Dermatology Practical & Conceptual

Brodalumab in the Treatment of Plaque Psoriasis Localized in Difficult-to-Treat Areas: A Narrative Review

Maria Vittoria Cannizzaro[1], Giulia Coscarella[1,2], Andrea Chiricozzi[1,2]

1 Dermatologia, Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy
2 Dermatologia, Dipartimento Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

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Corresponding Author: Giulia Coscarella, MD, Dermatologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Rome, Italy Tel.: +39-320.6223136 Email: giuliacoscarella@gmail.com

ABSTRACT

Introduction: Psoriasis is a common chronic, immune-mediated, inflammatory skin disease that in certain localization results difficult to treat. Psoriatic lesions in difficult-to-treat areas might be hardly managed as no standardized therapeutic approach and the application of topical treatments might have great limitations. Systemic agents, including biologic therapies, have been proven effective in treating this subgroup of patients. In particular, current evidence has shown beneficial effects with the use of brodalumab, a fully human IgG2 monoclonal antibody antagonizing the IL-17 receptor A subunit (IL-17RA).

Objectives: The aim of this narrative review was to collect published data about efficacy and safety of brodalumab in the treatment of psoriasis occurring in difficult-to-treat areas.

Methods: Data on brodalumab effectiveness and safety deriving from both trials and real-world setting that had been published in the last 15 years were collected for this review, together with clinical findings issued during international meetings.

Results: In phase 3 trials, brodalumab demonstrated to be effective in promoting a rapid response in scalp psoriasis as well as in generalized pustular psoriasis and erythrodermic psoriasis. Nail psoriasis demonstrated marked clinical improvement after treatment with brodalumab. Amelioration of palmo-

plantar psoriasis was also described in brodalumab-treated patients. Various retrospective real-world studies reported a complete clearance of psoriatic lesions in difficult-to-treat areas, including genitalia, through short-term brodalumab treatment.

Conclusions: Brodalumab, combining rapid and sustained efficacy with a favorable safety profile, may be a valid therapeutic option for severe variants of psoriasis as well as for psoriasis localized in difficult-to-treat areas.

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disease that is associated with a wide array of comorbidities [1,2], as well as with detrimental physical effects, disability, reduced psychological wellbeing and impaired quality of life (QoL) [3]. Silvery scales on an erythematous plaque can affect any body area, though scalp, nails, palm and soles, or genitalia may be recalcitrant to therapies, hence are defined difficult-to-treat areas [4,5].

Patients affected by psoriasis in difficult-to-treat areas might experience difficulties in performing topical treatments, stigmatization of the disease and a marked impact on QoL [5,6]. Albeit the percentage of affected body area is minimal, psoriasis localized in these regions may represent a challenging condition for physicians.

The scalp is one of the first sites to be affected, and its involvement, occurring in about 80% of patients, increases with disease duration. Scalp psoriasis presents with erythema, scaling, and pruritus, often resembling seborrheic dermatitis [7-9]. To assess disease severity and treatment response, the Psoriasis Scalp Severity Index (PSSI) is commonly used [10].

Nail psoriasis is seen in up to 80% of psoriatic patients, being the only psoriatic manifestation in 6% of cases. Nail psoriasis correlates with disease severity and its presence is associated with higher risk of developing psoriatic arthritis. Clinical manifestations of nail psoriasis may vary whether affecting nail matrix, nail bed, the proximal nail fold or the hyponychium [11,12]. The NAPSI is an objective assessment instrument that is used to assess the severity of nail psoriasis and the area of involvement of the nail unit [10]).

Palmoplantar psoriasis (PPP) can appear as hyperkeratotic, pustular, or with mixed morphologies; itching, pain, and fissuring are the most complained symptoms [13]. Palmoplantar Psoriasis and palmoplantar pustolosis are monitored using the Palmoplantar Psoriasis Area and Severity Index (PPASI) and the Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI), respectively [10].

Though no standardized treatment approach exists, biologic therapies have been proven effective in treating patients with psoriasis in difficult-to-treat areas. Mounting evidence has proven beneficial effects with the use of brodalumab, a fully human IgG2 monoclonal antibody antagonizing the IL-17 receptor A subunit (IL-17RA), that has been approved for the treatment of plaque psoriasis at the induction dose of 210 mg s.c. at weeks 0, 1, and 2 and at the maintenance dose of 210 mg every 2 weeks [14,15]. The administration of brodalumab provides a rapid improvement in disease severity and a favorable safety profile in moderate-to-severe psoriasis. In addition, data from comparative studies show a faster onset of action with brodalumab compared to other biologic therapies, as early as after 2 weeks of treatment [16]. Efficacy of brodalumab on psoriasis is well documented from both RCT and real-world data showing increasing percentage of patients achieving PASI 75, 90 and 100 response rates through 24 weeks of treatment [17], even in patients who failed previous biologics, including selective anti-interlukin (IL)-17 agents. As reported in comparative studies from RCT AMAGINE 1/2/3, brodalumab demonstrated to be effective and faster also for patients with difficult-to-treat areas, even compared with other biologic agents [16,18].

Objectives

The aim of this narrative review was to collect published data about efficacy and safety of brodalumab in the treatment of psoriasis occurring in difficult-to-treat areas.

Methods

We carried out a search of the English-language literature regarding difficult-to-treat psoriasis and treatment, with special focus on brodalumab effectiveness in both trial and real-world setting. We used the following databases: PubMed, Embase, Google Scholar, ResearchGate, and Scopus. Keywords used were: “psoriasis”, “difficult-to-treat psoriasis”, “psoriasis treatment”, “IL-17 inhibitors”, “Anti-IL-17RA”, “brodalumab”. All articles published in the last 15 years and data from recent international meetings were reviewed.

Results

Psoriasis Pathogenesis and Druggable Targets

Psoriasis pathogenesis is multifaceted, being characterized by the involvement of a wide array of both immune and tissue cells and by the increased signals of different cytokines (TNF-α, IL-23, IL-17A, IL-22, IFN -γ) [19]. Though, multiple immune pathways contribute to the inflammatory process, the IL-23/Th17/IL-17A molecular axis is considered crucial in the pathogenesis of psoriasis and IL-17A is the pivotal effector cytokines in this pathogenic model [20-21].

IL-17A belongs to the IL-17 cytokine family, consisting of six members (IL-17A-F) which signal through dimeric receptors that included five receptor subunits (IL-17RA to IL-17RE) [22,23]. The receptor complex binding to both IL-17A and IL-17F, consists of two subunits: IL-17RA and IL-17RC, while IL-17C acts through a receptor composed by the subunits IL-17RA and IL-17RE. IL-17E (also called IL-25) acts through a receptor composed of the subunits IL-17RA and IL- 17RB, whereas IL-17B and IL-17D have a ligand-receptor interaction not well-defined. IL-17RD acts as an alternative heterodimer with IL-17RA and is also important in mediating IL-17A signaling [24-25] (Figure 1).

The expression of IL-17A, IL-17C, and IL-17F is increased up to eightfold in psoriatic lesions compared to non-lesional skin with the greatest increase being detected for IL-17C and IL-17F, though IL-17A results the most biologically active (up to 30-fold more active than IL-17F) [22,26,27].

Mounting evidence supporting the central role of IL-17A in psoriasis includes the upregulation of both IL-17A and its related genes in lesional and non-lesional skin of patients with psoriasis. The increased expression of IL-17A derives from immune cells involved in psoriasis pathogenesis such as T helper (h) cells, T cytotoxic (c) 17, innate lymphoid cells (ILC)3, mast cells, and neutrophils, that infiltrate lesional skin and contribute to its abundant expression [27]. In vitro, IL-17 affects the expression of a large set of genes (more than 600 up- or down-regulated gene probes) in a reconstituted human epidermis model, and its effects are amplified by the synergism with other cytokines, including IL-22 and TNF-α, strengthening the production of chemokines,

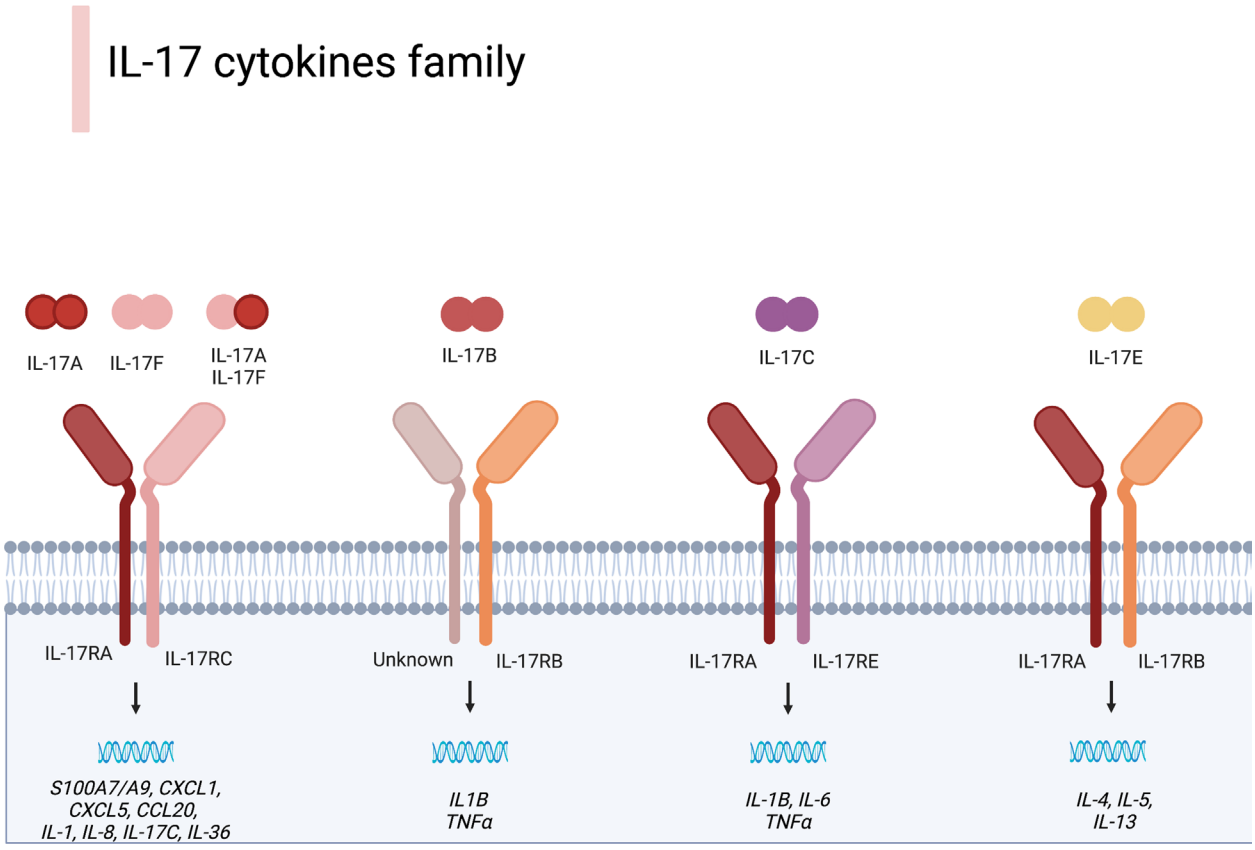

Figure 1. IL-17 cytokines family. The IL-17 cytokine family members signal through different dimeric receptor complexes that include five subunits (IL-17RA to IL-17RE).

Binding to receptor complex, IL-17 cytokines are able to induce the expression of specific downstream genes, mostly transducing for pro-inflammatory mediators.

CCL, CXCL Chemokine ligand; IL Interleukin; TNF-α = Tumor necrosis factor alpha.

pro-inflammatory cytokines, and antimicrobial peptides (AMPs). They key psoriasis-signature genes are mostly induced by IL-17 stimulation on keratinocytes and, conversely to signals mediated by other pivotal cytokines, IL-17A signal greatly characterizes the psoriasis lesional skin transcriptome [28-30].

Similarly to IL-17A, IL□17F and IL□17C act in synergy with other cytokines, such as TNF-α or IL□1, inducing expression of antimicrobial peptides (AMPs), chemokines and proinflammatory cytokines, which promote innate immune responses, the recruitment of inflammatory cells, and keratinocyte activation and proliferation [31]. Furthermore, an interplay between IL□17A, IL□17F and IL□17C has been described, and both IL□17A and IL□17F, as well as IL□17C, acting in autocrine manner, are able to induce the expression of IL□17C in keratinocytes [32]. IL□17A, IL□17A/F and IL□17F exert their effects on a range of tissue cells, of which keratinocytes and fibroblasts are the main target cells in the skin [33] (Figure 2). Keratinocyte response to either IL-17C or IL-17A stimulation are very similar, with strong induction of S100A7/A9 proteins and antimicrobial proteins and cytokines or chemokines including CXCL1, IL-1, IL-8, CCL20, and IL-36. IL-17C also stimulates Th17 T cells to increase synthesis of IL-17A/F and IL-22 promoting an autoimmune activation [34,35]. Indeed the IL-17RA/RE receptor complex is expressed on both epithelial and TH17 cells, with IL-17C that amplifies its own signal, inducing the expression of its receptor on TH17 cells, especially when pooled with IL-6, TGF-β, IL-1, and IL-23 [36-38]. There is an important bidirectional relationship between IL-17A and IL-17C, because IL-17A is a strong inducer of IL-17C in keratinocytes and IL-17C can induce high-level synthesis of IL-17A in T lymphocytes. Because IL-17C is produced in massive quantities by keratinocytes (eg, production in psoriasis is 100-fold higher than IL-17 A [35], the actions of this cytokine may come to lead the IL-17 response axis in chronic inflammatory conditions. IL□17C may thereby amplify the inflammatory response by further enhancing the production of inflammatory mediators, including C□C motif chemokine ligand 20 (CCL20), which attracts IL□17□producing T cells. Additionally, IL□17C was shown directly to induce expression of IL□17A and IL□17F in mouse Th17 cells [36].

Therapeutic Agents Used in the Management of Moderate-to-Severe Plaque Psoriasis

Treatment of patients affected by hard-to-treat psoriasis is often challenging. The anatomical structure of affected sites may hamper the application and reduce the absorption of topical treatments [39,40]. Physical therapies may be effective for palmoplantar areas, but time consuming. Traditional therapies (cyclosporine, methotrexate, acitretin, dimethyl fumarate) can provide some benefits, but often not well tolerated or aggravated by side effects. A new small molecule, apremilast, demonstrated to be effective on PSA and PSO,

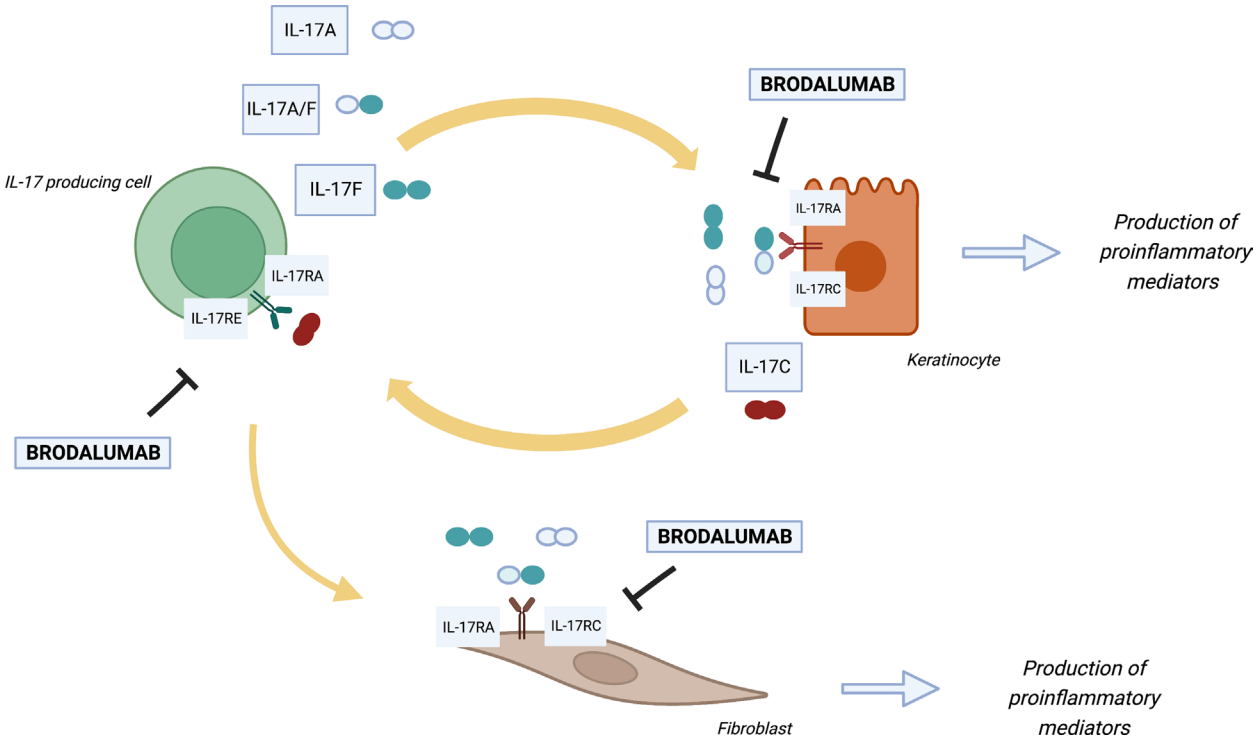

Figure 2. Key psoriasis pathogenic circuits mediated by IL-17 cytokines.

IL□17A strongly induces IL-17C expression in keratinocytes. IL-17C amplifies its own signal through the induction of IL-17C receptor on Th17 cells and the increase of IL-17A synthesis. IL-17A and IL-17F exert their effects on other tissue cells, such as fibroblasts, inducing the production of several proinflammatory mediators. Other inflammatory loops result in the induction of IL-17C on Th17 cells.
IL = Interleukin.

Table 1. Results from clinical trials and real-world experiences related to brodalumab efficacy in difficult-to-treat psoriasis.

Author	Drug	Trial/NCT	Endpoints	Design	Regimen/dose	N	specific outcomes for diffcult-to-treat areas	Baseline severity in diffcult-to-treat areas	Follow-up
Elewski, J Dermatolog Treat 2022	Brodalumab, Placebo	Amagine-1	W12 (induction period)	RCT	BDL210 Q2W Placebo Q2W	222 219	PSSI75 PSSI100	PSSI>15 (out of PASI72)	W12 PASI75 in 89% W12 PASI100 by 63.4% W12 PASI75 by 9.5% W12 PASI100 by 3.2
Nakagawa, J Dermatol Sci. 2016	Brodalumab Placebo	NCT01748539	W12	RCT	BDL 210 Q2W Placebo	37 38	PSSI NAPSI (22pts) DLQI	PSSI 43.7 NAPSI 6.3 DLQI10.7 PSSI 26.2 NAPSI7.2 DLQI9.4	W12 PSSI -94.5% W12 NAPSI-47.6% W12 DLQI -9 W12 PSSI -12.6% W12 NAPSI -7.6% W12 NAPSI -2.2
Elewski, J Dermatolog Treat 2022	Brodalumab, Ustekinumab	AMAGINE-2/3	W12/24/36/52	RCT	BDL210 at W0, W1, W2, then Q2W UST45/90 at W0/ W4 then Q12W	104 179	NAPSI (target)	NAPSI 9.6 (4) NAPSI 9.9 (3.6)	W52 NAPSI 1.6 W52 NAPSI 2.5
Yamasaki, Br Jd, 2017	Brodalumab	NCT01782937	W52	Open Label	BDL 210mg GPP	12	PSS PSSI NAPSI DLQI	PSS 4.4 PSSI 16.7 NAPSI 10.8 DQLI 7.9	W52 PSS 0 in 91% W52 PSSI -82 W52 NAPSI -67.5 W52 DLQI -5.5
Gregoriu, JEADV 2021	Brodalumab	-	Prosp-open, W24		BDL 210 at W0, W1, W2, W3 then Q2W	30	NAPSI (finger)	NAPSI 19.6 DLQI 22.8	W24 NAPSI 2.3 W24 DLQI 3.7
Politou, Am Acad Dermatol. 2020	Brodalumab	ABSTRACT	W12	Case report	BDL 210	4	PPPGA		W12 PPGA 0
Nakao, Ejd, 2018	Brodalumab	-		Case report	BDL 210 mg	1	PPPASI	PPPASI 13.2	W24 PPPASI 4.0
Pinter, Journal f Dermatology 2019	Brodalumab	-		Case Series	BDL 210 mg	4	PPGA	Mean 8	ET mean 8
Okubo, Jeadv Poster 2022	Brodalumab	ABSTRACT	W16		BDL 210 Placebo	126	PPPASI	Mean change in PPASI total score	13.73 8.45

BDL = brodalumab; DLQI = Dermatology Life Quality Index; NAPSI = Nail Psoriasis Severity Index; PGA = Physician Global Assessment; PSS = Psoriasis Symptoms Scale; PSSI = Psoriasis Scalp Severity Index; PPPASI = Palmoplantar Pustulosis Psoriasis Area and Severity Index; Q2W = every other week; RCT = randomized clinical trials.

including difficult areas including nails and scalp [41]. Different classes of biologic agents have been also approved for the treatment of moderate-severe psoriasis, and anti-TNFs represented the first approved biologic class. Patients may experience beneficial effects through p40IL-12/23 inhibition (ustekinumab) or through IL-23 blockade (guselkumab, risankizumab, tildrakizumab). Comparative studies demonstrated superiority of anti-IL-17 agents compared with ustekinumab in treating difficult areas [42-48]. Nowadays, four anti-IL-17 agents are approved for the treatment of plaque psoriasis: secukinumab and ixekizumab are directed against IL-17A, bimekizumab neutralizes both IL-17A and IL-17F, while brodalumab antagonizes IL-17RA. Substantial clinical efficacy was achieved in patients treated with secukinumab and ixekizumab. Recently, elevated efficacy, with even higher response rates compared to secukinumab or ixekizumab, was demonstrated in phase III studies testing bimekizumab, indicating that IL□17F also contributes to drive skin inflammation in psoriasis [46,47]. Moreover, the simultaneous inhibition of several IL□17 family cytokines induced by brodalumab, has been shown to be efficacious in the treatment of psoriasis [48-49].

Brodalumab extensively suppresses tissue response to IL-17 cytokine impulse, normalizing the expression of IL-17-dependent genes, in tissue cells, particularly keratinocytes. This modulation is dose dependent and after 12 weeks of treatment a profound molecular response, with >95%-improvement in differentially expressed psoriasis genes was obtained [43]. This effect is rapidly detected with greater magnitude than with other biological agents, resulting in a lower residual alteration of gene expression compared with ustekinumab and etanercept [50].

The distinctive mechanism of blocking multiple IL-17 family cytokines (IL-17A, E, F, C) may account for the effectiveness of brodalumab in achieving skin clearance in psoriasis patients, comprising those with inadequate response to other biologics, in particular the anti-IL-17 [51].

Data from RCT and real-world experiences showed efficacy of brodalumab also in treating difficult areas and severe variants of psoriasis, such as generalized pustular and erhytrodermic psoriasis.

Data From Randomized Controlled Trials

Scalp Psoriasis

Brodalumab showed to be effective and rapid on scalp psoriasis as reported in a post-hoc analysis from the phase 3 AMAGINE 1 study (a randomized, placebo-controlled, phase 3 study, NCT01708590) which detected improvement rates from baseline in mean PSSI seen as early as at week 2 in patients receiving brodalumab versus placebo (PSSI: 67.6% versus 6.7% at week 2). Treatment response was maintained with further reduction in PSSI through week 12 (92.8% versus 14.4%; P value <0.001). At week 12, PSSI75 was achieved by 89% of patients receiving brodalumab, compared with 9.5% of patients receiving placebo, while PSSI100 was observed in 63.4% of brodalumab-treated patients versus 3.2% of the placebo group [48,52].

Brodalumab effectiveness was also confirmed in a subanalysis of a phase 2, randomized, placebo-controlled trial (NCT01748539) reporting a mean PSSI improvement rate of 94.5% after 12 weeks of therapy with brodalumab 210 mg Q2W from baseline, versus 12.6% of placebo-treated patients (P = 0.001) [53].

Data deriving from another study conducted on patients affected by severe forms of psoriasis, namely generalized pustular (GPP) and erythrodermic (PsE), also revealed great efficacy of brodalumab therapy in reducing skin manifestations, including scalp psoriasis lesions, with improvements in PSSI score occurring in 80.9% of all treated patients (including GPP and PsE) at week 12 and in 90% of all patients after 52 weeks of treatment, concurrently with Dermatology Life Quality Index (DLQI) ameliorations throughout the observation period (DLQI scoring 0 or 1 was achieved by 80% of patients at week 52) [54].

Nail Psoriasis

Brodalumab effects on psoriatic nails were assessed in two trials. Head-to-head trials, AMAGINE-2 and AMAGINE 3 trials, comparing brodalumab with ustekinumab, included 283 patients with nail involvement [52]. Patients randomized to brodalumab 210 mg every two weeks (BLD210 q2w) had a greater reduction in mean nail-target NAPSI score compared with those randomized to ustekinumab 45/90 mg every 12 weeks (UST45/90 q12w), at week 12 (43.7% versus 31.8%, P < 0.05), with further improvements at week 24 (76.9% versus 58.9%, P < 0.05), and at week 36 (82.4% versus 69.0%, P < 0.05). A greater amelioration was also seen at week 52 in the brodalumab arm (83.1% versus 75.0%), although statistical significance was not reported. At week 24, 31.6% of patients achieved a complete resolution of nail psoriasis (NAPSI100) in the brodalumab arm compared with 18.8% in ustekinumab subcohort (P < 0.05). At week 52, 63.8% of brodalumab-treated and 39.1% of ustekinumab-treated patients achieved NAPSI100 (P < 0.05), respectively. Safety was comparable between brodalumab and ustekinumab treatment groups (adverse events: 57.3% versus 56.3%; severe adverse events 1.2% versus 1.0%) [52].

Improvement of nail psoriasis has also been reported in the Japanese trial (NCT01748539) on 22 patients (out of 38) treated using 210mg brodalumab with total NAPSI score reduction of 47.6% after 12 weeks (mean NAPSI change from baseline in the placebo group was 9.6% at week12) [53].

In a prospective open-label trial with 30 patients affected by nail psoriasis treated with brodalumab 210 mg q2w, a significant improvement was observed after 12 and 24 weeks of treatment compared with baseline (P < 0.001: mean finger absolute NAPSI score at the BL: 19.6, W12: 9.6, W24: 2.63; mean toes absolute NAPSI at the BL 24.9; W12: 16.1; W24: 7.2)54. NAPSI improvement was also associated with a decrease of DLQI, from a mean value of 22.8, to a mean value of 3.7, after 24 weeks of treatment. Adverse events (AE) incidence (10.0%) was low, and no seriousAEs occurred.

A recent network meta-analysis of head-to-head trials investigating the complete resolution of nail psoriasis identified ixekizumab as the biologic agent with the highest response rate (RR: 1.4, 95%CI= 0.73-3.1) resulting superior to brodalumab (RR: 0.92, 95%CI= 0.14-7.4), guselkumab (RR: 0.81, 95%CI= 0.40-1.8), infliximab (RR:0.90,95%CI=0.19-4.6)andustekinumab(RR:0.33,95% CI= 0.083-1.6), using adalimumab as reference [55].

Palmoplantar Psoriasis

Preliminary results of a multicenter, randomized, double-blind, placebo-controlled phase 3, Japanese study on 126 patients affected by palmoplantar pustulosis showed great improvement in the brodalumab-treated group. After 16 weeks of treatment, total PPPASI score change from baseline was significantly higher with brodalumab: 13.73 versus placebo 8.45% (P = 0,0049) with 16.0% of patients treated with brodalumab who achieved PPPASI-90 response compared with versus 0.0% of placebo [56].

Results from a Phase 4 clinical trial investigating efficacy of brodalumab in the treatment of palmoplantar psoriasis have not been published yet (NCT04622033).

Rare and Severe Forms of Psoriasis

An open-label, multicenter, long-term phase III study in Japanese patients affected by rare and severe form of psoriasis has been conducted [57]. Out of 30 patients treated with 210 mg brodalumab, 12 were affected by GPP and 18 patients by erythrodermic psoriasis. The primary endpoint was the Clinical Global Impression of Improvement (CGI). Ten patients with GPP and 16 with erythrodermic psoriasis completed the study and CGI was achieved in 11 patients with GPP and 18 with erythrodermic psoriasis after a 52-week treatment (last observation carried forward). The most commonly reported adverse event was nasopharyngitis (33.3%) and five serious adverse events occurred during the study; none of the serious adverse events was considered related to treatment. Overall brodalumab demonstrated to be safe and significantly improved symptoms of patients with either GPP or erythrodermic psoriasis throughout the 52-week observation period [57].

Real-World Data on Brodalumab Effectiveness and Safety for Hard-to-treat Psoriasis Areas

Real-world data reported in a retrospective longitudinal study on 90 patients with moderate-to-severe plaque psoriasis treated for 12 months, demonstrated complete clearance of scalp, nails, palmo-plantar areas and genitalia [58]. Efficacy of brodalumab on palmoplantar psoriasis was also described in case reports or case series [59].

Politou et al reported successfully response to brodalumab in 4 patients, obtaining PPPGA score 0 at week 16, after secukinumab failure [60].

In a case report, a patient suffering from PSO and PPP, who previously failed adalimumab and secukinumab, was successfully treated with brodalumab, with clinical improvement observed after 2 weeks and the complete clearance after 6 months [61].

Contrasting findings were described in a case series consisting of four patients treated for PPP, obtaining partial response only in one patient, while the three other patients had no response or worsening of PPP. One patient had a partial response and after 7 months, due to worsening of arthralgia and bad tongue symptoms, brodalumab was stopped [62].

Conclusions

The successful management of patients affected by psoriasis in difficult-to-treat areas still represents an unmet therapeutic need that has been partially covered by currently available therapeutic options. Brodalumab, combining rapid and sustained efficacy with a favorable safety profile, may be a valid therapeutic option not only for plaque psoriasis but also for severe variants of psoriasis as well as for psoriasis localized in difficult-to-treat areas.

An expert panel recently sought to define the best areas of action for brodalumab, clarifying the optimal place-in-therapy for this drug. Through a Delphi methodology, the expert panel agreed in considering brodalumab an appropriate therapeutic choice when there is involvement of difficult-to-treat areas, such as scalp/nails or palmo-plantar area [17]. Moreover, the expert panel highlighted the benefits of brodalumab in treating psoriasis in difficult-to-treat areas, including the amelioration obtained on pruritus. In addition, the expert panel noted that the scalp tends to be the first site to clear from psoriasis as well as the first site where the disease recurs whether brodalumab fails.

The advantage of brodalumab in inhibiting multiple pathogenic IL-17 cytokines through 17RA blockade, is clinically reflected by a rapid response and high rate of skin clearance, even in the treatment of psoriasis localized in difficult-to-treat areas. Nevertheless, having limited data deriving from both trials and real-world studies, further evidence is

necessary to support the beneficial effects of brodalumab in these peculiar forms of psoriasis.

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