Management of Psoriasis Patients with Serious Infectious Diseases

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ABSTRACT

The management of patients affected by moderate-to-severe psoriasis may be challenging, in particular in patients with serious infectious diseases [tuberculosis (TB), hepatitis B and C, HIV, COVID-19]. Indeed, these infections should be ruled out before starting and during systemic treatment for psoriasis. Currently, four conventional systemic drugs (methotrexate, dimethyl fumarate, acitretin, cyclosporine), four classes of biologics (anti-tumour necrosis factor alpha, anti-interleukin (IL)12/23, anti-IL-17s, and anti-IL-23], and two oral small molecules (apremilast, deucravacitinib) have been licensed for the treatment of moderate-to-severe psoriasis. Each of these drugs is characterized by a unique safety profile which should be considered before starting therapy. Indeed, some comorbidities or risk factors may limit their use. In this context, the aim of this manuscript was to evaluate the management of patients affected by moderate-to-severe psoriasis with serious infectious diseases.

Keywords: Psoriasis; Infectious disease; Tuberculosis; Hepatitis B and C; HIV; COVID-19; Biologic treatments; Systemic treatments

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Key Summary Points

Why carry out this study?

The management of patients affected by moderate-to-severe psoriasis may be challenging, in particular in patients with serious infectious diseases.

Therefore, the infectious risk as well as the presence of a severe infectious disease should be considered in treatment decisions.

What was learned from the study?

Patients should be screened for tuberculosis, hepatitis B and C, and HIV before starting the majority of systemic treatments for psoriasis.

Our review evaluated the management of patients affected by moderate-to-severe psoriasis with serious infectious disease.

Each of the currently approved systemic drug for psoriasis (conventional systemic drugs, biologics, oral small molecules) is characterized by a unique safety profile which should be considered before starting therapy.

INTRODUCTION

Psoriasis is a chronic inflammatory disease affecting up to 3% of the worldwide population, usually presenting as well-defined erythematous-desquamative plaques covered by whitish or silvery scales, predominantly found on elbows, knees, scalp, and the lumbar areas (plaque psoriasis, about 90% of cases) [1–4]. However, other clinical presentations can be distinguished such as guttate psoriasis, erythrodermic psoriasis, pustular psoriasis, and inverse psoriasis [1–4].

Recent knowledge on psoriasis has led to the consideration of this disorder as a systemic disease. Indeed, several comorbidities can be associated with psoriasis including psoriatic arthritis (PsA), cardiovascular diseases, neurological and psychiatric disorders, chronic inflammatory bowel disease, and endocrine disorders [5–8]. In this context, appropriate and well-designed treatment is needed, targeting not only the skin manifestations but the psoriatic disease as a whole.

Although mild psoriasis is usually well controlled with topical prescription therapies based on the combination of calcipotriol and betamethasone, the management of moderate-to-severe forms of the disease may be challenging [9, 10]. Indeed, conventional systemic treatments [methotrexate (MTX), dimethyl fumarate, acitretin, cyclosporine (CsA)] may be contraindicated in cases with comorbidities (cardiovascular disease, hepatic or renal failure, etc.) or risk of adverse events (AEs). Another therapeutic option is phototherapy, which may be limited by logistical issues [9, 10].

Recently, the introduction of biological drugs, specifically targeting interleukins (IL) involved in psoriasis pathogenesis, including anti-tumour necrosis factor alpha (TNF-α), anti-IL-12/23, anti-IL-17s, and anti-IL-23s, have revolutionized the management of psoriatic disease, with an excellent profile in terms of safety [9, 10]. However, biologics may also have some considerations to be mindful of before initiating treatment, such as the use of anti-TNF-α, which is contraindicated in patients with multiple sclerosis and advanced hearth failure, the risk of reactivating latent infection, or triggering or worsening inflammatory bowel diseases (anti-IL-17 drugs) [11–13]. Indeed, routine blood tests should be performed before starting biological treatment, and the risk of hepatitis, tuberculosis, and HIV should be ruled out [11–13]. Finally, apremilast and deucravacitinib are two oral small molecules (OSM) approved for psoriasis management. Although apremilast has no contraindication for patients affected by severe infections, deucravacitinib has the same limitations as biological drugs [14, 15].

In this context, the aim of this study was to investigate the management of patients with serious infectious diseases who were affected by moderate-to-severe psoriasis. This review focuses on serious infectious disease [tuberculosis (TB), hepatitis B and C, HIV, COVID-19] which should be considered before starting and during systemic treatment for psoriasis. Moreover, a special focus on COVID-19 infection is discussed.

Conventional OSM and biologics were considered, with a special emphasis on the latter. This manuscript is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Tuberculosis

TB is an infectious disease, caused by *Mycobacterium tuberculosis*, and is still one of the 10 leading causes of death worldwide [16]. TB is transmitted by air, through respiratory secretions released into the air by a contagious individual, for example through saliva, sneezing, or coughing. In immunocompetent hosts, the immune system is able to control the infection and an asymptomatic condition called latent tuberculous infection (LTBI) develops, which is estimated to affect about a quarter of the world's population [16]. It is estimated that 5–10% of individuals with LTBI, if untreated, develop active tuberculous disease during their lifetime [16]. The main risk factors for reactivation of LTBI include HIV infection, organ transplantation, silicosis, close contact with individuals with active TB, and the use of therapies that suppress or modulate the immune system [17].

Systemic therapies approved for the treatment of psoriasis, both conventional and biological, act by suppressing or modulating the activity of specific cells and/or cytokines that play a key role in the immune response, and thus are associated with possible reactivation of LTBI. Concerning conventional systemic agents, it should be noted that LTBI screening is not recommended in the summary of product characteristics (SmPC) of acitretin, CsA, or fumarates [18–20]. However, whereas for acitretin and fumarates there have never been reports of LTBI reactivation [21, 22], for CsA, LTBI reactivation has been reported in patients undergoing organ transplantation and treated with high doses of the drug [21]. Screening for LTBI is recommended in the SmPC of MTX, and cases of LTBI reactivation during treatment with MTX have

been reported [23, 24]. A new group of drugs for the treatment of psoriasis are OSM, including apremilast and deucravacitinib. Apremilast, a phosphodiesterase-4 inhibitor, has shown a good safety profile and can be used without risk of reactivation in patients with LTBI. Indeed, the apremilast clinical trials (ESTEEM 1 and ESTEEM 2) also included seven patients with a history of previously treated Tb, of whom four had LTBI and were enrolled without prophylaxis before starting treatment with apremilast. No cases of Tb reactivation were detected in these patients [25].

Of note, unlike apremilast, screening for TB is required to start deucravacitinib therapy [26]. Among biological drugs, TNF-α inhibitors were the first to be approved for the treatment of psoriasis. Clinical trials and real-life data have amply demonstrated that therapy with anti-TNF-α is a high-risk factor for LTBI reactivation [27, 28]. Early randomized controlled trials (RCTs) on infliximab showed a fourfold increase in the risk of TB infection [29, 30]; subsequently, other studies reported an increased risk of TB in patients treated with TNF-α antagonists relative to a placebo group, with relative risk ranging from 1.6 to 25.1 [31]. Data in the literature show an increased risk of LTBI reactivation with infliximab and adalimumab, followed by etanercept. The increased risk of TB reactivation in patients treated with TNF-α inhibitors may be explained by the immune role of this cytokine. In fact, by increasing the phagocytic activity of macrophages and the production of reactive nitrogen and oxygen intermediates, TNF-α facilitates the intracellular killing of mycobacterium, synergistically with interferon gamma [32]. In addition, TNF-α is involved in the formation and maintenance of the tubercular granuloma, thus preventing the dissemination of mycobacteria in the bloodstream [33]. Ustekinumab, a monoclonal antibody targeting the shared p40 subunit of the cytokines IL-12 and IL-23, has been associated with cases of LTBI reactivation, probably related to the inhibition of IL-12, which plays an important role in the Th1 immune response against *M. tuberculosis* [34].

Clinical trials conducted on IL-17 and IL-23 inhibitors found no safety concerns in relation to an increased risk of TB reactivation in

patients with LTBI [35, 36]. In the IMMhance phase 3 clinical trial, 31 patients with LTBI at baseline were treated with risankizumab, an IL-23p19 inhibitor, and none of them developed TB reactivation at 55 weeks of follow-up [37]. In a real-life study of 10 patients with LTBI who did not undergo chemoprophylaxis and were treated with the IL-17A inhibitor secukinumab, none of the patients developed TB reactivation during up to 84 weeks of follow-up [38]. Recently, Manzanares et al. conducted a retrospective multicentre study of 35 patients with untreated LTBI undergoing biological therapy for psoriasis with different drugs [risankizumab (21), guselkumab (5), tildrakizumab (5), ixekizumab (2), secukinumab (1), and brodalumab (1)]; no cases of TB reactivation were observed [39]. Finally, Torres et al. conducted a retrospective observational study of 405 patients with psoriasis and diagnosed LTBI treated with biological therapy, of whom 112 did not undergo chemoprophylaxis for LTBI. The authors showed only one case of TB reactivation in a patient with LTBI, who had not undergone chemoprophylaxis, after 14 months of treatment with ixekizumab. The TB reactivation rate was 0.46% and 0% for IL-17 and IL-23 inhibitors, respectively [40].

Current guidelines recommend screening for TB infection before starting any biological therapy, regardless of the drug chosen [41]. Screening includes a complete history and physical examination, tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) test, and chest X-ray. If a diagnosis of LTBI is made, anti-TB chemoprophylaxis should be carried out before starting biological therapy [41]. Several treatment regimens are available for the treatment of LTBI. Those most commonly used in clinical practice involve the use of isoniazid (INH) (5 mg/kg; max dose: 300 mg) for 6 months or INH (5 mg/kg; max dose: 300 mg)+rifampicin (RIF) (10 mg/kg; max dose: 600 mg) for 3 months, with the possibility of starting biological therapy after 1 month of chemoprophylaxis [42].

Hepatitis B and C

Hepatitis B is an infectious disease caused by a DNA virus of the *Hepadnaviridae* family. Hepatitis B is a major global health problem. Indeed, it can cause chronic infection and puts people at high risk of death from cirrhosis and liver cancer [43]. The virus can spread through contact with infected body fluids like blood, saliva, vaginal fluids, and semen. It can also be passed from a mother to her baby. In adults, the disease become chronic in about 5–10% of cases. The risk of chronicity increases as the age at which the infection is acquired decreases; in fact, in infants infected shortly after birth, it occurs approximately nine times out of 10. Hepatitis C is caused by the hepatitis C virus (HCV), which belongs to the *Flaviviridae* family. Transmission occurs mainly via the apparent and inapparent parenteral route. The initial acute HCV infection is in most cases asymptomatic; however, up to 85% of cases will become chronic. In addition, 20–30% of patients with chronic hepatitis C develop cirrhosis and, in approximately 1–4%, subsequent hepatocarcinoma [43]. Systemic therapies for psoriasis can lead to reactivation of chronic viral hepatitis by interfering with cytokines involved in the control of viral infection. Therefore, current guidelines recommend screening for hepatitis B and C before starting both conventional (MTX, CsA) and biological therapies for psoriasis [42]. In contrast, as already seen for LTBI, apremilast does not require screening for hepatitis B and C to initiate treatment. Laboratory screening should include evaluation of the following parameters: (1) for hepatitis B: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HbcAb), and anti-HBs, and in the case of positive HbsAg or HbcAb, also HBV DNA (hepatitis B virus); (2) for hepatitis C: anti-HCV, and by positivity, HCV-RNA [42].

In cases of active hepatitis B and/or C, the decision to undertake biological therapy must be evaluated in consultation with a hepatologist in order to assess the safest drug class and concomitant antiviral therapy [44]. In the case of inactive HBV carriers (HbsAg+, anti-HBc+, HBV DNA<2000 IU/ml, normal transaminase levels) treated with high-to-moderate-risk immunosuppressive therapy (i.e. anti-TNF-α, ustekinumab, CsA), there is a risk of reactivation of viral infection, and patients should undergo prophylactic antiviral treatment with lamivudine or entecavir prior to the initiation of biological therapy.

Conversely, inactive HBV carriers who are prescribed low-risk immunosuppressive therapy (i.e. MTX, acitretin, apremilast, IL-17 inhibitors, IL-23 inhibitors) need to be monitored for viral reactivation by determining alanine aminotransferase (ALT) and HBV DNA levels every 3 months [45, 46]. In the case of HbsAg negativity and HbcAb positivity, the choice of antiviral prophylaxis or quarterly monitoring of transaminases and viral markers can be made on the basis of HBV DNA positivity or negativity, possibly after consultation with a hepatologist and/or infectiologist and after considering the patient's risk factors [42]. Of note, HBV prophylaxis should be started at least 2 weeks prior to the administration of a biologic and continued for up to 6 months after discontinuation of the biologic [47]. Current guidelines recommend a hepatological consultation in the event of a positive screening for hepatitis C [42]. However, the risk of reactivation of latent infection (anti-HCV positivity and HCV-RNA negativity) appears to be lower for hepatitis C than for hepatitis B [48], and moreover, definitive and effective treatments for HCV infection are now available. Nevertheless, clinical trials and real-life studies show a significantly different risk of reactivation of hepatitis B and C for the several classes of systemic drugs used to treat psoriasis.

Concerning conventional systemic therapies, MTX has direct hepatic toxicity, and in most international guidelines, the use of MTX is contraindicated in HbsAg+ or HCV+ patients due to the risk of progression to fibrosis or cirrhosis [49–51]. However, there are conflicting opinions in the literature, as some real-life studies do not show an increased risk of fibrosis in patients with long-term MTX treatment [52]. Given the availability of alternatives, MTX is not a first choice of treatment in this patient setting today. Similarly, CsA has an important immunosuppressive effect and for this reason is not a first-line option for the treatment of psoriasis in patients with positive screening for HBV and/or HCV [47]. Finally, acitretin is associated with a low risk of reactivation of hepatitis B and C and may be considered a viable alternative in the absence of therapeutic options, with a better efficacy/safety profile for the treatment of psoriasis [42, 49]. As far as OSM are concerned, apremilast has an excellent safety profile, as it can also be used in patients with cancer or active infections, and does not require screening for HBV and HCV before starting therapy [53]. Unlike apremilast, screening for viral hepatitis is mandatory before starting deucravacitinib therapy. Among biological drugs, the risk of viral reactivation or opportunistic infections is reported to be higher with TNF-α inhibitors [54, 55]. Clinical trials show a higher risk of HBV reactivation for infliximab and adalimumab than for etanercept [56].

Given the importance of IL-12 in counteracting infections by intracellular pathogens, the IL-12/23 inhibitor ustekinumab is associated with an increased risk of HBV reactivation [57]. A 2018 meta-analysis of 28 HBV+ patients treated with ustekinumab and not receiving antiviral prophylaxis showed three cases of HBV reactivation [58]. However, there is growing evidence that IL-17 and, in particular, IL-23 inhibitors are less likely to cause HBV and HCV reactivation than anti-TNF-α [48, 59, 60]. Nevertheless, a multicentre study of 46 patients treated with secukinumab in the absence of antiviral prophylaxis recorded seven cases (15.2%) of HBV reactivation [61]. Several real-life studies, however, showed a very low risk of HBV reactivation in HbsAg+ patients treated with secukinumab and receiving concomitant antiviral prophylaxis [47]. Regarding HBcAb positivity with HbsAg and HBV DNA negativity, prophylaxis should be evaluated on a case-by-case basis. Conversely, in the absence of antiviral prophylaxis, the incidence of HCV reactivation is very low but still possible [62]. With regard to IL-23 inhibitors, the risk of reactivation of hepatitis B and C also appears to be very low. Several real-life studies have demonstrated the safety of guselkumab, risankizumab, and tildrakizumab in these patient settings [60, 63, 64]. In any case, the current guidelines provide the same recommendations as for the other biological classes [42].

HIV

Human immunodeficiency viruses (HIV-1 and HIV-2) belong to the genus *Lentivirus*, and the

infection that they cause, if left untreated, is responsible for acquired immunodeficiency syndrome (AIDS) [65]. HIV remains a major global public health issue, with an estimated 39.0 million [33.1–45.7 million] people living with HIV at the end of 2022 [66]. The prevalence of psoriasis in the HIV+ population ranges from 1 to 3%, a rate very similar to that in the general uninfected population [67]. The treatment of psoriasis in HIV-infected patients is challenging, given the profound state of immunosuppression that the infection causes. Psoriasis in HIV+ patients is often severe and resistant to first-line therapy represented by topical agents, phototherapy, highly active antiretroviral therapy (HAART), and acitretin, which, while presenting no safety problems, prove ineffective in almost all cases. In addition, HIV infection may be responsible for flare-ups of pre-existing psoriasis, and recalcitrant psoriasis in patients with no history of the disease can also be the initial clinical presentation of the HIV infection [68].

Since HIV-positive patients are excluded from clinical trials, the totality of data on the proper therapeutic management of psoriasis in HIV patients comes from real-life studies. With regard to conventional systemic therapies, MTX and CsA have an important immunosuppressive effect, and consequently their use in this patient setting should not be considered in view of the immunodepressed state caused by HIV infection. As already seen for LTBI and viral hepatitis, apremilast also represents an effective and safe therapeutic option in HIV+ patients, as evidenced in several case reports in the literature, despite having considerably lower efficacy than biological drugs. [69–71]. Most of the cases in the literature concern HIV patients treated with TNF-α inhibitors [72]. Myers et al. analysed 39 HIV+ patients suffering from psoriasis and treated with anti-TNF-α, showing therapeutic success in the majority of cases, without the occurrence of serious AEs. Only six patients experienced serious AEs or opportunistic infections [72]. Real-life data for ustekinumab also seem to demonstrate good efficacy and excellent safety in the treatment of psoriasis in HIV+ patients [72]. Indeed, therapeutic success was achieved in the majority of patients, and in some studies it was shown that the CD4+ count not only remained stable

but even improved [73]. Furthermore, there are case reports of HIV+ patients successfully treated with ustekinumab after loss of efficacy of adalimumab or etanercept.

Interleukin 17 and IL-23 inhibitors have shown promising results and a good safety profile in the treatment of psoriasis in patients with chronic infections, such as viral hepatitis and LTBI [40, 51, 59]. Likewise, data in the literature seem to confirm the same results in terms of efficacy and safety in HIV+ patients. The American Academy of Dermatology and National Psoriasis Foundation (AAD-NPF) guidelines recommend the use of anti-IL-17 monoclonal antibodies in HIV patients who have been receiving antiretroviral therapy and have a well-controlled viral load [44]. Specifically, with regard to IL-17 inhibitors, there are several case reports in the literature showing that these are an effective and safe therapeutic option for the treatment of psoriasis in HIV+ patients [74, 75]. Similarly, data on the use of IL-23 inhibitors in HIV+ patients are reassuring. Orsini et al. reported four cases of HIV-infected patients treated with risankizumab; in all four cases, therapeutic success was achieved, with no evidence of viral reactivation and no serious AEs, with two out of four patients being treated with risankizumab over a 2-year follow-up period [76]. Finally, regardless of the therapy practised, periodic laboratory monitoring of the CD4+ count and multidisciplinary collaboration with an HIV specialist infectiologist is of crucial importance given the complex management of these patients [77].

COVID-19

COVID-19 is a highly contagious respiratory tract infection caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The first confirmed cases occurred in China in December 2019, and since then over 760 million cases and 6.9 million deaths have been recorded, with these numbers constantly increasing [78]. The COVID-19 pandemic, officially declared on 11 March 2020, had a devastating impact on health, society, and the economy worldwide [79]. Fortunately, the massive worldwide vaccination campaign

was a success and minimized the impact of the pandemic on human life [80]. Dermatological clinical practice has also been profoundly affected by the COVID-19 pandemic, not only because the infection is often accompanied by skin manifestations [81], but also because SARS-CoV2 infection can induce flare-ups of chronic inflammatory skin diseases such as atopic dermatitis and psoriasis [82]. The most important issue, however, was to establish the correct therapeutic management of moderate-to-severe psoriasis during the COVID-19 pandemic, since, at least theoretically, both conventional systemic therapy and biological drugs, by interacting with the immune system, may lead to an increased risk of SARS-CoV2 infection as well as a more severe course of COVID-19. Psoriasis is also often accompanied by comorbidities such as obesity and increased cardiovascular risk, which are clear risk factors for severe COVID-19 [83].

Today, after 4 years of real-life experience in the management of moderate-to-severe psoriasis during the COVID-19 pandemic, we can conclude that patients treated with biological therapy have infection rates comparable to those of the general population and a low rate of hospitalization for COVID-19 [84–86]. In particular, the use of TNF-α inhibitors as monotherapy for immune-mediated inflammatory diseases (IMIDs) showed a lower rate of hospitalization and/or death due to COVID-19 than other commonly used therapies such as azathioprine, MTX, and JAK-inhibitors [87]. These findings could be explained by the fact that in patients with severe COVID-19, a cytokine storm is present, characterized among other things by elevated TNF-α levels, which seem to correlate directly with organ damage and a worse disease outcome [88]. These hypotheses are confirmed by several cases of patients with COVID-19 and treated with TNF-α inhibitors with favourable outcomes [89]. Similarly, as shown in the study conducted by Kridin et al., IL-17 inhibitors also did not increase the risk of SARS-CoV2 infection or COVID-19 complications (hospitalization and death) in psoriatic patients, either in comparison with psoriasis patients treated with MTX or relative to those treated with non-systemic/non-immunomodulating therapies [90]. Similar evidence is available for IL-23 inhibitors; in fact,

as highlighted by Hu et al., these drugs appear to reduce the risk of COVID-19 and long COVID in patients treated for psoriasis [91].

In addition, numerous studies have shown that biological drugs such as adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, and guselkumab can reduce the risk of SARS-CoV2 infection as well as prevent the evolution to severe COVID-19 [92–94]. Apremilast has also shown a significant protective effect against SARS-CoV2 infection, and therefore this OSM can be considered a safe therapeutic alternative in COVID-19 patients due to its unique and selective mechanism of action [95, 96]. In conclusion, it is clear from the multitude of data in the literature that biological drugs for the treatment of psoriasis do not lead to an increased risk of SARS-CoV2 infection or a worse outcome for COVID-19. Furthermore, during the COVID-19 pandemic, despite initial uncertainties and fears, adherence rates to psoriasis therapy were higher among patients treated with biological drugs than among those treated with conventional therapies or topical agents [97, 98]. Therefore, in patients with COVID-19, it is possible to continue current biological therapy by evaluating the individual case in accordance with good clinical practice guidelines. Finally, it was shown that biological treatment did not alter the immune response to the COVID-19 vaccine [99].

DISCUSSION

The risk of severe infection should be ruled out before and during systemic treatment for psoriasis [100]. In this context, we performed a review of the current literature to evaluate the impact of TB, hepatitis B and C, HIV, and COVID-19 infection on psoriasis treatment. As regards TB, LTBI screening is not necessary before starting acitretin, CsA, and fumarates. However, cases of LTBI reactivation during treatment with CsA have been reported. Conversely, LTBI should be ruled out before starting MTX. As regards biological drugs and OSM, LTBI should be ruled out before starting treatment, except for apremilast.

However, it should be emphasized that the latest approved classes of biologics (anti-IL-17 and anti-IL-23) do not seem to carry an increased risk of TB reactivation, found in patients treated with anti-TNF-α and ustekinumab.

Similarly, hepatitis B and C should be screened before initiating treatment with conventional (MTX, CsA), OSM (excluded apremilast) and biological therapies for psoriasis. It should be emphasized that in the case of inactive HBV carriers, patients receiving high-to-moderate-risk immunosuppressive therapy (i.e. TNF-α inhibitors, ustekinumab, CsA), prophylactic antiviral treatment is required, whereas inactive HBV carriers who are prescribed low-risk immunosuppressive therapy (i.e. MTX, acitretin, apremilast, IL-17 inhibitors, IL-23 inhibitors) need to be monitored for viral reactivation by determining ALT and HBV DNA levels every 3 months. Nevertheless, consultation with a hepatologist and/or infectiologist, also considering the patient's risk factors, is mandatory.

The treatment of psoriasis in HIV-infected patients is challenging, given the profound state of immunosuppression that the infection causes. On one hand, psoriasis in HIV+ patients is often severe and resistant to first-line therapy; on the other hand, HIV infection may be responsible for flare-ups of pre-existing psoriasis, and recalcitrant psoriasis in patients with no history of the disease can be the initial clinical presentation of the HIV infection. As far as conventional systemic therapies are concerned, MTX and CsA have an important immunosuppressive effect, and consequently their use in this patient setting should not be considered. Also in this case, apremilast is an effective therapeutic option. As regards biologics, data are scant. However, data on the use of use of IL-17 and IL-23 inhibitors in HIV+ patients are reassuring. Certainly, a multidisciplinary collaboration with an HIV specialist infectiologist is of crucial importance given the complex management of these patients.

Finally, despite initial doubts on systemic treatment for psoriasis at the beginning of the COVID-19 pandemic, apremilast and biologics were shown to be safe, regardless of the mechanism of action.

It should be emphasized that bimekizumab, the most recently approved monoclonal antibody targeting IL-17A and IL-17F [101], has not been discussed in our manuscript. Despite increasing real-life data showing its effectiveness and safety [102–104], there are no data about the use of this drug in patients with serious infectious disease. However, drug insert package reported that careful consideration is necessary when contemplating the utilization of bimekizumab in individuals with a chronic infection or a background of recurrent infection [105]. Moreover, treatment with bimekizumab should be avoided in patients with any clinically significant active infection until the infection has subsided or has been appropriately addressed [105].

To sum up, the management of psoriasis patients with severe infections may be challenging. Excluding the risk of these severe infections, as well as learning to manage them to ensure patients' access to the right systemic drug, is crucial for offering patients a tailored approach. Certainly, other specialists such as infectiologists and hepatologists should be considered to manage patients with severe infections.

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Declarations

Conflict of Interest. Matteo Megna, Giuseppe Lauletta, Nello Tommasino, Antonia Salsano, Teresa Battista, Angelo Ruggiero, Fabrizio Martora, and Luca Potestio is an Editorial Board member of *Dermatology and Therapy*. Luca Potestio was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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