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## Case Report

### **Efficacy of tildrakizumab 200 mg for treating difficult-to-treat patient populations with moderate to severe plaque psoriasis**

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#### **Authors' contributions**

Study conception and design: PD, MM; and MT.

Acquisition of data: PD, MM; and MT.

Drafting of the manuscript: PD, MM; and MT.

Critical revision: PD, MM; and MT.

**Ethical approval:** All the procedures adopted in this study were in respect to the ethical standards of the World Medical Association Declaration of Helsinki.

**Consent for publication:** The subjects provided their written informed consent to publish the cases included in this manuscript (including publication of images).

#### **Competing interests**

Paolo Dapavo has participated in advisory boards for Eli Lilly, Novartis, Leopharma, UCB, Abbvie, Almirall, Janssen, Sandoz, and Bristol. Matteo Megna has acted as speaker or consultant for Abbvie, Eli Lilly, Novartis, UCB, Leo Pharma, Almirall, Janssen. Marina Talamonti has served as advisory board member and consultant for AbbVie, Almirall, Eli Lilly, and Company, Janssen, Leo Pharma, Novartis, and has received speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Leo, Novartis, Sanofi Genzyme, Sun Pharma, and UCB Pharma. The authors declare to have no additional financial involvement with organizations or entities with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. Almirall S.p.A. Italy sponsored the editorial assistance for the writing and had no role in the content of the manuscript.

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## Abstract

Psoriasis is an inflammatory chronic disease of the skin typically located on the extensor surfaces of the body, and the trunk. Patients with psoriasis can often present multiple characteristics, such as lesions located in difficult-to-treat (DTT) areas or a high severity of the disease which can negatively affect their quality of life. There is a lack of consensus in identifying the best therapy for these complex patient populations, especially after the failure of one or multiple lines of therapy. In this regard, we report a case series describing patients with psoriasis located in different DTT areas or presenting a high *Psoriasis Area and Severity Index* score at baseline and treated ineffectively with prior lines of therapy. Finally, patients achieved complete remission following therapy with tildrakizumab 200 mg (anti-IL-23p19), highlighting its potential efficacy in these patient populations.

## Introduction

Psoriasis is an inflammatory chronic disease mainly affecting the skin and joints. With a global prevalence of 2-3%, psoriasis can show different phenotypes, all sharing similar symptoms, such as burning, itching, and soreness.<sup>1</sup> The most common form of the disease is plaque psoriasis, representing almost 80% of cases. Plaque psoriasis is characterized by well-defined erythematous patches or plaques typically located on the extensor surfaces of the body, the trunk, and gluteal fold. Nevertheless, psoriasis often affects sensitive and DTT areas such as the face, the scalp, nails, genitals, palms and soles, the tibial region or intertriginous areas, negatively impacting patients' quality of life.<sup>2-4</sup> Unfortunately, treatment of these areas with topical drugs remains challenging. Different hypotheses can explain the lack of effectiveness of these therapies, such as an inadequate penetration of topical compounds, poor treatment adherence, excessive sensibility of the areas to aggressive topical treatments, or morphological characteristics of the area.<sup>5</sup> Moreover, when psoriasis affects these areas, patients often receive inadequate treatment, resulting in a higher burden of disease which then requires other types of therapy.<sup>6</sup> Recent data have shown the efficacy of biologics for treating psoriasis localized to the nails, palmoplantar regions, and the scalp.<sup>5</sup> Nevertheless, large controlled trials as well as studies based on real world evidence testing the effects of this class of drugs in patients with psoriasis located in DTT areas are limited, and the treatment of this patient population remains challenging.<sup>3, 5</sup> Galluzzo and co-workers reported the results of a retrospective real world study demonstrating the effectiveness and safety of treatment with tildrakizumab 100 mg (recombinant humanized monoclonal antibody that specifically binds to the subunit p19 of interleukin-23) for 28 weeks in patients with psoriasis localized in the genital region, scalp, nails, palms and soles, highlighting the promising effects of the antibody in these patients.<sup>6</sup>

Psoriasis severity is measured based on PASI score as well as other classification indexes, with the severity of the disease expressed as PASI score inversely correlating with quality of life.<sup>1, 7</sup> Relative and absolute PASI reductions are typically used in clinical trials to evaluate clinical efficacy.<sup>8</sup> In studies with PASI-based patient stratification, a lower disease severity at baseline was associated with a higher probability of achieving PASI improvement with different types of treatment, highlighting the challenge of treating patients showing higher disease severity.<sup>8-10</sup>

In this case series we described outcomes of different patient populations with DTT plaque psoriasis following a therapy based on tildrakizumab 200 mg, administered after the failure of prior lines of therapy with traditional topical agents, systemic drugs, and/or different biologics.

## Case Report 1

A 37-year-old Caucasian man with moderate to severe plaque psoriasis was followed since 2016 in our center. The patient had a 15-year history of psoriasis localized in the pre-tibial/tibial region, previously treated with traditional topical and systemic therapies (respectively, calcipotriol/betamethasone [stopped owing to poor compliance], and methotrexate 15 mg administered weekly for 6 months and discontinued for gastric intolerance [ingravescent nausea]). Moreover, the patient was successfully treated with secukinumab 300 mg (anti-IL17 antibody) administered by subcutaneous injection with initial dosing at weeks 0, 1, 2, 3 and 4, and followed by monthly maintenance dosing. Despite an optimal initial response, this was unfortunately followed by a loss of

response after 3 years of therapy (Fig. 1A), consistent with a residual PASI 6, and itch [visual analogue scale (VAS)] 10.

Considering the medical history of the patient, including the prior lines of treatment administered, a therapy based on risankizumab (anti-IL-23 antibody) 150 mg [injected subcutaneously (s.c.)] was subsequently initiated. After approximately 9 months, in which the patient experienced a partial response, a loss of efficacy was reported as shown in Fig. 1B (residual PASI 4, itch VAS 6).

Considering the efficacy of tildrakizumab reported in patients with plaque psoriasis localized in DTT areas, as well as the possibility to select a higher tildrakizumab dosage (200 mg) for treating patients with a high burden of disease, as described in the tildrakizumab Summary of Product Characteristic (SmPC),<sup>6, 11</sup> we decided to treat the patient with this agent. Tildrakizumab 200 mg was administered by s.c. injection at weeks 0 and 4, followed by subsequent injections every 12 weeks. After 4 months we observed clinical benefits (residual PASI 3, itch VAS 3), as highlighted in Fig. 1C. After 7 months from initiation of tildrakizumab 200 mg, the patient achieved complete remission which was ongoing at the time of writing, with residual PASI 1 and itch VAS 2 (Fig. 1D).

## Case Report 2

A 59-year-old Caucasian woman with moderate to severe plaque psoriasis was examined in our center in 2021. The patient had a history of plaque psoriasis of more than 12 years, localized mainly on the trunk, extensor surfaces of the limbs, legs, and the scalp. The patient had a body weight of 95 kg, and a medical history of obesity ([body mass index (BMI)] of 31.7), hypertension and chronic venous insufficiency. Psoriasis was previously treated for many years with traditional topical therapies (corticosteroids and vitamin D analogues) when it was mainly restricted to the elbows and knees. Moreover, methotrexate 15 mg weekly had been administered for 6 months after an extension of erythematous desquamative plaques on the lower and upper limbs was observed. The patient was subsequently treated successfully with adalimumab (anti-TNF) 40 mg every 2 weeks, achieving an initial PASI90 response. However, after 31 months a secondary loss of response was detected, characterized by worsening of the erythematous desquamative plaques on the limbs and new skin manifestations on the scalp and the trunk, heavily impacting the patient's quality of life ([Dermatology Life Quality Index (DLQI)] 24) (Fig. 2A, D and G).

Considering the indication to use a higher dosage of tildrakizumab to improve clinical benefits for patients above 90 kg body weight and with high disease burden, we administered tildrakizumab 200 mg to our patient in accordance with the posology specified in the SmPC (s.c. injections at weeks 0, 4 and every 12 weeks).<sup>11</sup> After 4 weeks of therapy, we observed clinical benefits (PASI = 4.8 and [body surface area (BSA)] of 8%, and DLQI 9) (Fig. 2B and E) and, after 16 weeks, the patient reached complete remission (PASI 0, BSA 0%, and DLQI 0), as shown in Fig. 2 (C, F and H).

## Case Report 3

A 52-year-old Caucasian man with severe plaque psoriasis was followed in our center from 2023. The patient presented with an 11-year history of chronic plaque psoriasis localized on the trunk, including gluteal fold, and the limbs (Fig. 3A and B), no family history of psoriasis or acknowledged psoriatic arthritis manifestations, and a body weight of 81 kg (BMI 27.4). Additionally, the patient has been treated for hypercholesterolemia with gemfibrozil and ezetimibe, and for hypertension with olmesartan medoxomil and hydrochlorothiazide. The patient is an active smoker (3 cigarettes/day), with no explicit allergies or alcohol intake. Moreover, his psoriasis has been previously treated for many years with traditional topical therapies (corticosteroids and vitamin D analogues), but the presence of the indicated comorbidities had not allowed the administration of systemic treatments. The patient showed a basal PASI score of 45 and DLQI of 27 (Fig. 3A and B), indicating the high burden of his disease. Considering that tildrakizumab SmPC allows the possibility to administer a dose of 200 mg in patients with high disease burden at the physician's discretion for improving clinical benefits, we selected this option (s.c. injections at weeks 0, 4 and every 12 weeks).<sup>11</sup> After 4 weeks of therapy, we observed clinical benefits (PASI 20, DLQI 10; Fig. 3C and D), and after 16 weeks a complete remission was observed (PASI 2, DLQI 1; Fig. 3E and F).

## Discussion

Different therapy types are currently available for treating moderate to severe plaque psoriasis, including biologic agents which have demonstrated to be generally effective and safe.<sup>2</sup> However, patients with certain characteristics, such as psoriasis located in DTT areas, high basal PASI score and/or failure of prior lines of treatment, can show a lower response to these therapies. Here, we presented three complex cases of patients with moderate to severe plaque psoriasis showing a complete remission following treatment with tildrakizumab 200 mg.

Typically, DTT areas include the scalp, the face, genitals, nails, palms of hands or feet, and lower legs.<sup>2,3</sup> Among effective biologics to treat this challenging patient population, tildrakizumab 100 mg has been recently shown to be able to reduce the static [Physician's Global Assessment of Genitalia (sPGA-G)] (3,3 to 0,2), [Psoriasis Scalp Severity Index (PSSI)] (36,2 to 2,7), [Nail Psoriasis Severity Index (NAPSI)] (48,4 to 15,7) and PASI (5,3 to 0) at week 28.<sup>6</sup> Nevertheless, patients recruited in the study by Galluzzo and co-workers were not previously treated with biologics but only with at least one conventional treatment, including phototherapy or systemic therapy (such as acitretin, methotrexate, or cyclosporine). Additionally, patients enrolled in the study were treated with tildrakizumab 100 mg, while the efficacy of the higher tildrakizumab dosage as suggested in the SmPC has not been explored.<sup>6</sup> The tildrakizumab SmPC indicates that tildrakizumab 200 mg may provide greater efficacy in patients with high disease burden as well as a body weight above 90 kg.<sup>11</sup> Considering the higher burden of disease often observed in patients with psoriasis located in DTT areas or with a high severe disease, we selected tildrakizumab 200 mg for treatment and achieved notable clinical benefits for our patients.

Despite the major advance in the development of new biologic therapies for psoriasis, the lack (primary failure) or the loss of response over time (secondary failure) of these agents represent additional clinical challenges in treating psoriatic patients.<sup>12</sup> Loss of response is the most common reason for therapy withdrawal, and it is a relevant concern for patients and clinicians, especially when psoriasis is located in DTT areas.<sup>5</sup> In these cases, a switch to another biologic agent is suggested to improve patient outcomes. The British Association of Dermatologists' Guidelines 2017 describes which factors should be taken into account when switching among biologics, including pharmacology, washout, and patient clinical conditions as well as patients' opinion about the potential benefits of switching therapy.<sup>12</sup> Unfortunately, there is still a gap of knowledge in defining which alternative biologic agent can be selected to obtain the best clinical response after treatment failure with prior biologics.<sup>12</sup> A pooled analysis of reSURFACE 1-2 and P05495 studies showed that, although tildrakizumab efficacy was usually higher in biologic naïve patients (considering PASI 90 and PGA), at the higher dose of 200 mg tildrakizumab showed a similar response evaluated as PASI 100 independently from prior treatments with biologics.<sup>13</sup> Moreover, the data of reSURFACE 1-2 in partial responders or non-responders to etanercept therapy showed that switching to tildrakizumab 200 mg resulted in reaching PASI75 in approximately 80% of patients after two doses, suggesting that tildrakizumab 200 mg could be an efficient and rapid therapeutic option for patients who failed prior treatment with this agent.<sup>14</sup>

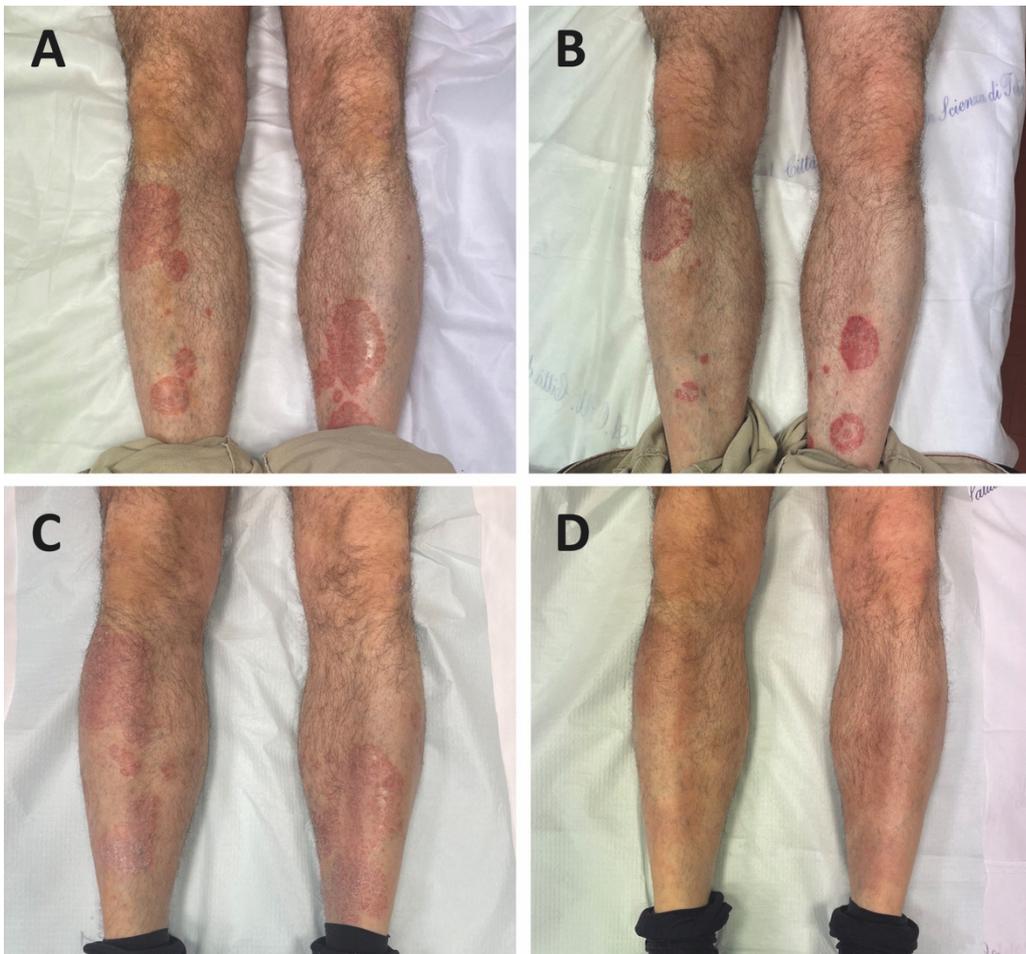
Regarding basal PASI score, where patients were stratified by PASI at baseline ( $\text{PASI} \leq 20$ ,  $\text{PASI} > 20$ ), a higher percentage of patients with  $\text{PASI} > 20$  responded to tildrakizumab 200 mg (59,4%) compared to tildrakizumab 100 mg (48,6%), suggesting potentially improved benefits of tildrakizumab 200 mg in patients with a higher disease severity.<sup>13</sup> Clinical study evidence indicates a higher efficacy (achieving PASI 90) with secukinumab (anti-IL17A inhibitor) compared with guselkumab (IL-23p19 inhibitor) at short timepoints (weeks 3 and 12) in patients with moderate to severe plaque psoriasis, suggesting the potential use of secukinumab for rapidly reduce the severity of disease in patients with a high PASI basal score. Guselkumab also showed a superior long-term efficacy (PASI 90 at week 48) in this study.<sup>15</sup> In this context, the option to treat patients with a higher tildrakizumab dosage (200 mg) may potentially facilitate reaching a faster PASI response in this patient population.

## Conclusions

Although further studies are needed to directly compare the efficacy of tildrakizumab 100 mg and 200 mg in complex patient populations, in this case report series we highlighted the efficacy of tildrakizumab 200 mg in patients with moderate to severe plaque psoriasis located in DTT areas or with high basal PASI score who failed prior lines of treatment with conventional drugs and/or biologics.

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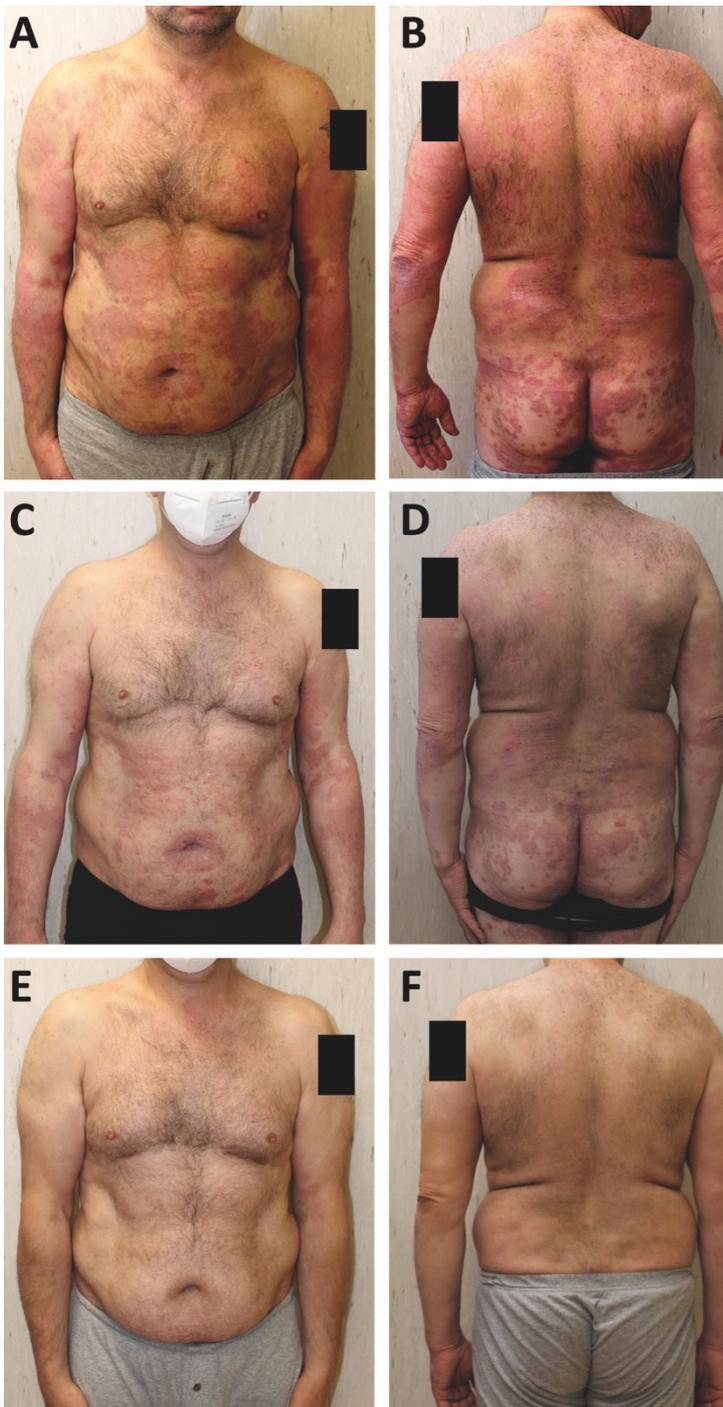
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**Fig. 1. Clinical benefits following tildrakizumab 200 mg therapy in a patient with plaque psoriasis located on the anterior surface of the tibiae. A. Initial presentation of the patient lower legs. B. Loss of response following 9-month treatment with risankizumab 75 mg. C. Clinical benefits after 4-month therapy with tildrakizumab 200 mg. D. Complete remission reached after 7-month treatment with tildrakizumab 200 mg.**



**Fig. 2. Efficacy of tildrakizumab 200 mg in treating plaque psoriasis in different locations, included the scalp. A, D, G. Presentation of psoriasis after 31 months of adalimumab-based therapy. B, E. Clinical benefits after 4-week therapy with tildrakizumab 200 mg. C, F, H. Complete remission after 16-week treatment with tildrakizumab 200 mg.**



**Fig. 3. Clinical benefits of tildrakizumab 200 mg in a patient with severe plaque psoriasis located on the trunk, arms, and buttocks. A, B. Presentation of plaque psoriasis at baseline. C, D. Clinical benefits of tildrakizumab 200 mg after 4 weeks of treatment. E, F. Complete remission obtained after 16 weeks of therapy with tildrakizumab 200 mg.**