INTRODUCTION

Psoriasis (PsO) is a chronic, immune-mediated, inflammatory condition presenting with an estimated prevalence of 2.6% and 3.6% in the USA and Northern Europe populations, respectively.\(^1\)\(^2\) Pathophysiological mechanisms consist of a complex interplay between genetic, environmental, and immune triggers, which ultimately leads to the dysregulation of the immune system.\(^2\) Generally, PsO manifests with plaques located in the most commonly exposed areas, such as the elbows and knees, although it can affect virtually any site of the body, including palms, soles, scalp, nails, and genitals.\(^1\)\(^-\)\(^3\)

Treatment with methotrexate, cyclosporine, and tumor necrosis factor (TNF) inhibitors has been associated with an increased risk of latent tuberculosis infection (LTBI) reactivation. Therefore, guidelines for the management of LTBI in patients treated with anti-TNF therapy have been developed.\(^5\) Nonetheless, treatment with targeted biological drugs, such as anti-interleukin (IL)-17, shows a lower risk of reactivating LTBI.\(^4\)\(^,\)\(^5\)

Interleukin-17A represents a key cytokine in the pathogenesis of PsO, by initiating and promoting inflammation and structural damage. Produced by Th17 cells, leukocytes, and mast cells, it activates critical signaling pathways that represent specific targets of advanced pharmacological inhibition therapy.\(^6\) Secukinumab selectively inhibits IL-17A and was the first and only fully human anti-IL-17A approved in both the USA and Europe.\(^7\) With ongoing observational studies providing considerable information on the long-term effectiveness and safety, Secukinumab has already proved to be a valuable aid for the treatment of moderate-to-severe PsO.\(^7\)\(^,\)\(^8\)

In the present case series, three cases of moderate-to-severe PsO that were treated with Secukinumab are described. Although LTBI prophylaxis was not feasible due to various comorbidities, the targeted treatment did not result in the reactivation of the infectious disease.
2 | CASE PRESENTATIONS

2.1 | Case 1

A 70-year-old man with smoking habit presented with plaque PsO diagnosed 30 years prior to the present examination. His past medical history was significant for type 2 diabetes mellitus (DM) treated with insulin therapy, non-alcoholic steatohepatitis (NASH), and cardiometabolic syndrome characterized by mixed dyslipidemia, hypertensive heart disease associated with high cardiovascular risk, hyperuricemia, morbid obesity, chronic kidney disease, and multiple ischemic strokes. Physical examination disclosed PsO plaques mainly located at nails and scalp (Figure 1A) and a baseline BMI of 31, PASI 16, and DLQI 24. Abdominal ultrasonography showed signs of severely hyperechogenic liver disease. Conventional treatment with methotrexate was administered for 16 weeks resulting in gastrointestinal disturbances and severe elevation of alanine transaminase (ALT) and aspartate transaminase (AST), reaching levels three times higher than normal values that persisted for 3 months after drug suspension.

2.2 | Case 2

A 62-year-old man with smoking habit presented with plaque PsO with palmoplantar and articular involvement (Figure 1C,D). Baseline examination revealed PASI 18, DLQ 21, and BSI 33.4 years. The patient had previously been treated with DAA for HCV-related chronic hepatitis and tested negative for HCV RNA during the last screening. His past medical history was relevant for dyslipidemia, COPD, and a 10-year history of peripheral neuropathy. Treatment with acitretin for 6 months did not result in clinical improvement and caused elevation of liver enzymes five times the normal values and was therefore suspended.

2.3 | Case 3

A 74-year-old man with smoking habit with a history of pulmonary TB diagnosed at an early age presenting with CT signs of a previous active infection was examined for drug-resistant PsO. Past medical history was significant

Figure 1 (A, B) Baseline evaluation of nails and scalp, PSSI 0; (C, D) front and back images showing palmoplantar and articular involvement
for emphysematous COPD, hypertensive cardiopathy, positive serum anti-HBc IgG, liver steatosis, and prostate hypertrophy managed with pharmacological treatment. Baseline examination revealed PASI 21 and DLQI 27 (Figure 1B). After 1 month of treatment with apremilast, the patient suffered severe eczematous dermatitis and worsening of his PsO. When treated with isoniazid for possible LTBI reactivation, the onset of severe hepatotoxicity resulted in a 2-week drug suspension (Figure 1B).

3 | RESULTS

Following the failure of the DMARD treatment and after extensive counseling, all patients signed informed written consent to start treatment with Secukinumab. The first and the second patient achieved absolute PASI 0 and PASI 1 respectively at 16 weeks following treatment initiation with persisting results at 52- and 96-week follow-up (Figure 2A,C,D). The third patient achieved PASI 1 at an 8-week follow-up with evidence of a stable clinical condition after the 24th week (Figure 2B). Clinical follow-up twice a year and annual X-ray were performed for the first two patients. For the third patient, a clinical examination was performed at 24 weeks. None of the three patients exhibited signs of LTBI reactivation, and their clinical and psychological conditions were significantly improved at the last follow-up.

4 | DISCUSSION

Novel therapies based on biological agents target specific cytokines and inflammatory mediators inhibiting unique pathways of the innate and the adaptive immune system. Notwithstanding their innovative impact on the treatment of immune-mediated disorders, such therapies carry a higher burden of opportunistic infections compared with standard pharmacological treatments. Dysregulation of the immune system can result from various genetic and environmental factors, as it was recognized for PsO; therefore, understanding the role of key immune mediators and their pathways enables the improvement of drug design and patient care. In recent years, the pharmacological modulation of the immune system offered by biological drugs has proven to be a breakthrough advancement for the treatment of PsO; nonetheless, new concerns regarding the higher risk of LTBI reactivation following biological treatment have been expressed.

Tumor necrosis factor (TNF) has an established role in regulating the host immune response to the intracellular infection of M. tuberculosis. For instance, recent evidence shows a higher rate of LTBI reactivation when TNF-α inhibitors are adopted for the treatment of PsO. Further research has unveiled another key component of the immune regulation following infection with Koch's bacillus. Although the exact mechanisms are not yet fully understood, IL-17 has been reported to exert either protective or damaging roles during TB infection. Recent evidence shows that IL-17A inhibitors can reduce the extension of pathological lesions and the bacterial load during chronic infections by downregulating neutrophil activation. Furthermore, peripheral blood mononuclear cell cultures and in vivo mouse models express significantly increased levels of IL-17A when exposed to M. tuberculosis. Along with this growing evidence, conflicting results have been gathered concerning human patients presenting with LTBI who were treated with IL-17A inhibitors. In contrast with few reports describing cases of LTBI reactivation during anti-IL-17A therapy, a pooled safety analysis of 10 phase II or III clinical trials in patients with moderate-to-severe plaque psoriasis showed no cases of reactivation. Registral trials examining post-marketing data report how among 96,000 patients treated with secukinumab, only five exhibited TB infection without evidence of previous LTBI.

Secukinumab is a novel biological agent that inhibits IL-17A selectively and was approved for the treatment of moderate-to-severe PsO in the European Union in 2015. In parallel to other systematic studies, Kaushik et al. offered further insight into Secukinumab's effectiveness and safety when compared to other biologic drugs. Anti-IL-17A, which shows a similar safety profile to apremilast, is recommended as first-line therapy in patients with LTBI.

Several factors must be taken into consideration for the risk of LTBI reactivation during biologic therapy. Antitubercular drugs (isoniazid and rifampicin) are burdened by a high risk of short- and long-term hepatic and neurologic toxicity. Therefore, a careful patient examination should be conducted to identify possible adverse effects of these drugs. In the current series, three patients presented with several hepatic comorbidities and demonstrated deterioration of general clinical condition when treated with hepatotoxic therapies such as methotrexate and isoniazid. Since LTBI prophylaxis could not be initiated, Secukinumab was eventually administered. PsO manifestations subsided shortly after drug administration, with the first two patients achieving PASI 1 at 16 weeks and the third achieving PASI 1 at 8 weeks. Annual chest X-rays revealed no clinical or radiological symptoms of TB reactivation. In line with previous reports, the current cases show that Secukinumab represents a safe treatment that is not associated with the possibility of reactivation in patients with LTBI who are not candidates for anti-tuberculosis prophylaxis.
Monoclonal antibodies represent a breakthrough discovery of modern era pharmacological therapy. Nonetheless, further research is needed to continuously improve patients’ condition. Preclinical data and growing real-life evidence demonstrate the safety profile of Secukinumab in patients treated with systemic therapy. To prevent high toxicity prophylaxis in patients with comorbidities, treatment strategy guidelines are awaited.

In conclusion, with recent clinical advances and the availability of biological agents that function through multiple pathways, all patient variables and comorbidities should be considered and enabled to guide management decisions to ensure the best possible outcome for each patient.

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CONFLICT OF INTEREST
The author has no conflict of interest to declare.

AUTHOR CONTRIBUTIONS
Dr. Fiorella was involved in the conception and design of the work, data acquisition and analysis, and the drafting of the manuscript. Is also accountable for all the relevant aspects to ensure the proper response to queries related to the accuracy or integrity of any part of the present manuscript.

ETHICAL APPROVAL
The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The paper is exempt from the ethics committee approval since it is related only to three case reports.

CONSENT
Written informed consent for publication (including images) has been obtained from the patient.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.
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