – including psoriatic patients on biologics [58–65]. Such flares were mostly reported after the second vaccine dose [63] and the mean interval between SARS-CoV-2 vaccination and psoriasis flare was shown in a study to be 9.3 days [66]. Also, no association was found between psoriasis flares induced by SARS-CoV-2 vaccination and patient age, sex, disease duration, baseline or pre-vaccination disease severity, psoriatic arthritis, current biologics use, comorbidities, vaccine types nor human leukocyte antigen (HLA)-C genotypes [66]. The pathogenetic mechanism behind psoriasis exacerbations may be related to the increased TNFα and interferon (IFN)-γ production by CD4 + T cells induced by the vaccination [67]. Importantly, both cytokines were shown to be able to trigger the inflammatory cascade of psoriasis [68,69]. However, psoriasis flares following SARS-CoV-2 vaccination in patients on biologics appear rare and a causal relationship is not established as it is based on sporadic spontaneous case reports whereas billions of doses of COVID-19 vaccines have been administered globally. Similarly, PsA flares following SARS-CoV-2 vaccine in patients on biologics are possible, but uncommon. Indeed, a study that included 126 patients with rheumatic musculoskeletal diseases

Table 2. Studies evaluating the safety of SARS-CoV-2 vaccines in psoriatic patients treated with biologics.

SARS-CoV-2 vaccine	Size of study population (n)	Patients on biologic treatment (%)	Relevant findings	Reference
BNT162b2	436 PsO (78 vaccinated)	100%	No vaccination-related adverse effects observed; similar PASI reduction in vaccinated vs not vaccinated.	[55]
N/A	369 PsO	100%	No serious vaccination-related adverse events reported	[56]
BNT162b2 and mRNA-1273	150 PsO (50 vaccinated)	100%	No vaccine-related adverse effects reported except for a case of PsO exacerbation	[57]
BNT162b2 and mRNA-1273	126 RMD (26 PsA), 85 controls	38.9%	Low incidence rate of disease reactivation; similar adverse effect occurrence vs controls	[70]
BNT162b2	40 PsA	100%	No change in PsA disease activity following vaccination.	[71]

PsO psoriasis; PASI Psoriasis Area Severity Index; RMD Rheumatic Musculoskeletal Diseases; PsA Psoriatic Arthritis.

(26 of whom with PsA) reported only three cases of disease flares following vaccination: two patients had PsA (one of them was on a TNFα inhibitor) and one patient rheumatoid arthritis [70]. The infrequency of SARS-CoV-2 vaccine-associated PsA flares was also confirmed by a study, which included 40 PsA patients on TNFα inhibitors and found no changes in PsA clinical disease activity following vaccination [71].

3.2. Response

A few studies that exclusively enrolled psoriatic patients provide evidence of the limited impact of biologics on SARS-CoV-2 vaccination in these patients (Table 3). Damiani et al. reported four cases of psoriatic patients treated with biologics, all of whom developed IgG anti- S1- Receptor Binding Domain (RBD) against SARS-CoV-2 following vaccination [72]. Cristaudo et al. assessed the humoral response to the BNT162b2 vaccine in 48 psoriatic patients on biologics (combined with methotrexate in three patients) and found no statistically significant difference in the antibody response of psoriatic patients versus controls (geometric mean of concentration four weeks post booster: 262.05 vs 259.06 AU/mL, p = 0.658) [73]. However, patients also receiving methotrexate had lower antibody titers than those on biologic monotherapy (P = 0.001) [73]. Partly similar results were reported by Mahil et al. in a study on 84 psoriatic patients and 17 controls. While seroconversion rates after a single BNT162b2 vaccine dose were lower in patients receiving immunosuppressants than in healthy controls (78%, 95%CI 67–87 vs 100%, 95%CI 80–100), neutralizing activity against wild-type SARS-CoV-2 was preserved in those receiving targeted biologics compared with controls (median 50% inhibitory dilution 269 [interquartile range 141–418] vs. 317 [213–487]) [74]. Conversely, neutralizing activity was significantly lower in patients receiving methotrexate (129 [IQR 40–236]) than in controls (p = 0 · 0032) [74]. After two vaccine doses, there were no significant differences in neutralizing antibody titers between those on methotrexate, biologics, and controls. However, a lower proportion of patients on biologics and methotrexate had detectable T-cell responses following the vaccine compared with controls (74% and 62% vs 100%, p = 0.022) [75]. Ultimately, a study on 102 psoriatic patients treated with biologics and 55 controls found no significant differences in anti-SARS-CoV-2 antibody levels between patients and controls (median [IQR range] 1681.0 U/mL [600.0–4844.0] vs 1984.0 U/mL [1000.0–3136.0]; P = 0.82) [76].

Further evidence on the limited impact of biologics on the serological response to SARS-CoV-2 vaccination can be derived from studies which enrolled patients with immune-mediated inflammatory diseases including, among others, psoriatic patients on biologics. Venerito et al. compared the antibody response to the BNT162b2 vaccine of 40 PsA patients (33 of whom with coexisting psoriasis) treated with TNFα

Table 3. Studies evaluating the immunogenicity of SARS-CoV-2 vaccines in psoriatic patients treated with biologics.

SARS-CoV-2 vaccine	Size of study population (n)	Patients on biologic treatment (%)	Immunogenicity	Reference
BNT162b2	4 PsO	100%	Antibody response detected in all patients.	[72]
BNT162b2	48 PsO, 48 controls	100%	No differences in the antibody response vs controls	[73]
BNT162b2	84 PsO, 17 controls	80%	No differences in neutralizing antibody titers vs controls after 2 vaccine doses.	[74,75]
BNT162b2 and mRNA-1273	102 PsO, 55 controls	100%	No significant differences in antibody levels vs controls.	[76]
BNT162b2	40 PsA, 40 controls	100%	No significant differences in antibody levels vs controls.	[71]
BNT162b2 and mRNA-1273	26 chronic inflammatory diseases (4 PsO, 2 PsA), 42 controls	77%	Reduced antibody response vs controls	[77]
BNT162b2	84 IMID (8 PsO), 182 controls	43%	Reduced antibody responses in IMID patients (regardless of the treatment) vs controls	[78]
BNT162b2 and AZD1222	120 IMID (107 PsO, 25 PsA)	74%	Reduced antibody response in patients on nonbiologic immunomodulators vs biologics	[79]
BNT162b2	51 IMID (24 PsO and/or PsA), 26 controls	59%	Reduced antibody response in patients on MTX vs biologics	[80]
BNT162b2, CX-024414, ChAdOx1 nCoV-19, Ad.26.COV2.S	1,692 IMID, 647 controls	51%	Similar seroconversion rate for most biologics (except anti-CD20) vs controls.	[81]

PsO psoriasis; PsA psoriatic arthritis; IMID immune mediated inflammatory diseases; MTX methotrexate; TNFi TNF inhibitors.

inhibitors (alone or in combination with conventional systemics) and did not find different antibody levels in patients compared to controls (19,227.4 ± 11.8460.45 AU/mL, p = 0.08) [71]. Conflicting results were found in a study on a small sample of 26 patients with chronic inflammatory diseases (of whom 4 patients with psoriasis and 2 with PsA) treated with conventional systemics or biologics who underwent vaccination with mRNA-1273 and BNT162b2 [77]. In that study, IgG titers were significantly lower in patients with chronic inflammatory diseases compared to controls, with no significant differences between TNFα inhibitors vs conventional systemics vs anti-interleukin 17 [77]. Similar results were found in study conducted on 84 patients with immune-mediated inflammatory diseases (including 8 patients with psoriasis) and 182 healthy controls which evaluated the development of anti-SARS-CoV-2 IgG after the BNT162b2 vaccine using optical density (OD) [78]. Patients with immune-mediated inflammatory diseases had delayed and reduced response to the vaccine compared to controls (OD = 6.47 ± 3.14 vs 9.36 ± 1.85, p < 0.001), whilst the response of patients on biologic or targeted-synthetic disease-modifying antirheumatic drugs was not different from that of patients on conventional systemics (6.49 ± 2.91 vs 6.26 ± 3.00, p = 0.97) or not receiving any treatments (6.49 ± 2.91 vs 6.64 ± 3.70, p = 0.97) [78]. This led the authors to hypothesize that the reduced response to SARS-CoV-2 vaccination may be based on the disease itself rather than its treatment [78]. However, these findings may not be generalizable to psoriasis considering the small number of psoriatic patients in the two latter studies. Indeed, other studies that included larger samples of psoriatic patients reported a differential impact of biologics and conventional systemics on SARS-CoV-2 vaccination. Al-Janabi et al. evaluated the antibody response to BNT162b2 or AZD1222 vaccine in 120 participants with immune-mediated inflammatory diseases treated with immunomodulators, including 107 patients with psoriasis and 25 with PsA [79]. In that study, conventional systemics reduced the odds of a detectable antibody response compared with biologics (adjusted OR 0.31, 95%CI 0.08–1.17 for total antibodies against SARS-CoV-2 spike protein S1 receptor-binding domain; OR 0.18, 95%CI 0.06–0.59 for anti-S1 IgG) [79]. Similar findings were reported by Haberman et al., who evaluated the response to the BNT162b2 vaccination in 51 patients with immune-mediated inflammatory diseases (of whom 24 with psoriasis and/or PsA). In that study, the percentage of patients demonstrating antibody responses was significantly higher in patients treated with biologics or JAK inhibitors than in those on methotrexate (91.9% vs 62.2%, p < 0.001) [80]. Furthermore, a Dutch cohort study which included 2,339 patients with immune-mediated inflammatory diseases (6.5% with dermatological diseases including psoriasis) showed that the relative risk for seroconversion after COVID-19 vaccination for most immunosuppressants was not significantly reduced compared to controls (RR 1.02, 95%CI 0.81–1.29 for TNFα inhibitors; 1.01, 95%CI 0.64–1.52 for ustekinumab) [81]. However, substantial reductions in antibody titers were observed for anti-CD20 agents, and moderate reductions for TNFα inhibitors, dupilumab, intravenous and subcutaneous immunoglobulin and methotrexate (predicted fold in antibody titer for TNFα inhibitors 0.55, 95%CI 0.47–0.64) [81]. Importantly, the authors concluded that reductions in antibody titers are not likely to translate into a clinically significant loss of protection, at least not in the short term, given that neutralization capacity and recall responses were shown to be unaffected [81]. This latter observation is in line with the findings of a study which assessed the risk of SARS-CoV-2 breakthrough infections in 3,207 COVID-19 vaccinated patients with immune-mediated inflammatory diseases treated with immunosuppressants (both targeted and conventional systemic agents), 8% of whom with dermatological diseases. In that study, no difference in the odds of SARS-CoV-2 breakthrough infections were observed versus controls (adjusted OR 0.88, 95%CI 0.66–1.18), although the authors advised that caution may be warranted for patients on anti-CD20 therapy [82].

To conclude, SARS-CoV-2 vaccines appear safe and effective in patients with psoriasis treated with biologics. Accordingly, dermatology societies worldwide advocate active vaccination of these patients [83–85]. Indeed, the National Psoriasis Foundation advised that psoriatic patients who do not have contraindications to vaccination should receive a COVID-19 vaccine as soon as it becomes available to them, and that patients continue their biologic or oral therapies for psoriasis and/or PsA in most cases [83–85].

4. Conclusions

Current data suggests that the use of biologic agents in psoriatic patients does not lead to an increased COVID-19 infection risk or worse outcome. Furthermore, SARS-CoV-2 vaccines appear safe and effective in patients with psoriasis treated with biological agents.

5. Expert opinion

International registries have been developed to improve our understanding of how factors such as immunomodulatory therapies and comorbidities affect outcomes of COVID-19 in patients with psoriasis. PsoProtect and PsoProtect me are two important open access tools for health care providers and patients to report outcomes of COVID-19 in individuals with psoriasis [86]. The first important lesson on the use of biologics learned from psoriasis is that the risk of hospitalization and death due to COVID-19 was shown not to be increased in patients with psoriasis on biologics, and to be even reduced in those treated with TNFα inhibitors [14–21,27]. While earlier in the pandemic the lack of data led to a marked decrease in the initiation of biologics in psoriasis (of up to 57% in France compared to 2019 [2]), several studies have now provided a solid background for dermatologists to initiate biologic treatments [8–12,14–21]. The second lesson learned is that biologics are even safer than nonbiologic agents in psoriatic patients in relation to COVID-19 outcome, and they have less impact on COVID-19 vaccine antibody response [21,73,74]. Should these findings be confirmed by further studies, they may prompt further discussion on the place in therapy of biologic agents during the COVID-19 pandemic in some subsets of patients with moderate-to-severe psoriasis. Indeed,

the current approach to moderate-to-severe psoriasis [87,88], which would list phototherapy or conventional systemic agents as methotrexate as first line treatments, has its limitations in relation to COVID-19. Conventional systemic agents currently represent the first treatment for most patients with moderate-to-severe psoriasis. However, as biologics have shown a better safety profile in relation to COVID-19 and to have a more limited impact on COVID-19 vaccination [21,62,63], an earlier use of these agents may be hypothesized in patients who are at highest risk of poor COVID-19 outcome in case of inadequate response to COVID-19 vaccination, such as elderly patients or those with underlying comorbidities [89,90]. Among comorbidities, obesity – which was found in a study to affect as many as 30.6% of psoriatic patients – was indeed associated with susceptibility to COVID-19 (OR 2.42, 95%CI 1.58–3.70), COVID-19 severity (OR 1.62, 95%CI 1.48–1.76), and with hospitalization (OR 1.75, 95% CI 1.47–2.09), mechanical ventilation (OR 2.24, 95%CI 1.70–2.94), intensive care unit admission (OR 1.75, 95%CI 1.38–2.22) and death (OR 1.23, 95%CI 1.06–1.41) in COVID-19 patients [90].

Ultimately, current evidence suggests that biologics are safe and do not significantly impact serological response to COVID-19 vaccines, although further research is needed on the impact of the different classes of biologics on COVID-19 vaccination. While psoriasis flares have been reported following vaccination in psoriatic patients treated with biologics [58–65], they appear rare and should not discourage vaccination. This is particularly important as many psoriatic patients are even more likely to benefit from the COVID-19 vaccination than the general population given that many of the comorbidities associated with psoriasis, such as obesity, are also associated with a worse COVID-19 outcome.

Declaration of interest

P Gisondi has been a consultant and/or speaker for Abbvie, Almirall, Amgen, Janssen, Leo-pharma, Eli Lilly, Novartis, Pierre Fabre, Sandoz, Sanofi and UCB. G Girolomoni has served as consultant and/or speaker for AbbVie, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Eli-Lilly, Leo Pharma, Novartis, Pfizer, Regeneron, Samsung bioepis, Sanofi and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they consult and/or receive grants from many companies that make psoriasis products and that they are a member of the National Psoriasis Foundation Task Force on COVID-19. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Funding

This paper was funded by Fondazione Cariplo ID Project 2020-1363 (Title: Impact of COVID-19 infection on patients affected by inflammatory skin disease on immuno-suppressive therapies COVISKIN).

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