Review Article

Ustekinumab: In Psoriasis and Beyond—A Dermatological Perspective

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Abstract

Background: Ustekinumab is an interleukin 12/23 inhibitor, approved by the US-FDA for the management of moderate-to-severe plaque psoriasis and psoriatic arthropathy.
Purpose: This review aims to describe the dermatological implications and applications of ustekinumab.
Methodology: PubMed and Google Scholar were searched for scholarly articles related to ustekinumab and its utility in dermatology using the search terms "Ustekinumab" AND "Psoriasis" AND "dermatological diseases". Studies utilising Ustekinumab in psoriasis and other dermatological indications were analysed and formulated into a systematic review discussing the utility of the drug in psoriasis, as well as other dermatological conditions.
Results: Ustekinumab is a valuable biologic agent for the management of psoriasis and psoriatic arthropathy, as well as other dermatological disorders like hidradenitis suppurativa, lichen planus, pityriasis rubra pilaris, Behcet's disease, lupus erythematosus, alopecia areata and pyoderma gangrenosum.
Conclusion: Ustekinumab's usage is not limited to psoriasis. Its benefit extends to many more dermatological conditions. It is considered to be the biologic of choice in childhood psoriasis and adult psoriatic patients with concurrent Crohn's disease. Besides, it has an acceptable safety profile.

Keywords

Ustekinumab, Psoriasis, Hidradenitis suppurativa, Pyoderma gangrenosum

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Introduction

Ustekinumab is a human monoclonal antibody generated from transgenic mice using techniques of genetic engineering. It targets and blocks the p40 subunit, shared by interleukin (IL)-12 and 23, thereby inhibiting ensuing signaling, differentiation, and cytokine production, pivotal in inflammatory diseases.[1] Currently, ustekinumab is approved by the US Food and Drug Administration for the treatment of moderate-to-severe plaque psoriasis in adults and children (≥6 years of age) and active psoriatic arthropathy (PsA).[2] Apart from these approved indications, ustekinumab has been used "off-label" for a number of inflammatory dermatological disorders.[3] However, most publications stating the off-label utility of ustekinumab are confined mainly to case reports and small case series, with a lack of systematic reviews. In this appraisal, aside from discussing ustekinumab's role in psoriasis, its application in various other inflammatory dermatoses will be emphasized.

Methodology

We searched PubMed and Google Scholar with the keywords "Ustekinumab" AND "Psoriasis" AND "Psoriatic arthropathy" AND "Hidradenitis Suppurativa" AND "Lichen planus" AND "Pityriasis rubra pilaris" AND "Behcet's disease" AND "Lupus erythematosus" AND "Alopecia areata" AND "Atopic dermatitis" AND "Pyoderma gangrenosum." A total of 150 articles were evaluated from 2006–2023. Of them, 126 articles were included in the review. Sixty-six articles contained studies, case series, and case reports that were employed for final analysis. The search strategy is illustrated in Figure 1.

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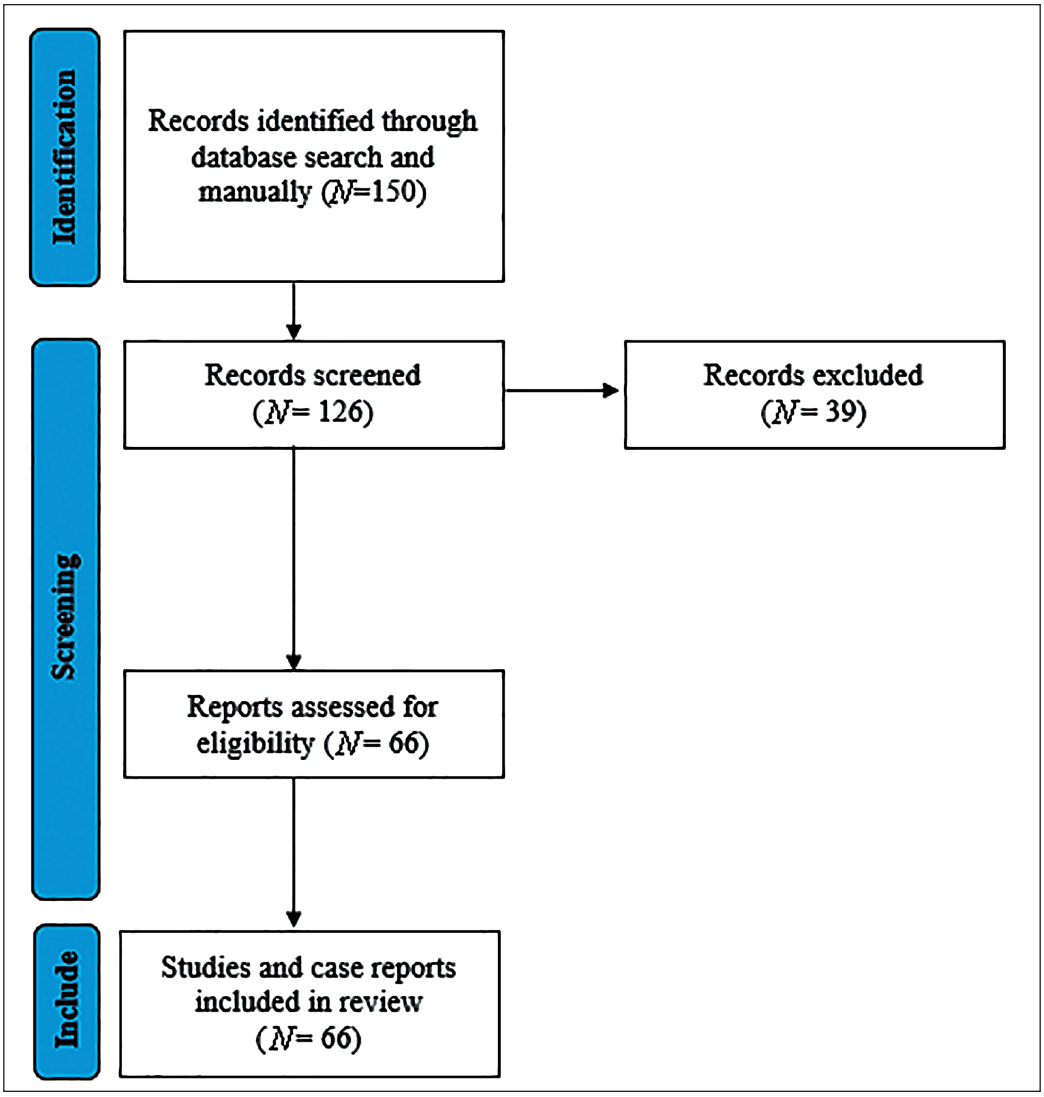

Figure 1. Schematic of the Search Strategy.

Clinical Uses

Plaque Psoriasis

Psoriasis is a chronic inflammatory disorder with predominant cutaneous features and systemic involvement, affecting 1%–3% of the global population, with plaque psoriasis accounting for 90% of the cases.[4,5] According to the new psoriasis model, the IL-23/Th17 axis contributes significantly to the development of psoriasis.[6] Activation of Th17 by IL-23 and subsequent generation of proinflammatory cytokines like IL-17, tumor necrosis factor-alpha (TNF-α), IL-26, and IL-29 majorly promote the recruitment of inflammatory cells, with eventual epidermal hyperplasia.[7] Ustekinumab blocks IL-23 and subsequently targets upstream cytokines, unlike downstream cytokines (viz., TNF-α and IL-17) targeted by other biological agents, enabling ustekinumab to be dosed at lesser frequencies when compared to other classes of biological drugs.[8] Moreover, blockade of IL-23 also plummets levels of IL-17 and IL-22, furthering ustekinumab's anti-inflammatory effects.[9]

The efficacy and safety of ustekinumab in plaque psoriasis has been illustrated through four large phase III randomized placebo-controlled trials (PHOENIX 1/2, PEARL, and LOTUS) and one phase III randomized active comparator trial (ACCEPT).[10–14] In both PHOENIX studies, Psoriasis Area Severity Index (PASI) 75 responses at week 12 were observed in 66.4%–75.7% of ustekinumab-treated patients, which was strikingly greater than the placebo group (3%–4%). Besides, with ongoing treatment, improvements were sustained, and the incidence of adverse effects did not reveal anything alarming.[10,11] The PEARL and LOTUS studies correspondingly delineated statistically significant improvements in PASI 75 in the ustekinumab group when compared to placebo at week 12 ($p < 0.001$), which were

maintained through week 36.[12,13] Furthermore, in the ACCEPT trial, PASI 75 was observed in 67.5%–73.8% of patients treated with ustekinumab and 56.8% of patients in the etanercept group, with comparable safety profiles in both groups.[14] Interestingly, consistent data regarding the efficacy and safety of ustekinumab has been noted through 5 years of follow-up, with dose escalation (90 mg every 8 weeks) resulting in a greater reduction of psoriasis in those patients unresponsive to the lower dosing (45 mg).[15] However, following cessation of ustekinumab therapy, exacerbations of psoriasis occur in most patients. Unfortunately, currently, there is no available data supporting the long-term use of ustekinumab, mandating further research in this field.[16]

Though superior to etanercept in plaque psoriasis, PASI 90 values from randomized controlled trials (RCTs) have displayed ustekinumab's inferiority to secukinumab (57.6% vs. 79%, respectively) and risankizumab (42% vs. 75.3%, respectively).[17,18] Nevertheless, ustekinumab does have value in the management of plaque psoriasis and has been associated with rapid and clinically significant amelioration of moderate-to-severe plaque psoriasis, with apparent results as early as 2 weeks following treatment initiation and maximum responses obtainable by 24 weeks of sustained therapy. Besides, it is the preferred biological in pediatric psoriasis and in adult patients with Crohn's disease (CD). Furthermore, its widely spaced dosing schedule at weeks 0, 4, and then every 12 weeks, offers an added advantage over the older biological agents that require more frequent administration.[10,11,15,19]

PsA

PsA is a chronic inflammatory arthritis observed in around 20% of psoriasis patients, associated with diverse clinical features. Although there are numerous therapeutic agents for PsA, discovering newer agents to treat PsA is readily embraced, owing to its refractoriness to various treatments.[20] Ustekinumab's efficacy in PsA has been substantiated by two phase III randomized placebo-controlled trials (PSUMMIT 1/2) and one randomized controlled active comparator trial (ECLIPSA).[21–23] The PSUMMIT trials (at 24 weeks) delineated an American College of Rheumatology-20 score in 42.4%–49.5% of participants receiving ustekinumab, which was almost double when compared to the placebo group (20.2%–22.8%),[21,22] and in the ECLIPSA study (at 24 weeks), the primary endpoint (defined as the Spondyloarthritis Research Consortium of Canada (SPARCC) index of 0) was demonstrated in 73.9% of subjects receiving ustekinumab and 41.7% of patients on TNF-α blockers.[23] Besides, enthesitis also demonstrated a favorable response to ustekinumab, along with a decline in radiological disease progression.[21–23] This can be explained by the central role of the proinflammatory cytokine IL-23 in the development of enthesitis, with IL-23 blockade silencing the inflammatory effects of IL-23-sensitive cells in the entheses, and subsequent blockade of downstream inflammatory mediators like IL-17, IL-22, and TNF-α.[24,25] However, synovitis in PsA does not show much response to ustekinumab, as synovitis in PsA is less sensitive to IL-12/23 inhibition.[25]

Interestingly, systematic reviews and meta-analyses have propounded the beneficial effects of combining ustekinumab with etanercept, adalimumab, golimumab, and certolizumab in recalcitrant cases of PsA and psoriasis with dose adjustments (ustekinumab being administered as 90 mg/12 weekly in these special scenarios). This integrated approach can be of particular value in the management of patients presenting with both PsA and psoriasis unresponsive to biological monotherapy. As various biologics act differently on cutaneous psoriasis and PsA (owing to the different pathogenesis), this concoction could have a role to play. However, the risk of infection and cardiovascular disease cannot be undermined while initiating this approach. Although there have been reports without encountering any adverse effects, flares of herpes zoster, retro-tonsillar abscess, erysipelas, and bacterial pneumonia have been confronted.[26–28]

Pustular Psoriasis

Pustular psoriasis comprises a clinically heterogeneous variant of psoriasis with both generalized and localized presentations. Generalized pustular psoriasis (GPP) usually has an acute or even fulminating course, but subacute forms are also commonly encountered. Localized forms of pustular psoriasis are usually confined to the hands and feet and tend to have a chronic discourse.

GPP

In GPP, there is a high risk of serious complications if appropriate treatment is not promptly instituted. Currently, there are two case reports and one case series demonstrating the successful management of GPP with ustekinumab, details of which have been outlined in Table 1.[29–31]

Acrodermatitis Continua of Hallopeau

In acrodermatitis continua of Hallopeau (ACH), ustekinumab has proven to be highly advantageous, as represented in four case reports (Table 1).[32–35] Apart from its conventional dosing, ustekinumab dose escalation (from 45 to 90 mg, even if body weight is <100 kg) in those cases of ACH where therapeutic responses are short-lived can be attempted.[32,33] Additionally, combining acitretin with ustekinumab in recalcitrant ACH is associated with a synergistic clinical outcome.[34] Generally, by 28 weeks of treatment with ustekinumab, acceptable lesional clearance is observed in ACH, with marked improvement in the Dermatology Life Quality Index (DLQI).[35]

Palmoplantar Pustulosis

Palmoplantar pustulosis (PPP) is a localized variant of pustular psoriasis characterized by sterile pustules along with erythematous-desquamative lesions involving the palms and

Table 1. Reports Highlighting the Utility of Ustekinumab in Different Variants of Psoriasis.

Serial No.	Variant of Psoriasis	Authors	Study Design	Patient Profile	Reported Outcome	Adverse Effects
1	GPP	Daudén et al.[29]	Case report	47-year-old man. Unresponsive to conventional antipsoriatic therapy as well as infliximab and efalizumab.	Within 4 weeks of the first dose of ustekinumab (label dosing) visible reduction of lesions were noticed. At week 12, Psoriasis Area Severity Index declined from 23.3 to 3.1 and body surface area from 25% to 1.5%. At week 20, there was almost complete clearance of lesions.	None
2	GPP	Storan et al.[30]	Case report	90-year-old woman. Cyclosporine had to be discontinued owing to acute kidney injury. Unresponsive to methotrexate and adalimumab.	Within 4 weeks of ustekinumab (label dosing) perceptible changes were ascertained. Complete lesional clearance was observed with ongoing therapy.	None
3	GPP	Arakawa et al.[31]	Case series of four patients	Four women (age: 20–50 years). Failed previous treatments included cyclosporine, methotrexate, acitretin, and TNF-α blockers.	Ustekinumab (label dosing) produced sustained remission in all four patients.	None
4	ACH	Cymerman et al.[32]	Case report	20-year-old woman unresponsive to CsA.	Successful outcome seen when ustekinumab was up-dosed from 45 to 90 mg (despite patient's weight being <100 kg).	None
5	ACH	Adas et al.[33]	Case report	61-year-old man unresponsive to etanercept.	Though lesions began to disappear after two doses of ustekinumab (label dosing) (45 mg SC), it was short lived. Escalation of dose to 90 mg resulted in excellent sustained improvement.	None
6	ACH	Saunier et al.[34]	Case report	A 53-year-old active smoker male unresponsive to TNF-α antagonists and anakinra.	Successful therapeutic outcome following combination of ustekinumab (label dosing) with acitretin.	None
7	ACH	Shi et al.[35]	Case report	24-year-old man unresponsive to Chinese medicine, acitretin, and phototherapy.	Complete resolution of lesions by 28 weeks following ustekinumab (label dosing) therapy.	None
8	PPP	Pinto-Almeida et al.[39]	Case report	30-year-old woman suffering from the disease for 5 years and unresponsive to conventional antipsoriasis therapy.	Following ustekinumab (label dosing) therapy, clinical improvement was evident within 3 weeks and complete resolution observed by 16 weeks.	None
9	PPP	Bertelsen et al.[40]	Case series of 11 patients	Eight women and three men. Age group: 35–70 years.	Ustekinumab (label dosing) demonstrated complete response in one patient, partial response in six patients, no response in two patients and aggravation of lesions in two patients.	None

(Table 1 continued)

(Table 1 continued)

Serial No.	Variant of Psoriasis	Authors	Study Design	Patient Profile	Reported Outcome	Adverse Effects
10	PPP	Gerdes et al.[41]	Case series of four patients	Four women.Age ranging from 49 to 70 years. Three smokers and one non-smoker. Previous failed biologics included efalizumab, adalimumab, etanercept, and infliximab.	Slow improvement was seen in two patients. In the other two, lesions aggravated following ustekinumab therapy.	None
11	PPP	Morales-Munera et al.[42]	Case series of five patients	Two men and three women. Age group: 30–50 years. Failed treatments included cyclosporine, methotrexate, PUVA, acitretin, leflunomide, efalizumab, and TNF-α blockers.	Ustekinumab (label dosing) demonstrated remarkable alleviation of lesions following two doses, and complete resolution by week 20 in all patients.	None
12	PPP	Buder et al.[43]	Case series of nine patients	Six men and three women. Mean age ~48 years. Previous failed treatments included PUVA, UVB, acitretin, methotrexate, cyclosporine, leflunomide, adalimumab, infliximab, golimumab, etanercept, fumaric acid esters, and certolizumab.	Ustekinumab given as per label dosing. Two patients had complete resolution of lesions. Four patients demonstrated 75% improvement. Three patients had no response.	None
13	Palmoplantar psoriasis (non-pustular)	Bulai Livideance et al.[44]	Case series of two patients	29-year-old woman and 42-year-old man. Previous failed treatments included standard antipsoriasis agents and TNF-α antagonists.	Following ustekinumab (label dosing) treatment, dramatic improvement was witnessed after the third dose, in both patients.	None
14	Palmoplantar psoriasis (non-pustular)	Nuno-Gonzalez et al.[45]	Case report	56-year-old man with severe disease and unresponsive to isotretinoin.	Within 4 months of ustekinumab (label dosing) therapy, complete resolution of lesions was observed.	None
15	NP	Patasi et al.[46]	Open-label uncontrolled non-randomized study	27 study subjects with moderate to severe plaque psoriasis with nail involvement. NAPSI median score at baseline was 73.	Following ustekinumab (label dosing) therapy, NAPSI median score plummeted to 37 at week 16, 9 at week 28, and 0 at week 40.	None
16	NP	Rich et al.,[47]	Retrospective evaluation	Retrospective evaluation of NP in 766 patients from the PHOENIX 1 trial in comparison to placebo.	Following ustekinumab therapy, statistically significant improvement was observed versus placebo ($p < 0.001$).	None
17	NP	Rallis et al.[48]	Case report	A 38-year-old man with NP and plaque psoriasis with failure of conventional antipsoriasis therapy and etanercept.	Within 4 weeks follow administration of the second dose of ustekinumab (label dosing), complete cure was obtained.	None

Notes: ACH: Acrodermatitis of Hallopeau; GPP: Generalized pustular psoriasis; PPP: Palmoplantar psoriasis; NP: Nail psoriasis; NAPSI: Nail Psoriasis Severity Index; SC, subcutaneous; TNF-α: Tumor necrosis factor-α; UVB: Ultraviolet B. Label dosing: 45 mg given at weeks 0, 4, and then every 12 weeks (when weight <100 kg); 90 mg given at weeks 0, 4, and then every 12 weeks (when weight >100 kg).

soles. The responsiveness of PPP to ustekinumab has been mixed, with profitable outcomes on the one hand and poor to paradoxical responses on the other. The positive effects of ustekinumab in PPP have been linked to the blockade of IL-23, which in turn prevents IL-17 secretion from Th17 cells, with the consequent impediment of neutrophil influx and neutrophil-mediated inflammatory responses.[36] On the contrary, poor or paradoxical responses associated with ustekinumab have been attributed to stimulation of interferon-α (IFNα) synthesis (following blockade of IL-23 and Th17 activity). Activation of T cells by IFNα goes on to produce TNF-α and IL-17, which in turn sustain inflammatory cascades for the development of psoriatic plaques and pustules. Besides, serum in PPP patients demonstrates increased levels of IL-17 and IL-22-related cytokines without significant elevation of IL-23 and IL-8 (thereby accounting for why ustekinumab is not effective in every patient).[37,38] Currently, there are only case reports and case series exemplifying the utility of ustekinumab in PPP (Table 1),[39–43] highlighting the need for RCTs to further strengthen these observations.

Palmoplantar Psoriasis (Non-pustular)

This type of psoriasis affects the skin of the palms and soles, featuring hyperkeratotic plaques and causing significant functional disability. Often, the response to this variant of psoriasis to treatment is delayed, accounted for by the presence of subclinical trauma and chronic pressure amounting to systematic koebnerization.[44] By antagonizing IL-23, ustekinumab indirectly blocks IL-22 and prevents the occurrence of epidermal hyperplasia and acanthosis.[45] The utility of ustekinumab in non-pustular palmoplantar psoriasis has been elaborated in two case reports (Table 1).[44,45]

Nail Psoriasis

Nail psoriasis (NP) commonly manifests in patients with plaque psoriasis and PsA, causing cosmetic disfigurement that profoundly distresses the patient. Treatment for NP can be quite challenging owing to the intricate nail anatomy compared to the usual skin. Besides, if NP is the sole manifestation of the disease, prior to starting any systemic therapy, both pros and cons need to be adequately weighed. A practical suggestion would be to initiate topical therapy, and if unresponsive, intramatriceal drug injections could be an avenue to contemplate, owing to the localized approach, which has higher levels of safety and cost-effectiveness when compared to systemic therapy. A literature search revealed one open-label, uncontrolled, non-randomized study, one retrospective evaluation of NP from the PHOENIX trial, and one case report depicting the beneficial role of ustekinumab in NP (Table 1).[46–48] However, Iqarashi et al.[49] in their report failed to elucidate a significant improvement in the Nail Psoriasis Severity Index (NAPSI) with ustekinumab for NP.

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory skin disease arising from hair follicles, particularly affecting intertriginous zones, often associated with systemic comorbidity.[50] The utility of ustekinumab in HS has been described in one phase II open-label trial, one multicenter retrospective study, and a few case series (Table 2).[51–56] The role of ustekinumab in HS is associated with inhibition of IL-23 and IL-12. It has been hypothesized that inflammation in HS is caused by abnormal Notch signaling. These signals induce differentiation of outer hair root sheath cells, which are destroyed easily and release keratins that trigger macrophage activation via Toll-like receptors. This consequently activates dendritic cells which release IL-23 to activate Th17 cells. Furthermore, IL-12 and IL-23 are also produced by CD^{68+} and CD^{32+} macrophages in lesions of HS. This subsequently deteriorates the balance between Th17 and regulatory T cells. By suppressing both IL-23 and IL-12, ustekinumab enables the restoration of this imbalance.[57,58]

Despite the above postulation, Gkine and Bewley[59] displayed the development of HS with ustekinumab in a 19-year-old Caucasian woman treated for psoriasis. The reason for this remains unclear, but it has been suggested to be a probable paradox reaction to anti-IL12/2. Physicians should therefore be aware of this potent complication, with ustekinumab, in the event of which other treatment options for HS need consideration.

Pyoderma Gangrenosum

Pyoderma gangrenosum (PG) is an ulceronecrotic neutrophilic dermatosis characterized by painful ulcers commonly involving the lower extremities.[60] Currently, ustekinumab's efficacy in PG has only been highlighted in case reports.

Gonzalez et al. demonstrated ustekinumab to be effective in treating PG in a 29-year-old woman with CD who had failed to respond to adalimumab. Ustekinumab was initiated at a dose of 260 mg intravenously (IV), following which the patient improved tremendously. The patient was then maintained on ustekinumab at 90 mg every 8 weeks. With this treatment, the patient remained in remission.[60]

A French report further established the profitability of ustekinumab in a 56-year-old woman with plaque psoriasis/PsA, wherein PG had been precipitated following adalimumab therapy. Following three doses of ustekinumab (45 mg subcutaneously (SC), as per the standard protocol for plaque psoriasis), PG had completely healed along with clearance of psoriasis lesions.[61]

Nunes and colleagues likewise outlined the utility of ustekinumab in treating PG in a patient with CD resistant to treatment with azathioprine, cyclosporine, and infliximab. Complete healing of PG was witnessed after administration of the first dose of ustekinumab (520 mg IV). The patient was then maintained on ustekinumab 90 mg SC every 8 weeks.[62]

Table 2. Reports Detailing the Utility of Ustekinumab in HS.

Serial No.	Authors	Details	Remarks
1	Takeda et al.[51]	A 29-year-old man with HS along with concomitant CD.Ustekinumab was initiated at 390 mg IV, followed by 90 mg SC every 8 weeks as per the regimen approved for CD.	Lesions disappeared after 10 months of treatment with ustekinumab. However, every 2–3 months, small HS lesions relapsed for which prednisolone 5 mg/day for 3–5 days was given to achieve complete remission. Moreover, HS severity demonstrated reduction from 4-6 (moderate severity) to 1 (mild severity) following treatment with ustekinumab; as per the International HS Severity Score System.
2	Blok et al.[52]	A phase II open-label study.17 patients with moderate-to-severe HS received ustekinumab, (45 or 90 mg SC) at weeks 0, 4, 16, and 28.	At week 40, moderate to marked improvement in mSS was identified in 82% of subjects, with 47% of them achieving HiSCR.
3	Romani et al.[53]	14 HS patients resistant to at least one prior biologic drug, were given ustekinumab (as per the treatment schedule in CD). Patients received an intravenous infusion of ustekinumab adjusted based on body weight (≤55 kg, 260 mg; 55–85 kg, 390 mg; and ≥85 kg, 520 mg), followed by SC maintenance dose of 90 mg every 8 weeks.	HiSCR was achieved in 50% of the participants and 71.42% of patients presented with significant pain reduction and improvement in quality of life at week 16 of ustekinumab therapy. Besides, patients tolerated the treatment well with no adverse effects.
4	Sanchez-martinez et al.[54]	Six patients were treated with ustekinumab for HS.	HiSCR was achieved in only three patients.In two patients, there was reduction in the International HS Severity Score by 50% and 33.33%.In one patient, no improvement was seen, thereby showing that the response of ustekinumab may vary in different patients, even at dosages utilized for CD.
5	Gulliver et al.[55]	Three patients with HS (Hurley stage II and III) were treated with ustekinumab as per the standard psoriasis protocol. DLQI score ranged from 8 to 12.	At 6 months, one patient showed complete disease remission, while a 25%–49% improvement was seen in the second patient and no change was noticed in the third.Besides, a moderate but statistically significant relationship between the Visual Analogue Scale and DLQI score ($p < 0.01$) was observed.
6	Scholl et al.[56]	Utility of high dose ustekinumab as per the dosing in CD, in combination with antibiotics and limited or extensive surgical procedures was evaluated in three patients of HS (Hurley stage IIc–III).	At 12 months of follow-up, in the first patient, complete remission of inflammatory lesions was obtained. Second patient demonstrated 40% improvement in pain, mSS, and DLQI. In third patient only marginal improvement of DLQI and pain scores were reported; despite stable disease activity, and overall reduced active nodule count (from 19 to 5).

Note: CD: Crohn's disease; DLQI: Dermatology Life Quality Index; IV: Intravenous; HiSCR: Hidradenitis Suppurativa Clinical Response; HS: Hidradenitis suppurativa; mSS: Modified Sartorius Score; SC: Subcutaneous.

Ustekinumab's role in PG was further highlighted in a report from North Carolina, wherein PG induced by secukinumab in a patient with psoriasis was successfully treated with ustekinumab (90 mg SC on weeks 0, 4, and then every 8 weeks). Significant improvement was noticed after two doses of ustekinumab, with almost complete re-epithelialization of the ulcer.[63]

Another publication revealed ustekinumab in combination with vacuum-assisted closure (VAC) therapy to be highly effective in treating PG in a 62-year-old man who had been diagnosed with myelodysplastic syndrome. Ustekinumab (90 mg SC, standard psoriasis regimen) was commenced owing to treatment failure with corticosteroids, thalidomide, infliximab, adalimumab, and immunoglobins. Within 2 weeks of the first

dose of ustekinumab, dramatic improvement was observed, following which VAC therapy was applied every 5 days to the ulcer. This treatment was continued for 8 weeks, with complete healing occurring at 20 weeks. Ustekinumab was then continued every 8 weeks as maintenance for 18 months. This revealed surgical treatments to be advantageous along with biological therapy once the correct immunosuppressive environment was achieved in treating PG.[64]

The role of ustekinumab in PG can be attributed to the heightened expression of IL-23 in tissue samples from PG lesions at both transcriptional and protein levels.[65]

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory disorder of the skin characterized by intense pruritus and xerosis. The pathogenesis of AD is believed to be driven by a type 2 helper T-cell (Th2)-mediated immune response. However, during the chronic phase of the disease, there is a switch towards the Th1-mediated immune response, wherein IL-12 comes into play and brings about this change.[66–68] Besides, based on Th1/Th2 cell responses, evidence suggests the involvement of Th17 cells, in the immunopathology of AD. The exact mechanism of action of ustekinumab in AD is still not fully understood. Based on the above postulation, ustekinumab's role in AD occurs by downregulating Th1 and Th17 inflammatory pathways once it binds to IL-12 and IL-23.[69,70] However, despite these conclusions, the therapeutic effects of ustekinumab for AD have demonstrated disparity, ranging from complete responsiveness to no response at all, as demonstrated in RCTs, case series, and case reports (Table 3).[71–75]

Interestingly, AD, following ustekinumab therapy, has also been observed. Ishuyi and coworkers reported the emergence of AD in a 59-year-old man with psoriasis following ustekinumab treatment, with a SCORAD of 10 being reached after 172 weeks of ustekinumab therapy, and rapid improvement of AD after cessation of ustekinumab.[76] In another patient with concurrent psoriasis and AD, ustekinumab resulted in complete remission of psoriasis but worsening of AD with SCORAD values increasing from 9 to 15; and improvement of AD with subsequent halting of ustekinumab treatment.[77] The underlying mechanism for this can be ascribed to IL-12 blockade as well as indirect IL-17 inhibition, resulting in an immunological imbalance favoring increased activity of the Th2 pathway. The resultant Th2 dominance, in turn, accounts for AD-like symptoms.[77,78] This variation in clinical responses illustrates that ustekinumab may not be a very suitable agent for AD. Nonetheless, it can be tried as an unconventional drug in patients when treatment with approved biological drugs have failed.

Table 3. Reports Delineating the Use of Ustekinumab in AD.

Serial No.	Authors	Details	Remarks	Adverse Effects
1	Khattri et al.[71]	Phase 2 randomized placebo-controlled trial. Group 1 (16 patients) received ustekinumab (label dosing). Group 2 (16 patients) received placebo.	Both groups had optimal responses to ustekinumab at 8 weeks. At week 16, SCORAD 50 responses were higher in group 1.	Two patients had to be excluded from the study due to development of eczema herpeticum and contact dermatitis.
2	Saeki et al.[72]	Phase 2 randomized double-blind placebo-controlled trial. Group 1 (52 patients) received ustekinumab (label dosing). Group 2 (27 patients) received placebo.	No meaningful clinical difference was seen in both groups.	None
3	Nic-Dhonncha et al.[73]	An Irish case series of 10 patients treated with ustekinumab (label dosing). Two women. Eight men. Age range (20–50 years).	Only one patient delineated complete clinical response. In three patients, almost complete clinical response was seen. No response was seen in six patients.	None
4	Shroff and Guttman-yasky[74]	Case report of a 70-year-old woman with AD refractory to cyclosporine and MMF.	Complete response seen at week 19 following ustekinumab therapy.	None
5	Samorano et al.[75]	Case series of two patients. 47-year-old man. 20-year-old woman. Previous failed treatments included phototherapy, systemic steroids, cyclosporine, methotrexate, MMF, and etanercept.	Inadequate response was seen following ustekinumab treatment.	None

Note: AD: Atopic dermatitis; SCORAD: SCORing in Atopic Dermatitis; MMF: Mycophenolate mofetil.

Alopecia Areata

Alopecia areata (AA) is an autoimmune disorder resulting in non-scarring alopecia with a considerable impact on a patient's quality of life. Although there are a number of therapeutic agents for AA, that though effective, cannot be used for prolonged periods owing to safety concerns, and often cessation of treatment is heralded again by hair loss.[79,80] Currently, ustekinumab's utility in AA has been outlined in case reports and case series alone. The role of ustekinumab in AA is contributed by its antagonistic action on IL-12, which enables the development of naive T cells to Th1 cells.[81]

Alesia and colleagues demonstrated hair regrowth in three pediatric patients following ustekinumab treatment. Two patients received a stat dose of 90 mg of ustekinumab, and the third patient was given 90 mg of ustekinumab at months 0, 3, and 6. In all three patients, the SALT score improved by 71.43%–100%.[81] In another study, similarly, ustekinumab (90 mg SC) was found to be effective in AA, given at weeks 0, 4, and 16. Besides, in one patient with alopecia universalis, improvement was substantial, with regrowth of all body hair, eyebrows, and all of the scalp at week 49.[82] Again, ustekinumab's favorable effect on AA was iterated in a 39-year-old South Asian woman. Dosed at 90 mg (0, 4, and every 8 weeks), by 20 weeks, hair density had visibly increased.[83]

Lupus Erythematosus

Lupus erythematosus (LE) is associated with dysregulation of the IL-17/IL-23 axis along with a reduction in the total number of T-regulatory FoxP3+ cells. Increased levels of IL-23 produced predominantly by dendritic cells and macrophages promote the expansion of Th17 cells, which in turn elaborates IL-17 production, a cytokine significantly elevated in the skin of patients with systemic LE and discoid LE. IL-17 further stimulates the production of autoantibodies and inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-22, etc.) and chemokines (CCL2, CCL7, CCL29, CXCL1, and CXCL5). There is thus an imbalance between proinflammatory and anti-inflammatory cytokines with a deranged homeostasis. Ustekinumab, in LE, ameliorates this deranged homeostasis by preventing differentiation of T cells to Th17 via IL-12/23 inhibition.[84–87]

Though there are a number of case reports where ustekinumab has been beneficial in LE, RCTs are currently lacking in this context. Further details have been propounded in Table 4.[88–93] However, despite the propitious effect of ustekinumab in LE, it has also been reported to induce subacute cutaneous LE.[94] The cause of this reaction occurs secondary to the diversion of T cell differentiation to the alternative pathway of T helper cell IL-22 production via IL-6, leading to excess TNF-α production and stimulation of inflammatory responses.[95]

Bechet's Disease

The role of ustekinumab in Bechet's disease (BD) occurs via its antagonist activity against IL-23 and the associated Th17 pathway that plays a major role in BD.[96] Ustekinumab has demonstrated efficacy in two patients with multirefractory BD (unresponsive to colchicine, cyclosporine, methotrexate, azathioprine, anakinra, and anti-TNF-α agents).[97,98] In order to strengthen these findings, RCTs are warranted.

Pityriasis Rubra Pilaris

The exact mechanism of ustekinumab's action in pityriasis rubra pilaris (PRP) is unclear. Because of its IL-12 and IL-23 blocking properties and subsequent suppression of cytokine

Table 4. Reports Highlighting the Efficacy of Ustekinumab in LE.

Serial No.	Authors	Details	Remarks
1	De Souza et al.[88]	58-year-old woman with subacute cutaneous LE. Limited benefit from prior treatment that included hydroxychloroquine, dapsone, prednisone, azathioprine, mycophenolate mofetil, topical corticosteroids, and tacrolimus 0.1% ointment. Ustekinumab (45 mg SC) was administered as per its approved dosing in psoriasis.	Marked improvement of cutaneous eruption within 3–4 weeks of the first dose. Also, resolution of arthralgia and fatigue. Following second dose, patient went into remission for 7 months while receiving ustekinumab every 12 weekly. No adverse events were reported.
2	Winchester et al.[89]	41-year-old man with hypertrophic DLE as well as severe psoriasis. Unresponsive to methotrexate, hydroxychloroquine, cyclosporine, and topical steroids. Ustekinumab (45 mg SC) administered as per the standard psoriasis protocol.	Dramatic improvement of psoriasis within 2 months. DLE lesions at 2 months showed fewer scales with slightly less induration. DLE showed marked improvement, 6 weeks after the second dose of ustekinumab.

(Table 4 continued)

(Table 4 continued)

Serial No.	Authors	Details	Remarks
3	Dahl et al.[90]	79-year-old woman with refractory chronic cutaneous LE. Prior treatments given were topical and systemic glucocorticoids, hydroxychloroquine, azathioprine, thalidomide, methotrexate, topical calcineurin inhibitors, high dose intravenous immunoglobulins, and combination of these. Ustekinumab (45 mg SC) given at 0, 4, 16, and 34 weeks.	At 34 weeks of ustekinumab therapy, disease activity score reduced from 23 to 14 and Visual Analogue Score decreased to 5 from 10. Objectively, erythema on patients face, scalp, and fingers improved and ulcers of fingertips healed. No adverse effects were observed.
4	Chyuan et al.[91]	33-year-old woman. Concomitant psoriasis with SLE. Refractory to treatment with methotrexate and cyclosporine. Ustekinumab (45 mg SC) given according to standard dosing for psoriasis. Azathioprine was also given to prevent any flare of SLE.	Cutaneous lesions subsided. Lupus nephritis stabilized. No new flares were seen in other organ systems. No major infection occurred during the treatment course. Maintenance prednisolone dose reduced from 7.5 to 5 mg/day.
5	Varada et al.[92]	Ustekinumab (45 mg SC) administered to five patients, as per the standard psoriasis protocol, who had psoriasis and SLE.	Particular benefit of SLE features like oral ulceration, anemia, thrombocytopenia, and lupus nephritis was seen in four patients. One patient developed cellulitis and so treatment was stopped.
6	Romero-Mate et al.[93]	52-year-old woman with a 28-year history of disfiguring facial DLE. Recalcitrant to classical therapies including rituximab. Ustekinumab 45 mg SC was given as per psoriasis standard dose along with intralesional corticosteroids over most active lesions every 4–6 weeks.	Though slow, continuous improvement was noted.No remarkable side effects even after 4 years of continuous monotherapy with ustekinumab.

Note: DLE: Discoid lupus erythematosus; LE: Lupus erythematosus; SC: Subcutaneous; SLE: Systemic lupus erythematosus.

release and immune activation, ustekinumab has been used in patients with unremitting PRP. However, information on the effects of ustekinumab on PRP does not meet the requirements of evidence-based medicine.[99] Currently, there are only case reports describing the appositeness of ustekinumab in PRP, which are summarized in Table 5.[99–104]

Miscellaneous

In an anecdotal report, ustekinumab (45 mg SC/in the standard psoriasis dosage) was associated with dramatic clinical improvement of recalcitrant oral lichen planus (LP) within 12 weeks in a 72-year-old woman unresponsive to systemic or topical steroids, ciclosporin, acitretin, and azathioprine.[105] It has been suggested that IL-23 is markedly elevated in LP lesions, which is suppressed by the antagonizing effects of ustekinumab on IL-23 and Th17/Tc17 cells.[106]

Similarly, isolated reports have highlighted the utility of ustekinumab in synovitis acne pustulosis hyperostosis osteitis syndrome, bullous pemphigoid (BP), LP pemphigoid, and anti-laminin γ1 pemphigoid.[107–110] Interestingly, the occurrence of BP has been associated with ustekinumab therapy, suggesting other cytokine pathways responsible for the development of iatrogenic pemphigoid.[111–113]

Table 6 delineates the level of evidence supporting the off-label use of ustekinumab for various inflammatory dermatoses.

Adverse Effects

Reported cutaneous adverse effects associated with ustekinumab are pruritus, exfoliative dermatitis, LE tumidus, Jessner–Kanof's lymphocytic infiltrate, and injection site erythema.[114,115] Common extracutaneous side effects observed are nasopharyngitis, headache, arthralgia, fatigue, bronchitis/upper respiratory tract infection, sinusitis, back pain, abdominal pain, and fever (in higher dosing schedules).[116]

Serious side effects that need consideration include the risk of active tubercular infection, major adverse cardiovascular

Table 5. Reports Elucidating the Efficacy of Ustekinumab in Pityriasis Rubra Pilaris.

Serial No.	Authors	Details	Remarks
1	Di stefani et al.[99]	31-year-old man with refractory type I PRP. Previous unsuccessful treatments included cyclosporine, acitretin, and methotrexate. Ustekinumab (45 mg SC) was given as per the standard psoriasis regimen.	Within the first 4 weeks of treatment, marked improvement of erythema, pruritus, and nail lesions was observed. Complete remission was achieved after the third injection. Significant improvement was also reported in patient's quality of life.
2	Wohlrab and Kreft[100]	28-year-old man with suberythrodermic PRP. Acitretin and bath PUVA therapy led to marked recession of palmoplantar hyperkeratosis, but suberythroderma persisted. Ustekinumab 45 mg SC given as per the standard psoriasis protocol.	Following ustekinumab treatment, erythema had almost completely faded and with ongoing therapy, patient was completely free of symptoms.
3	Eytan et al.[101]	57-year-old man with type V erythrodermic PRP. Unresponsive to systemic retinoids, methotrexate, etanercept, efalizumab, and adalimumab. Ustekinumab 45 mg given SC initially, followed by 90 mg 9 weekly.	Dramatic improvement witnessed following ustekinumab treatment. Treatment continued for 36 weeks.
4	Chowdhary et al.[102]	52-year-old African-American woman with type I suberythrodermic PRP. Unresponsive to acitretin, methotrexate, minocycline, prednisone, UVB phototherapy, and topical clobetasol propionate. Ustekinumab 90 mg SC given stat and readministered at 4 weeks and then quarterly.	Within 8 weeks significant improvement observed. Body erythema had reduced by 80%.Significant reduction of pain was stated.
5	Feldmayer et al.[103]	40-year-old man with type I suberythrodermic PRP. Retinoids, methotrexate, and phototherapy were contraindicated in this patient. Ustekinumab 45 mg SC as per psoriasis protocol given.	Within 2 weeks of treatment improvement was seen and by 4 weeks almost complete remission was documented.
6	Aragon-Nigual et al.[104]	30-year-old man with type I PRP. Failure of acitretin and PUVA therapy. Ustekinumab 40 mg SC given as per standard psoriasis regimen.	Considerable improvement seen after 4 weeks of ustekinumab therapy with complete remission after 9 months.

Note: PRP: Pityriasis rubra pilaris; SC: Subcutaneous; UVB: Ultraviolet B.

events (MACEs), and potential oncogenic complications. However, analysis of published register-based data has not demonstrated higher rates of severe tubercular infections when compared to either anti-TNF-α or conventional antipsoriatic drugs.[117,118] Similarly, though a meta-analysis of RCTs reported an increase in MACEs during the first month of ustekinumab therapy, no significant increase in frequency of MACEs was observed when compared to placebo.[119] Regarding the oncogenic potential, despite scarce reports of malignant tumors, cancer incidence itself was low in clinical trials and register-based data.[118] Even with the reassuring data, before starting ustekinumab, appropriate monitoring of the drug is essential, details of which have been elucidated in Table 7.[120–123]

Use in Specific Populations

Pregnancy

Although there are several cases of pregnant patients treated safely with ustekinumab, mostly in gastroenterological indications, the German S3 guideline and also the summary of product characteristic (SmPC) do not currently recommend using this medication for psoriasis during gestation.[124]

Lactation

Only a few reports exist on the use of ustekinumab during lactation. The substance was found in breast milk in four out of

Table 6. Level of Evidence Supporting the Off-label Use of Ustekinumab for Various Inflammatory Dermatoses.

Serial No.	Off-label Indications in Dermatology	Level of Evidence for Ustekinumab Use
1	Generalized pustular psoriasis	D
2	Acrodermatitis continua of Hallopeau	D
3	Palmoplantar pustulosis	C
4	Palmoplantar psoriasis (non-pustular)	D
5	Nail psoriasis	B
6	Hidradenitis suppurativa	C
7	Pyoderma gangrenosum	D
8	Atopic Dermatitis	D
9	Alopecia areata	D
10	Pityriasis Rubra pilaris	D
11	Lupus	D
12	Bechet's disease	D
13	Lichen planus	E
14	Bullous pemphigoid	E
15	Lichen planus pemphigoid	E
16	Anti-laminin γ1 pemphigoid	E
17	SAPHO syndrome	E

Notes: A: Double blind study: At least one prospective randomized double blind controlled trial without major design flaws. B: Clinical trial with 20 or more subjects: Prospective clinical trials with 20 or more subjects, trials lacking adequate controls or another key facet design, which would normally be considered desirable. C: Clinical trial with less than 20 subjects: small trials with less than 20 subjects with significant design limitations, very large number of case reports (at least 20 such in literature). D. Series of 5 or less subjects: Series of patients reported to respond with at least five reports of the same in literature. E: Anecdotal case reports.

Table 7. Drug Monitoring for Ustekinumab.

Baseline	• Routine blood tests: complete blood counts(CBC), liver function test(LFT), Renal function test(RFT), CRP, ESR, serum electrolytes. • Varicella antibody status should be clarified, and vaccination considered in appropriate patients. • Screening for tuberculosis: Chest X-ray and interferon-gamma release assay. • Hepatitis B, C and HIV tests. • Pregnancy test needs to be done in females where pregnancy is a possibility.
Ongoing	• Routine blood tests including, CBC, urea, electrolytes, LFTs, CRP, ESR need to be done every 4-6 months. • Retesting for Hepatitis and HIV needs consideration if clinically indicated • Patients must be monitored clinically for development of severe infections (including TB), jaundice, malignancy, non-infectious pneumonia, posterior reversible encephalopathy syndrome, or serious skin conditions like exfoliative dermatitis. Patients should be encouraged to report any concerning symptoms. • Clinical monitoring for efficacy should be carried out using disease specific measuring systems for psoriasis, psoriatic arthritis and inflammatory bowel disease. • There are experimental data to suggest that monitoring serum drug levels may be beneficial during ustekinumab treatment, but this is not the current standard for care.

six breastfeeding patients with chronic inflammatory bowel disease (IBD). The highest concentration (0.72–1.57 mg/mL) was measured during 12–72 hours after drug administration.

The breastfed infants did not demonstrate any negative effects from it. Despite this, owing to limited evidence, ustekinumab is not currently recommended for lactating mothers.[124]

Pediatric

Ustekinumab can be used in pediatric patients with psoriasis. Besides, it is a safe and effective treatment option for pediatric and adolescent CD and Crohn's-like IBD.[125]

Future Direction

As of now, in highly recalcitrant dermatoses, the need for combination therapy is an avenue for further exploration with ustekinumab. Although the combination of ustekinumab with methotrexate[126] and acitretin[34] has been reported, simultaneous use with apremilast, fumaric acid esters, cyclosporine, and azathioprine are areas needing evaluation. Interestingly, the combination of ustekinumab and adalimumab for CD has been reported to have favorable results.[126] The need now arises to assess the utility of other biological drugs with ustekinumab in the form of dual biological therapy in those dermatoses showing partial responsiveness to ustekinumab.

Conclusion

Ustekinumab is a good biological drug for the treatment of psoriasis and PsA. Besides, it is the biological choice for pediatric patients with psoriasis owing to its weight-based dosing schedule. Moreover, currently, ustekinumab has been found to be effective in a number of off-label dermatological indications. Furthermore, it is well tolerated by patients with minimal side effects. Nevertheless, there are reports of serious adverse effects following ustekinumab usage. All these points need to be carefully evaluated prior to prescribing ustekinumab.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Declaration of Conflicting Interests

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