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Review Article

Ustekinumab in Dermatology: Approved Indications and Off-label Uses

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Abstract

Ustekinumab is a human antibody that interacts with the p40 chain shared by both interleukin (IL)-12 and IL-23. Treatment with ustekinumab can effectively inactivate the biological functions of IL-12 and IL-23 to control aberrant Th1 and Th17 immunological responses. Ustekinumab is the first unique IL-12/IL-23 blocker approved by the Food and Drug Administration for the treatment of patients with moderate or severe psoriasis. Subsequently, its application has extended as a therapeutic option for psoriatic arthritis and inflammatory bowel diseases. Given its therapeutic mechanism, usterkinumab may be used as a potential alternative for treatment of a variety of inflammatory skin conditions. More importantly, usterkinumab is relatively safe, as the associated adverse reactions are generally non-serious and rare; although continuous monitoring of its adverse events is warranted. Here, we discuss the therapeutic effects of ustekinumab and its clinical applications specifically in dermatology.

Introduction

Ustekinumab (CNTO-1275, Stelara) is a unique fully humanized monoclonal antibody (mAb) that interacts with the p40 chain shared by interleukin (IL)12/23 and functionally attenuates Type 1 T helper (Th1) and Type 17 (Th17) responses.[1] Ustekinumab was approved for treatment of adult patients with moderate to severe psoriasis by both the European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA) in January 2009 and September 2009, respectively. Subsequently, the FDA has expanded the approval for treatment of adolescents and children (≥6 years old) (Fig. 1). Although it was first approved for treatment of patients with psoriasis,[2–5] ustekinumab has proven effective for treatment of other immune-mediated disorders (IMD), including active psoriatic arthritis (PsA) and active forms of major inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease. Aside from these labeled indications, ustekinumab has been used "off-label" for other inflammatory diseases.[6] However, while multiple publications, mainly case reports and a small number of case series, have shown excellent results of ustekinumab when prescribed off-label for treatment of various skin conditions, there is a lack of systemic reviews in the literature. Hence, in this review we discuss ustekinumab's pharmacological effects, efficacy, and safety in the treatment of psoriasis. More importantly, this review offers a special emphasis on the potential applications of ustekinumab in dermatology, based on its specific mechanism of action to inactivate both IL-12 and IL-23, and extend its therapeutic applications to a variety of skin disorders.

Keywords: Ustekinumab; IL12; IL23; IL 12/IL 23 inhibitor; Biologic therapy.

Abbreviations: ACH, acrodermatitis continua of Hallopeau; AD, Atopic dermatitis; AE, adverse event; BD, Behçet disease; BP, bullous pemphigoid; DBT, dual biological therapy; EMA, European Medicine Agency; EP, erythrodermic psoriasis; FDA, Food and Drug Administration; GP, guttate psoriasis; GPP, generalized pustular psoriasis; GWAS, genome-wide association studies; HS, hidradenitis suppurativa; IFN, interferon; IL, interleukin; IMD, immune-mediated disorders; JAK2, Janus kinase 2; LE, lupus erythematosus; LP, lichen planus; mAb, monoclonal antibody; MCVE, major adverse cardiovascular event; MTX, methotrexate; ND, neutrophilic dermatoses; PG, Pyoderma gangrenosum; PP, pustular psoriasis; PPP, palmoplantar pustulosis; PRP, pityriasis rubra pilaris; PsA, psoriatic arthritis; QoL, quality of life; RCT, randomized placebo-controlled trials; SAPHO, Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis; SS, Sweet syndrome; STAT, signal transduction activation of transcription; TNF, tumor necrosis factor; TYK2, tyrosine kinase.

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Pharmacological mechanisms of ustekinumab

Successful mAb therapy began with the generation of chimeric, humanized, and, most recently fully human mAbs. Most mAbs that have been approved and are in the pipeline are indicated for the treatment of cancer, but there have also been other breakthroughs in the field of IMD.[1] Presently, one of the largest classes of mAb therapy includes mAbs that bind and neutralize tumor necrosis factor α (TNFα), a potent inflammatory mediator associated with various IMD, such as rheumatologic, dermatologic, and gastroen-

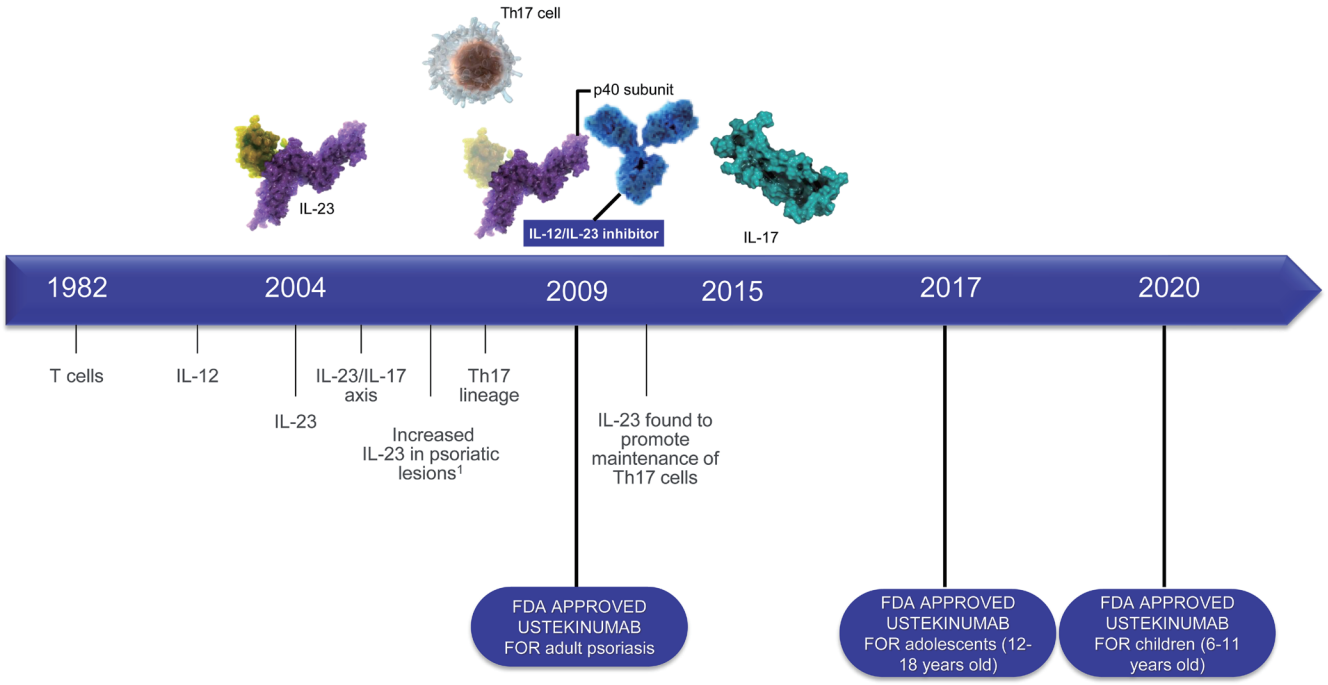

Fig. 1. Timeline of the development and approval of ustekinumab for psoriasis. FDA, Food and Drug Administration; IL, Interleukin; Th, T-helper.

terological diseases.[7] IL-12 and IL-23 are significant contributors to the pathogenesis of IMD.[8] IL-12 is a pro-inflammatory cytokine that consists of two different chain units designated by their average molecular weight as p40 and p35. The binding of IL-12 to its specific receptor (IL12Rβ1/IL12Rβ2), which is usually upregulated on pro-inflammatory T cells, stimulates tyrosine kinase 2 (TYK2) and Janus kinase 2 (JAK2) to activate signal transduction activation of transcription (STAT) 4. Once phosphorylated, STAT4 translocates to the nucleus where it modulates transcription of numerous genes, primarily interferon (IFN)-γ.[9] Thus, IL-12 promotes the differentiation of activated CD4+ T cells into Th1 cells, a subset of CD4+ T cells involved in the pathogenesis of several IMD.[10] IL-23 is also a heterodimeric cytokine formed by two chains of p19 and p40 (similar to IL-12). Engagement of IL-23 receptors (IL12Rβ1/IL23R) by IL-23 can activate STAT3 to induce IL-17, IL-22, and other cytokine production, leading to Th17 responses that contribute to the pathogenesis of various IMD and tissue damage.[1]

Within the skin, IL-17 can promote keratinocyte proliferation and the production of different chemoattractant molecules, such as CXCL1, CXCL8, and CCL20.[11–13] According to animal and human studies, there is a strong link between Th1/Th17 signaling dysregulation and certain IMD, like psoriasis, PsA, rheumatoid arthritis, and inflammatory bowel disease. Furthermore, genome-wide association studies (GWAS) have identified a strong association between genetic alterations that affect the Th1/Th17 axis and chronic inflammation.[14] Thus, in genetically susceptible individuals, over-activated IL-12 and IL-23 trigger aberrant Th1/Th17 responses, subsequently leading to IMD. Ustekinumab is a unique fully human IgG1 kappa mAb against that interacts with the p40 chain of IL-12 and IL-23 and blocks the binding of these two cytokines to their common receptor, IL12Rβ1. Importantly, ustekinumab preferably binds to soluble but not membrane-associated IL-12/IL-23 and does not usually induce complement activation or cell lysis through its immunoglobulin Fc domain.[1]

Figure 2 is an illustration of the mechanisms underlying the action of the drug in inflammatory skin diseases.

Ustekinumab current approved indications in dermatology

Plaque psoriasis is the only validated indication for ustekinumab in dermatology. Psoriasis is a frequent, chronic skin IMD marked by sharply well-circumscribed erythematous-squamous lesions and is significantly associated with systemic comorbidities.[15] The World Health Organization defines psoriasis as a serious, chronic, disfiguring, disabling, and non-communicable disease. Psoriasis affects approximately 2% to 3% of people worldwide, and 30% of cases are moderate to severe forms.[16] Psoriasis and its related comorbidities may substantially lower a patient's quality of life (QoL) and lead to a high degree of cumulative life course impairment.[17] Clinically, psoriasis can manifest with a multitude of phenotypes; 90% of cases display chronic plaque psoriasis (also named psoriasis vulgaris).[18] Therefore, all currently available treatments are approved for psoriasis vulgaris. Psoriasis can also exhibit other less common variants, including guttate, erythrodermic, and pustular psoriasis. Currently, the management of these variants relies on empiric therapies.[16]

During the past twenty years, the understanding of psoriasis pathogenesis has progressed considerably. The TNFα-IL23-Th17 axis has been recognized as a major inflammatory pathway for the pathogenesis of plaque-type psoriasis,[19] which is supported by immunological and genetic studies. While GWAS have shown a link between psoriasis pathogenesis and genetic alterations in the IL-23/IL-17 axis,[20] immunological researchers have stressed the important roles of IL-23 in the development and progression of psoriasis by enhancing Th17 responses. IL-17 is a key orchestrator of chronic inflammation in psoriasis. IL-17 induces the secretion of many other cytokines and chemokines, which promote the chemotaxis of immune cells to the site of inflammation and sustain the positive inflammatory loop and epidermal hyperplasia.[21]

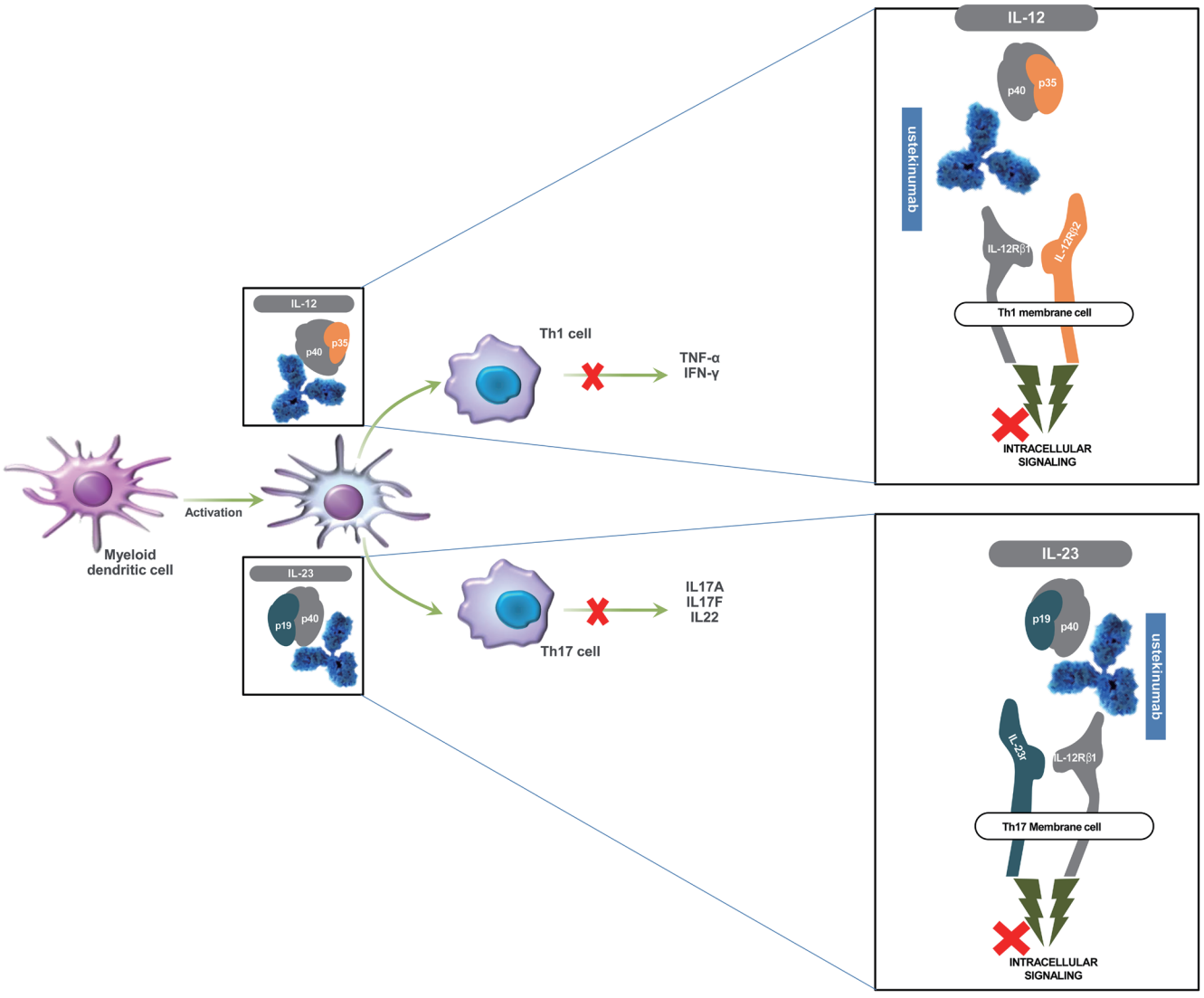

Fig. 2. The mechanisms of actions of ustekinumab in inflammatory skin diseases. IFN: Interferon; IL: Interleukin; Th: T-helper; TNF: Tumor necrosis factor.

However, until late last century, topical therapies and/or ultraviolet light therapies were the mainstay of psoriasis treatment. Subsequently, the first major therapeutic advancements have been conventional systemic drugs (methotrexate, cyclosporine, fumarates, and acitretin). Besides these older agents, the novel small molecule apremilast has recently expanded into the psoriasis armamentarium.[22] Although these treatments may benefit some patients, they have lower therapeutic efficacy and higher adverse events (AEs) owing to a non-specific modulation of the immune system. For example, the PASI 75 (a decrease in PASI score by 75%, the current benchmark of psoriasis treatment) of methotrexate is typically 35.5–41%.[22] The need for alternative and/or small molecule therapeutics and a better understanding of the immunopathogenesis of psoriasis have prompted the discovery of biological drugs directed against the aberrant immune response. Three main groups of biological agents, including blockers for TNFα, IL-23, and IL-17, have been approved for the treatment of psoriasis.

Ustekinumab is the first approved biological drug for treatment of chronic plaque psoriasis, based on its anti-IL-23 effect.[23] Ustekinumab, manufactured by Johnson & Johnson Pharmaceutical, is created by immunizing human mAb-producing mice with recombinant human IL-12. Currently, this biological drug is approved by the FDA for treatment of patients aged ≥6 years who have moderate to severe psoriasis and who are eligible for systemic treatment or phototherapy.[23] The efficacy-safety profiles of ustekinumab have been demonstrated through four large phase III studies: three placebo-controlled trials namely PHOENIX 1/2 and PEARL, and one active comparator-controlled trial (ACCEPT).[2–5] The results from these trials indicate that ustekinumab has a more favorable efficacy-safety profile compared to anti-TNFα drugs. A total of 2,000 psoriatic patients with moderate to severe disease participated in the PHOENIX 1/2 trials. After the initial induction doses of the drug administered subcutaneously every 4 weeks, followed by a maintenance dosage every 12 weeks, 66.4% to 75.7% of participants achieved PASI 75, which was significantly greater than in the placebo groups (3–4%). Moreover, while the improvement was maintained during the 3-month interval between doses, the incidence of AEs (52% and 49%, respectively) and serious AEs

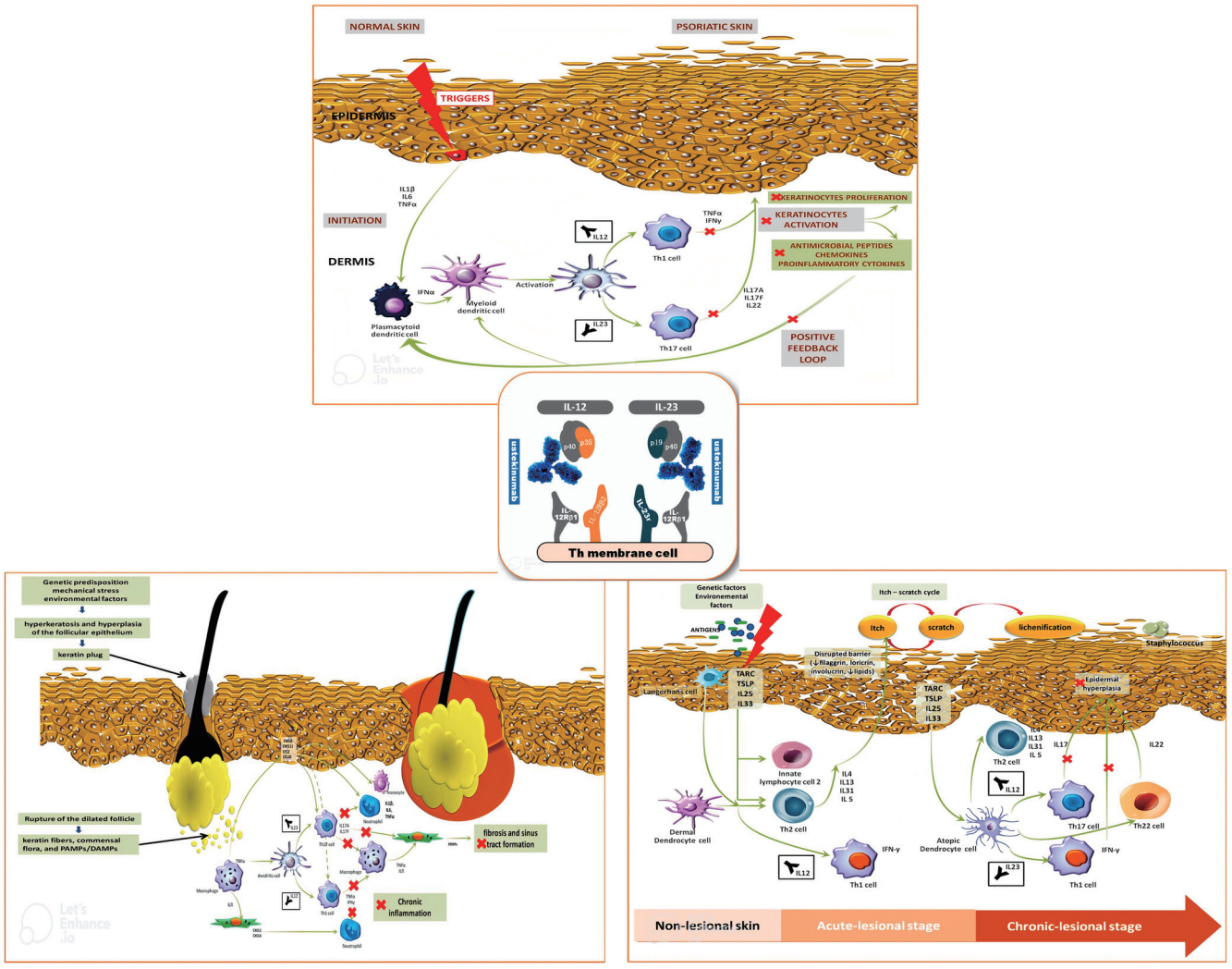

Fig. 3. Therapeutic effect of ustekinumab on psoriasis (top figure), atopic dermatitis (lower right figure), and hidradenitis suppurativa (lower left figure). IFN, interferon; IL, Interleukin; Th, T-helper; TNF, Tumor necrosis factor; TARC, thymus and activation regulated chemokine; TSLP, thymic stromal lymphopoietin.

(1.4% and 1.5%, respectively) were not significant between these two groups. In the ACCEPT trial, similar results were obtained in the ustekinumab group (67.5% to 73.8%) with a higher efficacy compared to etanercept (56.8%) and a comparable safety profile. Consistent data regarding the efficacy of ustekinumab and its safety profile were observed through 5 years of follow-up.[24] However, dose escalation (90 mg every 8 weeks) resulted in better improvement in psoriatic patients who failed to respond to the initial regimen. In addition, since most patients with psoriasis experienced a flare-up after stopping ustekinumab therapy, there is no available data to support the long-term use of this biological drug.[25]

Figure 3 is an illustration of the therapeutic effect of ustekinumab on psoriasis and two other major skin diseases, atopic dermatitis and hidradenitis suppurativa.

Ustekinumab off-label uses in dermatology

Ustekinumab has been used to treat many skin diseases given its distinct and targeted mechanism of action. However, robust evidence from well-designed studies addressing uncommon and life-threatening diseases is rare, and the scientific data available in this field are often restricted to small clinical reports. Thus, such limited evidence cannot support the use of ustekinumab as an initial therapy. On the other hand, there are a few low-level quality studies comparing IL-12/IL-23 blockers versus standard treatments. For this reason, ustekinumab should be reserved to treat cases that have failed or did not tolerate the first-line therapy and where other therapeutic alternatives are lacking. Table 1 summarizes the studies concerning the off-label use of ustekinumab.[26–122]

Ustekinumab for other subtypes of psoriasis

Psoriasis encompasses other infrequent variants namely guttate (GP), erythrodermic (EP), and pustular psoriasis (PP). GP accounts for nearly 2% of psoriatic patients and appears as red, scaly, small, raindrops-shaped papules that often erupt suddenly throughout the entire body.[123] Although there is no consensus on the treatment of GP, severe forms of GP are commonly treated with topical corticosteroids, phototherapy, immunomodulatory drugs, or even bio-

Table 1. Cases of diseases treated off-label with ustekinumab

Cutaneous disorders	Study	Study design	No of patients	Patient (s) Age (y)/sex	Prior systemic treatment	Ustekinumab dose (mg)	Reported efficacy/ outcomes	Serious AEs
GP	Brummer GC[26]	cs	6	29–42/3M–3F	CsA, Apr, Phototherapy	90 once/45Q4W/45Q4W, 90Q4W/90Q8W	Success 6/6	None
	Amarnani[52]	CR	1	56/1F	Phototherapy Aci	SD	Clearance	None
EP	Santos-Juanes[28]	CS	2	32 and 41/2F	CsA, MTX, SCS, PUVA, Efa, anti-TNFα	SD	Success 2/2; PASI 90	None
	Viguier[53]	CS	3		Anti-TNFα	SD	33% PASI 50	-1 sudden death; -Widespread skin Staphylococcus
	Wang[29]	CS	8	28–55/7M–1F	CsA , MTX, PUVA, Efa, alefacept, Aci, anti-TNFα	-7 patients: 45Q4W two doses, -1 patient: 45Q4W two doses + W16 + W 32	50% PASI 75; 50% PASI 90	None
	Pescitelli[27]	CS	22	NA/14M–8F	CsA, MTX, SCS, UVB Ret, anti-TNFα	SD	68.2%; PASI 90	None
GPP	Storan[30]	CR	1	90/1F	CsA, MTX, Ret, Ada	SD	Success 1/1	None
	Arakawa[32]	CS	4	20–50/4F	CsA, MTX, Ana, Aci , anti-TNFα	SD	Success 4/4	None
	Dauden[31]	CR	1	47/1M	None	SD	Success 1/1	None
	Matsumoto[54]	CR	1	70/1F	CsA, etretinate, IFX	Started at 45 then 90	Fail 1/1	None
PPP	Morales-Munera[55]	CS	5	30–50/2M–3F	CsA, MTX, PUVA, Aci, Efa, leflunomide, anti-TNFα	SD	Success 5/5	None
	Au[56]	open-label study	20	18- 85/9M–11F	Systemic therapy, anti-TNFα	SD	Improvement 12/20, Clearance 7/20	None
	Bulai Livideanu[57]	CS	2	29 and 42/1F and 1M	CsA, MTX, Ret, phototherapy, anti-TNFα	45 or 90, not regularly	Success 2/2	None
	Bissonnette[58]	RCT	15	NA/14F–1M		45Q4W two doses or placebo	No difference compared to placebo	1 leg cellulitis
	Husson[35]	CS (PPP + ACH)	30	NA	NA	NA	Success 21/30	2 PPP worsening, 1 Paradoxical psoriasis, 1 Pneumonia
ACH			4				Success 4/4	
	Adisen[59]	CR	1	50/1M	Dap, CsA, MTX, Ret, phototherapy,anti-TNFα	Start 90 then SD 45	Success 1/1	None
	Palacios-Alvarez[33]	CR	1	67/1M	MTX, phototherapy, Aci, anti-TNFα	SD 45	Success 1/1	None
	Saunier[60]	CR	1	53/1M	Aci , MTX, phototherapy, CsA, anti-TNFα, Ana	SD 45	Success 1/1	None

(continued)

Table 1. *(continued)*

Cutaneous disorders	Study	Study design	No of patients	Patient (s) Age (y)/sex	Prior systemic treatment	Ustekinumab dose (mg)	Reported efficacy/ outcomes	Serious AEs
	Cymerman[34]	CR	1	20/1F	CsA	SD 45	Success 1/1	None
	Adas[61]	CR	1	61/1M	Eta	45Q4W two doses then 90Q8W	Success 1/1	None
PRP	Ruiz Villaverde[62]	CR	1	45/1M	None	SD 45	Success 1/1	None
	Byekova[63]	CR	1	75/1M	IFX, Aci	SD 45	Success 1/1	None
	Chowdhary[64]	CR	1	52/1F	Aci, UVB, minocycline, SCS, MTX	SD 90	Success 1/1	None
	Di Stefani[65]	CR	1	31/1M	CsA, Aci, MTX	SD 45	Success 1/1	None
	Eytan[66]	CR	1	57/1M	MTX, Ret, PUVA, Efa, anti-TNFα	90Q8W	Success 1/1	None
	Humme[67]	CR	1	50/1M	Aci, PUVA, CsA, IFX	45–90	NA	CD30(+) anaplastic large cell lymphoma
	Lernia[68]	CR	1	29/1F	CsA, MTX, anti-TNFα, PUVA,	SD 45	Fail 1/1	None
	Lwin[69]	CS	2	20 and 49/1M and 1F	Ret, phototherapy	-1 patient: SD 45; -1 patient: Started at SD 45 then 90	Success 2/2	None
	Paganelli[70]	CR	1	78/1F	Ret, phototherapy, MTX, CsA, IFX	SD 45	Success 1/1	None
	Wohlrab[71]	CR	1	28/1M	Aci, Bath-PUVA,	SD 45	Success 1/1	None
	Aragón-Miguel[72]	CR	1	30/1M	Aci, PUVA	SD 45	Success 1/1	None
	Feldmeyer[73]	CR	1	40/M	None	SD 45	Success 1/1	None
	Kalogeropoulos[74]	CR	1	60/1M	Aci	SD 45	NA	Meningococcal and HSV-2 Meningitis
	Napolitano[75]	CS	5	28–62/3M–2F	CsA, SCS, Aci, MTX	SD 45	Success 4/5, 1partial improvement	None
	Craiglow[76]	CS	6	NA	NB-UVB, PUVA, Ret, MTX, CsA, anti-TNFα,	-5 patients: 0,7 mg/kg-1,1 mg/kg Q12W; -1 patient 1,2 mg/kg Q8W	Success 5/6, 1partial improvement	NA
	Matsuda[77]	CR	1	72/1M	SCS, Secu, IFX, etretinate, CsA, MTX, Apr	SD 45	Success 1/1	None
	Ponholzer[78]	CS	5	NA/3M–2F	NB-UVB, PUVA, Aci	-3 patients: SD 45; -1 patient: SD 90; -1 patient: Started at SD 45 then 90	Success 5/5	NA
HS	Gulliver[79]	CS	3	30–32/1M–2F	ATBs, Ret, anti-TNFα, SCS, Efa	SD 45	- HS-PGA: 2/3; - DLQI: 2/3; - Pain: 2/3	None

(continued)

Table 1. *(continued)*

Cutaneous disorders	Study	Study design	No of patients	Patient (s) Age (y)/sex	Prior systemic treatment	Ustekinumab dose (mg)	Reported efficacy/ outcomes	Serious AEs
	Sharon[80]	CR	1	55/1M	ISO, ATBs, SCS, MTX, ada, MMF	SD 45	Improvement 1/1	None
	Baerveldt[81]	CR	1	39/1F	Diclofenac/misoprostol, colchicine, CsA	SD 45	Improvement 1/1	None
	Santos-Pérez[82]	CR	1	50/1F	ISO, anti-TNFα, SCS	SD 45	Improvement 1/1	
	Blok[36]	open-label study	17	20–53/4M–13F	ATBs, ISO, anti-TNFα, SCS	SD	- HiSCR: 8/17; - DLQI: 07/17	urticaria
	Romani[83]	CS	12	19–60/9M–3F	ATBs, CsA, MTX, AZA, anti-TNFα, Ana	IV loading dose adjusted by weight then SC 90 Q8W	- HiSCR: 8/12; - DLQI: 11/12; - Pain: 11/12	None
	Scholl[84]	CS	3	25–31/2M–1F	ATBs, Ada, dapsone, Secu	IV loading dose adjusted by weight then SC 90 Q8 or 12W	- SAHS: 3/3; - DLQI: 3/3	None
	Takeda[85]	CR	1	29/1M	IFX, SCS	360 IV loading dose then SC 90 Q8W	Improvement 1/1	Non
	Montero-Vichez[86]	CS	10	14–52/6M–4F	ATBs, Ret, CsA, anti-TNFα, SCS, interferon, phototherapy,	SD	-HSPGA: 7/10; - Pain: 8/10	None
	Sánchez-Martínez[87]	CS	6	31–59/3M–3F	ATBs, Ret, MTX, finasteride, AZA, Ada	IV loading dose adjusted by weight then SC 90 Q8W	HiSCR: 3/6	None
	Hollywood[88]	CS	16	22–77/4M–12F	ATBs, Ana, metformine, liragultide, Dap, sironolactone, anti-TNFα.	NA	Improvement 8/16	Recurrent infection
	Smith[89]	CR	1	49/1F	Anti-TNFα.	SD 90	Primary Improvement	Multifocal myositis
	Provini[90]	CR	1	17/1F	ATBs, sironolactone, SCS, Ada	90Q8W then 90Q4W	Improvement 1/1	None
	Valenzuela-Ubiña[91]	CS	10	26–58/4M–6F	ATBs, Ret, MTX, finasteride, AZA, SCS, metformin, Dap, Ana, CsA, Anti-TNFα.	- 9 patients: 90Q8W; -1 patient: SD 45	-HSPGA: 9/10	None
Neutrophilic diseases								
PG	Goldminz[92]	CR	1	47/1M	SCS, Dap, MTX, CsA, AZA, Anti-TNFα.	90Q4W then 90Q8W	Complete healing	None
	Cosgarea[93]	CR	1	71/1M	SCS, CsA	NA	Complete healing	None
	Benzaquen[94]	CR	1	56/1F	Ada	SD 45	Complete healing	None
	Guenova[37]	CR	1	37/1F	SCS	Two doses 45Q4W	Complete healing	None

(continued)

Table 1. *(continued)*

Cutaneous disorders	Study	Study design	No of patients	Patient (s) Age (y)/sex	Prior systemic treatment	Ustekinumab dose (mg)	Reported efficacy/ outcomes	Serious AEs
	Nunes[95]	CR	1	45/1M	SCS, IFX, AZA, CsA	520 IV loading dose then SC 90 Q8W	Complete healing	None
	Piqueras-García[39]	CR	1	33/1F	SCS, 6-Mercaptopurine, CsA, Anti-TNFα, vedolizumab, tacrolimus	90 week 0, 4, 10 then Q8W	Complete healing	None
	Petty[40]	CR	1	50/1F	SCS, CsA, IFX	90 week 0, 4 then Q8W	Complete healing	None
	Low[96]	CS	3	36 –57/3F	SCS, MMF, Dap, IVIG	-1 patient: 90 week 0, 4 then Q6W then 45 Q3W; -2 patient: 90 week 0, 4 then Q8W then 45 Q4W	Complete healing 3/3	None
	Greb[97]	CR	1	50/1M	SCS, CsA, Anti-TNFα, Dap	90 Q8W then 90 Q6W then 135 Q6W	Significant improvement	None
	Fahmy[98]	CR	1	34/1F	Tacrolimus, AZA	90 week 0, 2 then Q8W	Complete healing	None
	López González[99]	CR	1	29/1F	ATB, SCS, Ada	260 IV loading dose then SC 90 Q8W	Complete healing	None
	Vallerand[100]	CR	1	47/1M	SCS, IVIG, MMP	520 IV loading dose then SC 90 Q8W	Significant improvement	None
	Nieto[101]	CR	1	62/1M	Ada, Azacytidine, CsA, IFX, IVIG, Thalidomide, SCS	90 Q8W	Complete healing	None
	Westerdahl[102]	CS	8	24–88/4M–4F	SCS, Anti-TNFα, colchicine, Ixe, ATB,	-3 patients: 90 Q8W; -1 patient: 90 Q12W; -2patients: 45 Q12W; -1 patient: 45 Q8W; -1 patient: 180 Q8W	Complete healing 7/8, improvement 1/8	None
	de Risi-Pugliese[38]	CS	4	30–44/1F	AZA, IFX, MTX, Ada, AZA, aminosalicylates, Mercaptopurine	-2 patients: 90 Q8W; -1 patient: 90 Q2W then Q8W; -1 patient: 90 Q4W then Q8W	Complete healing ¾; Significant improvement 1/4	None
APF			2	32 and 41/2F	SCS, Dap, ISO, CsA, colchicine, Ana, ATB, Ada	-1 patient: 90 Q8W; -1 patient: 90 week 0, 2 then Q8W	Significant improvement 2/2	None
SS			1	28/1M	Colchicine, MTX, SCS, Ada, Dap	90 Q8W	Fail 1/1	None
BD	Baerveldt[81]	CR	1	39/1F	diclofenac/misoprostol, colchicine, CsA	SD 45	Remission	None
	Lopalco[103]	CR	1	36/1F	SCS, colchicine, MTX, CsA, AZA, Anti-TNFα, Ana	SD 45	Remission	None

(continued)

Table 1. *(continued)*

Cutaneous disorders	Study	Study design	No of patients	Patient (s) Age (y)/sex	Prior systemic treatment	Ustekinumab dose (mg)	Reported efficacy/ outcomes	Serious AEs
	Mirouse[41]	Prospect-ive study	14	34–41/10M–4F	Colchicine, AZA, SCS, MMF, tocilizumab, tacrolimus	-11 patients: SD 90; -3 patients: SD 45	-Complete response: 9/14; -Partial response: 3/14; -Fail: 2/14	None
	Mirouse[104]	open-label study	30	33–45/16M–14F	Colchicine, SCS, thalidomide, hydroxyl-chloroquine, MTX, cyclophosphamide, AZA, MMF, everolimus.	SD 90	-Complete response: 18/30; -Partial response: 9/30; -Fail: 3/30	None
	London[105]	open-label study	15	NA/9M–6F	Colchicine, SCS	SD 90	-Complete response: 9/15; -Partial response: 2/15; -Fail: 4/15	None
AD	Puya[106]	CR	1	21/1F	SCS, UVB, CsA, Efa	SD 45	Complete response	None
	Agusti-Mejias[107]	CR	1	16/1F	SCS, phototherapy, AZA, CsA	SD 45	Complete response: SCORAD 0	None
	Shroff[108]	CR	1	70/1F	UVB, CsA, MMF	45 week 0, 3, 11 and 19	Complete response: SCORAD 0	None
	Fernández-Antón Martínez[42]	CS	4	23–29/4M	SCS, phototherapy, AZA, CsA, MTX, MMF	SD 45	Significant improvements	None
	Lis-Święty[109]	CR	1	21/1M	None	SD 45	Exacerbation	None
	Ishiuji[110]	CS	2	59 and 39/1M and 1F	None	SD 45	Exacerbation	None
	Samorano[111]	CS	2	47 and 20/1M and 1F	phototherapy, SCS, CsA, MTX, MMF, Eta	-1 patient: SD 45; -1 patient: 45 week 0, 6, 12	Fail 2/2	None
	Nic Dhonncha[112]	CS	10	20–50/8M–2F	phototherapy, AZA, CsA, MMF, Eta, Efa	SD 45 or 90	Significant improvements: 4/10; Fail: 6/10	None
	Saeki[113]	RCT phase 2	52 vs 27 placebo	20–57/36M–16F	phototherapy, SCS, CsA	SD 45 or 90	No significant improvement	None
	Wlodek[114]	CR	1	13/1F	SCS, AZA, CsA, MTX, MMF	SD 45	Partial improvement	None
	Khattri[115]	RCT phase 2	16 vs 15 placebo	NA/10M–16F	NA	SD 45 or 90	No significant improvement	None
	Weiss[116]	CS	3	27–55/2M–1F	SCS, phototherapy, CsA, MMF	45 week 0, 4, 12 then Q8W	Improvement 3/3	None
AA	Guttman-Yassky[43]	CS	3	NA/2M–1F	NA	SD 90 (3 doses)	Improvement 3/3	None
	Aleisa[44]	CS	3	9–16/3F	SCS,	1 patient: 90 week 0, 12, 24; 2 patients: one dose 90	Significant hair regrowth 3/3	None

(continued)

Table 1. *(continued)*

Cutaneous disorders	Study	Study design	No of patients	Patient (s) Age (y)/sex	Prior systemic treatment	Ustekinumab dose (mg)	Reported efficacy/ outcomes	Serious AEs
	Ortolan[117]	CS	4	8–44/2M–2F	SCS, CsA, MTX, ruxolitinib, tofacitinib	1 patient: 45 week 0, 60 week 90 week 12, 20; 1 patient: 90 Q8W; 2patients: 90 week 0, 4, 12	Fail 4/4	None
	Elkady[34]	CR	1	39/1F	Vitamines B complex	90 week 0, 4 then Q8W	Hair regrowth	None
Vitiligo					None		Repigmentation	
SAPHO	Wendling[46]	CS	3	32–61/3F	Phototherapy, MTX, CsA, Anti-TNFα	SD 90	Remission 1/3	Paradoxical psoriasis
	Firinu[117]	CR	1	NA/1F	anti-TNF-α, Ana	SD 90	Significant improvement	None
LP	Solimani[47]	CS	1	72/1F	CsA, SCS, Aci,AZA	SD 45	Significant improvement	None
	Webster[48]	CR	1	70/1F	Hydroxychloroquine	SD 45	Fail	None
LP pemphigoides	Knisley[118]	CR	1	71/1F	Cycline, nicotinamide, SCS, Dap, AZA, MMF Hydroxychloroquine	SD 45	Significant improvement	None
BP	Loget[49]	CR	1	88/1F	None	SD 45	Remission	None
antilaminin-γ1 pemphigoid	Majima[119]	CR	1	69/1M	SCS, Ada	NA	Remission	None
Cutaneous lupus	De Souza[120]	CR	1	58/1F	NA	SD 45	Remission	None
	Varada[122]	CS	1	68/1F	NA	NA	Remission	None
	Dahl[51]	CR	1	79/1F	SCS, hydroxychloroquine, AZA, thalidomide, MTX, IV IG	45 week 0, 4, 16, 34	Improvement	None
	Winchester[50]	CR	1	41/1M	MTX, hydroxychloroquine, CsA	SD 45 then 90	Significant improvement	None
	Mazgaj[122]	CR	1	65/1F	Chloroquine, Aci, MTX, CsA, thalidomide, lenalidomide, alitretinoin.	SD 45 then 90 Q8W	Remission	None

AA, alopecia areata; ACH, Acrodermatitis continua of Hallopeau; Aci, acitretine; AD, atopic dermatitis; Ada, adalimumab; AEs, adverse events; Ana, anakinra; anti-TNFα, tumor necrosis factor α inhibitor; APF, Amicrobial pustulosis of the folds; Apr, apremilaste; ATB, antibiotic; AZA, azathioprine; BD, Behçet disease; BP, bullous pemphigoid; CR, case report; CS, case series; CsA, cyclosporine; Dap, dapsone; Efa, efalusumab; EP, erythrodermic psoriasis; Eta, etanercept; GP, generalized psoriasis; GPP, generalized pustular psoriasis; HS, Hidradenitis suppurativa; IFX, infleximab; ISO, isotrétinoïne; IV IG, intravenous immunogolobulines; IV, intravenous; Ixe, ixekizumab; LP, lichen planus; MMF, mycophenolate mofetil; MTX, methotrexate; PG, pyoderma gangrenosum; PPP, palmoplantar pustuloses; PRP, Pityriasis rubra pilaris; Q(number)W, every (number) week; Ret, retinoid; SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis; SC, subcutaneous; SCS, systemic corticosteroids; SD, ustekinumab at weeks 0, 4, and then every 12 weeks. Weight <100 kg, 45 mg/weight >100 kg, 90 mg; secu, secukinumab; SS, Sweet syndrome.

logical therapy.[124] Successful use of ustekinumab in recalcitrant GP has been reported in only a few of cases. For example, Brummer *et al*[26] reported that treatment with ustekinumab successfully cleared lesions in six patients with resistant GP.

EP accounts for 1–2.25% of all cases and represents one of the most severe and potentially life-threatening subtypes of psoriasis. It manifests as erythema covering >75% of the entire skin surface.[123] There is little scientific evidence that supports biological therapy in EP owing in part to the paucity of high-quality studies. However, the efficacy of ustekinumab in this rare form of psoriasis was highlighted in multiple clinical studies[27–29,125,126] with impressive response despite the failure of a first-line anti-TNFα therapy. A multicenter retrospective study in Italy showed that 80% of EP patients achieved PASI 75 following treatment for seven months.[27]

PP is a rare form of psoriasis characterized by non-follicular small pustules on erythematous and edematous skin. There are three clinical forms of PP: generalized form (GPP), palmoplantar pustulosis form (PPP), and acrodermatitis continua of Hallopeau (ACH). It was postulated that the formation of pustules is caused by elevated levels of certain immune mediators, including IL-17F and IL-8, which can be targeted specifically by IL-23/IL-17 blockers. GPP (also known as von Zumbusch disease) can cause serious complications and can be life-threatening, especially if not diagnosed early and treated appropriately.[123] There are only a few case reports[30,31] and one case series[32] of GPP that have been successfully treated with ustekinumab. Arakawa *et al*[123] reported that ustekinumab therapy led to remission in four GPP cases for 17 months. PPP is a chronic, debilitating form of PP and is usually resistant to treatment. PPP manifests pustules as an erythematous base, hyperkeratosis, and scales, affecting both palms and soles.[123] Despite the lack of sufficient evidence supporting ustekinumab use for PPP, there have been some reports of a satisfactory response among patients with PPP, including significant improvement in the QoL.[127,128] ACH is an uncommon disease presenting with long-lasting sterile pustules specifically affecting the extremities of the digits.[123] This form of PP has been found invariably recalcitrant to available antipsoriatic therapies. There are some case reports and one retrospective study on the efficacy of ustekinumab in the treatment of ACH.[33–35] Treatment with ustekinumab effectively improved clinical symptoms in seven patients with ACH and cleared skin lesions in 75% of patients, similar to that of anti-TNFα therapy.

Ustekinumab for pityriasis rubra pilaris (PRP)

PRP is a rare disease characterized by erythematous and papulosquamous eruption and is classified into six major types depending on clinical aspects, age of disease onset, and outcome.[129] The etiology of PRP is still not completely understood, and its management relies heavily on small clinical studies. There are diverse treatments for PRP with varying outcomes, including topical corticosteroids, phototherapy, systemic retinoids, and immunosuppressive drugs. In recalcitrant cases, anti-TNFα therapy can significantly improve clinical symptoms, supporting the immunological pathogenesis theory. In refractory PRP cases, ustekinumab has been reported to be valuable. A review of the PubMed database and the Cochrane Library until September 2017 by Kromer *et al*,[130] included all studies that evaluated the risks and benefits of systemic treatments for PRP. There were about 182 studies (including 475 patients) on systemic treatment of PRP. Ustekinumab was successful in 62.5% of patients compared to adalimumab (46.4%), etanercept (53.3%), and infliximab (57.1%). The comparison between ustekinumab and acitretin (which is commonly considered as a reference treatment in PRP) showed a substantially elevated rate of excellent response in patients treated with ustekinumab (p = 0.001). The general AE reporting rate was 26.4%, but this was significantly elevated with retinoids (34.1%) then MTX (16.5%) and the lowest proportion was reported with biological agents (8.8%).

Ustekinumab for hidradenitis suppurativa (HS)

HS is a long-term inflammatory dermatosis that often causes serious morbidity and manifests mostly after puberty with inflamed nodules and painful deep-seated abscesses with sinus tracts mainly localized in body zones rich in apocrine glands including axillary and anogenital areas.[131] Although some drugs have been proven to be successful in managing HS symptoms, there is a lack of solid evidence supporting them. The pathogenesis of HS is complex, but TNFα and IL-17 are recognized as central players in HS pathogenesis.[132] One study suggests that gene polymorphisms in IL12Rβ1 may be linked to some severe forms of HS.[133] Currently, adalimumab, a type of anti-TNFα antibody, is the only biological agent available for the treatment of HS.[134] However, failure of treatment was common and consideration of second-line biological drugs, like ustekinumab, may be valuable for inhibiting Th17 responses. In this perspective, an open-label, uncontrolled trial was conducted in 17 patients with HS to determine the benefit of ustekinumab therapy. At week 40 when the clinical trial ended, 47% of patients achieved HiSCR-50 (50% improvement in HS inflammatory lesions), and >82% of cases obtained moderate or remarkable relief of their modified Sartorius score.[36]

Ustekinumab for neutrophilic diseases

Pyoderma gangrenosum (PG), Sweet syndrome (SS), subcorneal pustular dermatosis, and erythema elevatum diutinum are heterogeneous diseases that may be grouped as neutrophilic dermatoses (ND) hallmarked by a sterile, neutrophil-rich infiltrate on the skin.[135] Clinical management of ND is challenging due to the lack of universally accepted and validated guidelines. The standard treatment for idiopathic PG and SS is systemic corticosteroids, whereas dapsone is the first line of treatment for subcorneal pustular dermatoses.[136] However, the use of biological therapy, primarily TNFα blockers, anti-IL-1, anti-IL-17, and anti-IL-23, is rapidly expanding for the management of widespread and aggressive PG.[137] Although detailed knowledge of how biological drugs work for ND is lacking, the expression of several cytokines, including TNFα, IL-8, IL-17, and IL-23, is up-regulated in PG, which may explain the favorable clinical results obtained with biological agents such as ustekinumab.[37] A literature search found 21 out of 23 ND patients had responded positively to ustekinumab (17 PG, 4 amicrobial pustulosis of the folds, 1 Bowel-associated dermatosis-arthritis syndrome, and 1 SS), 16 (70%) were complete responders and 5 (21%) were partial responders, whereas no responses were seen in one PG and one chronic recurring Sweet syndrome.[38–40,138]

Ustekinumab for muco-cutaneous manifestations of Behçet disease (BD)

BD is a primary vasculitis that manifests specifically as repetitive attacks of oral-genital ulcers, cutaneous inflamed lesions, and uveitis with multiple organ system involvement, including the gastrointestinal, cardiopulmonary and nervous systems.[139] Whereas systemic vasculitis may lead to worse outcomes, repetitive aphthous ulcers often lead to substantial QoL impairment. These mucocutaneous lesions could be managed with colchicine, azathioprine, thalidomide, and more recently apremilast, although with varying success and potential serious AEs. However, increased knowledge of the immune mechanisms responsible for BD has prompted the

use of biological drugs to manage the more intractable mucocutaneous lesions. One randomized controlled, 4-week trial and several observational studies and case series have showed that TNF-α inhibitors are promising treatment options for recalcitrant mucocutaneous disease.[140] Additionally, emerging evidence suggests that Th1 and Th17 responses may contribute to the pathogenesis and progression of BD. This, together with higher IL23 levels and Th17/Th1 ratios in BD patients, suggest that ustekinumab may be reasonable and effective for the management of BD. In support of this, ustekinumab has been demonstrated to be effective in ameliorating recalcitrant oral aphthous ulcers in BD patients in clinical trials.[41,140]

Ustekinumab for atopic dermatitis (AD)

AD is a frequent pruritic inflammatory dermatosis, which commonly follows a remitting-relapsing chronic course and commonly develops in a patient with atopic diathesis.[141] The pathogenesis of AD is thought to be both skin barrier alteration and immune system dysfunction. The conventional treatments rely on topical anti-inflammatory drug medication and adequate skin hydration. However, systemic immunosuppressant medications are required for moderate to severe forms of the disease; although they are discouraged, owing to their transient efficacy and a poor AE profile.[142] The identification of new immune targets involved in the process of AD has prompted the development of innovative therapeutics, including biological therapy and small molecules. Studies have showed that IL17 and IL22 expression are upregulated in AD lesions and represent therapeutic targets for ustekinumab treatment.[42] Indeed, many studies have investigated the efficacy of IL-12/IL-23 inhibitors for patients with recalcitrant AD. Pan Y *et al*[143] conducted a systematic review on the current scientific literature up to September 2017 concerning the benefits of ustekinumab in AD. They found that this biological drug has been administered in 8 case reports and 2 randomized placebo-controlled trials (RCTs) of 107 cases. In general, the observational studies have shown more clinically relevant effects, whereas RCTs have not shown a significant advantage of ustekinumab over the placebo.

Ustekinumab for Alopecia Areata (AA) and Vitiligo

AA is a common IMD that causes temporary and permanent non-scarring alopecia.[144] Treatment of AA by conventional systemic therapy is hampered by its AEs and limited efficacy. Nevertheless, the discovery of the role of various immunological mediators, including Th1, Th2, and IL-23, in the pathological process of AA has opened a door to test the efficacy of ustekinumab for AA.[145] There are some reports on the therapeutic efficacy of ustekinumab for new onset AA and some cases with hair regrowth.[146] Guttman-Yassky *et al*[43] demonstrated that treatment with ustekinumab for 20 weeks improved clinical symptoms in three moderate-to-severe AA patients without AEs. Likewise, ustekinumab has safely ameliorated clinical symptoms in three pediatric patients with mild, moderate, and severe AA.[44]

Vitiligo is also a long-lasting IMD and consists of depigmented skin macules. Like AA, Th17 cells are the major immune players in vitiligo pathogenesis.[147] Therefore, it is reasonable to test the therapeutic efficacy and safety of ustekinumab for vitiligo. However, there is only one report on the use of ustekinumab for repigmentation in a patient with both psoriasis and vitiligo, and these findings contrast other observations.[45,148,149]

Miscellaneous

Ustekinumab has been reported for the treatment of miscellaneous cutaneous disorders, like SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis), lichen planus (LP), bullous pemphigoid (BP), and lupus erythematosus (LE). Some data have demonstrated an aberrant Th17 response in SAPHO patients, which suggests that ustekinumab may be promising for SAPHO syndrome.[46] However, only 5 SAPHO cases have been treated with IL-12/IL-23 blockers with mixed results on cutaneous symptoms, as less than half of the patients had improved symptoms.[150]

There is little evidence on the efficacy of IL12/IL23 blocker for LP. Although treatment with ustekinumab was reported to remarkably improve extensive erosive oral LP in one report,[47] ustekinumab treatment failed to show any efficacy in another report with concomitant psoriasis and erosive LP.[48] There are controversial reports on the therapeutic effect and deteriorative outcomes of ustekinumab in BP patients.[151,49]

Regarding systemic LE, a phase II RCT conducted by Ronald van Vollenhoven *et al*[152] to test the therapeutic effect of ustekinumab in 102 active systemic LE patients has revealed that addition of ustekinumab to standard therapy enhances therapeutic efficacy. Although peculiar cases of ustekinumab-induced lupus-like cutaneous reactions have been reported, many successful cases have been widely reported on the therapeutic efficacy of ustekinumab for cutaneous and discoid LE.[50,51,153]

AEs observed with ustekinumab

Most AEs associated with ustekinumab use are non-serious, occasional, and usually do not lead to drug discontinuation.[154] The most commonly encountered AEs are headaches, asthenia, abdominal pain, and upper respiratory infections. Local injection site reactions are also usually mild in severity and infrequent, probably due to a minimal injection regimen.[3] Moreover, there have been no reported differences in the frequency of AEs or abnormal laboratory tests between ustekinumab- and placebo-treated patients in clinical trials.[154]

IL-17 is a pro-inflammatory cytokine that can participate in immune responses against bacterial and fungus infections. Therefore, treatment with ustekinumab to block the IL-12/IL-17-related signaling may increase susceptibility to infections.[155] However, the infectious risk due to ustekinumab was low in clinical trials. Furthermore, analysis of published register-based data did not show higher rates of severe infections when comparing ustekinumab to either anti-TNF agents or conventional systemic therapies.[156,157] In particular, the potential risk of active tuberculosis infection due to ustekinumab seems to be reduced when compared to TNFα inhibitors.[158] In addition to infectious hazards, the most reported AEs of ustekinumab treatment are the risk of major adverse cardiovascular events (MCCEs); a meta-analysis of RCTs in 2011 reported an increase in MCCEs during the first months of drug exposure, although there was no significant increase in the frequency of MACEs when compared to placebo.[159] This report is correlated with experimental studies, in which the IL23/IL17 pathway negatively affects atherosclerotic plaques stability. Nonetheless, a case-control study of ustekinumab from the French National Health Insurance database involving more than 9,000 subjects during the period of 2010–2016, revealed a significant link between ustekinumab therapy and the onset of acute coronary syndrome, while stroke was identified only with high cardiovascular risk patients.[160] Another important concern regarding ustekinumab use is its potential oncogenic effect. Animal-based studies have revealed that blockade of IL12/IL23 signaling may increase the risk of malignancies.[161] However, despite scarce reports of

Table 2. Skin adverse events associated with ustekinumab

Adverse event categories	Specific skin reactions
Skin lesions related to the administration of treatment	Bruising, pruritus, pain, erythema, swelling, skin rash
Skin infections	Bacterial infections: cellulitis, mycobacterium abscessus, secondary syphilis, staphylococcal skin colonization; Viral infections: disseminated verrucae, condyloma acuminate, herpes zoster; Fungal infection: cutaneous candidiasis, Nocardia infection, disseminated sporotrichosis; Parasitic infections: plurifocal cutaneous leishmaniasis, cutaneous protothecosis
Skin neoplasia	Non melanoma skin tumors: basocellular carcinoma, spinocellular carcinoma; Malignant melanoma; Skin lymphomas/Lymphoproliferative disorders: Jessner-Kanof type, anaplastic large T cell lymphoma, mycosis fungoides; Multiple dermatofibromas
Immune mediated diseases	«de novo» psoriasis and exacerbation of prior psoriasis or psoriasis subtypes; Atopic-dermatitis and its exacerbation; Lupus-like paradoxical reaction; Alopecia areata; Skin vasculitis; Vitiligo; Dermatomyositis; Localized scleroderma (morphea); Lichen or lichenoid reaction; Frontal fibrosing alopecia; Linear IgA bullous dermatosis; bullous pemphigoid; Erythema multiforme; Erythroderma, exfoliative dermatitis and hypersensitivity reaction; Erythematous annular eruptions; Fixed drug eruption; Urticaria
Other skin events	Hidradenitis suppurativa; Seborrhoeic keratosis; Thrombotic thrombocytopenic purpura; Sarcoidosis-like paradoxical reaction; Wells syndrome; Erythema annulare centrifugum; Cutaneous focal mucinosis; Lentigines; Spiny follicular hyperkeratosis

IgA, Immunoglobulin A.

malignant tumors, cancer incidence itself was low in clinical trials and in register-based data.[157] There are neither observational studies, nor case reports on any increase of adverse outcomes in pregnant women.

Furthermore, ustekinumab treatment-related uncommon cutaneous and systemic AEs have been reported, including immune-mediated dermatological disorders. The most reported skin and systemic AEs associated with ustekinumab use are summarized in Tables 2 and 3, respectively.

Despite the reassuring data, the real-life, long-term safety of ustekinumab application still requires investigation across international, multicentric registry-based cohorts and from long-term outcome trials. Hence, greater vigilance should be applied when starting treatment: a thorough history, a holistic clinical examination with careful assessment for active infections (screening for possible tuberculosis, checking cardiovascular and neurological functions and ruling out any malignancy), along with laboratory workup (complete blood count and metabolic profile) should be considered before the initiation of ustekinumab. Subsequent laboratory tests and follow-up monitoring are recommended.

Future prospects

Currently, a myriad of biological drugs (either approved or used off label) are available for the treatment of skin diseases. For psoriasis, physicians have a plethora of biological drugs with different immunological mechanisms that could be used. Nonetheless, some patients can be resistant or show a declining response to biological agents over time.

Combination therapies with biological and conventional systemic drugs are well documented and have become a routine practice for many clinicians. However, for patients with a severe, debilitating skin disease, who do not respond to biological monotherapy and combination with conventional systemic agents, dual biological therapy (DBT) could be considered. However, uncertainty in the real safety profile of such a combination still exists, particularly for the high risk of opportunistic infection and MACEs, and data on the safety of such DBT in dermatology remain anecdotal. The limited number of case reports and case series mostly originated from gastroenterology and rheumatology-based studies and/or registries, but DBT has been used in many cases with PsA/psoriasis or inflammatory bowel diseases/psoriasis simultaneously. Available studies have shown that DBT ustekinumab/anti-TNFα blockers have better efficacy than each drug alone, although there are different safety profiles, without serious AEs. In dermatology, only one case of DBT of ustekinumab/adalimumab has been reported in a patient with a long-lasting, resistant PPP for a quasi-complete clearance over 4 months with a good overall tolerance. Thus, a window of opportunity does exist for the use of DBT with ustekinumab and other biological drugs for the treatment of psoriasis or other skin diseases, paving the way to a tailored, personalized treatment regimen. Despite the paucity of data, dermatologists can be inspired from the use of DBT in other fields, like gastroenterology and rheumatology. The main future challenges are to determine the optimal treatment dosing regimen and the best timing for DBT to result in the most effective and safest outcomes for patients.

Conclusions

Continual progression in psoriasis research has revealed the crucial role of Th17 responses in its pathogenesis. The successful treatment with IL-12/IL-23 blockers for moderate-to-severe psoriasis is considered a major scientific breakthrough, being the first non-TNFα targeted biological drug in the treatment of psoriasis and heralded as a new era of more precise biological therapy with higher efficacy and favorable safety profiles. Additionally, the recommended dosage regimen of ustekinumab is appropriate for most patients because its initial efficacy seems to be sustained fairly well over a 5-year treatment duration. The potential risk of infection or other AEs in patients with ustekinumab are mild, similar to that in placebo-treated patients, and there is no evidence of any overall increased risk in post-marketing reports. However, like other new biological drugs, high cost and unknown long-term effects limit the approval of this drug as a first-line treatment for moderate-to-severe psoriasis. Emerging data suggest that ustekinumab may be well tolerated and efficient for HS, PRP, and BD, as well as several

Table 3. Adverse systemic reactions associated with ustekinumab

Adverse reaction categories	Specific systemic reactions
Systemic allergic reactions to the administration of treatment	Flushing, anaphylactoid reaction, nausea, vomiting, blurred vision and/or confusion, dizziness, difficulty in breathing
Whole body (general disorders)	Asthenia, Flu-like symptoms, myalgia, anorexia, depression, sleep disturbance
Infections	*Bacterial infections*: latent tuberculosis reactivation, miliary tuberculosis, meningococcal meningitis, pneumonia, Clostridium difficile infection, Mycobacterium fortuitum ventriculoperitoneal shunt infection, perianal abscess, dental abcess, urinary tract infection, Staphylococcus aureus bacteremia with iliac artery endarteritis, Streptococcal sepsis; *Viral infections*: HSV-2 meningitis, Varicella zoster virus meningitis, acute hepatitis B, HBV reactivation, HCV reactivation, herpes simplex virus encephalitis, nasopharyngitis , Respiratory tract infections; *Fungal infection*: mycotic oesophagitis; *Parasitic infections*: Amoebic liver abscess, Ocular toxoplasmosis, severe acute toxoplasmosis
Neoplasia	Anal adenocarcinoma, cancer of anal fistula, endometrial cancer, esophageal cancer, hepatocellular carcinoma, pancreatic adenocarcinoma Malignant peritoneal mesothelioma, Gastric Mucosa-Associated Lymphoid Tissue Lymphoma, Exacerbation of Hodgkin's lymphoma, chronic lymphocytic leukaemia, multiple myeloma, papillary thyroid cancer, breast cancer
Cardiovascular events	Hypertension, congestive heart failure, dilated cardiomyopathy, unstable angina, Vasculitis, central retinal vein and artery occlusion
Gastrointestinal events/ Hepatobiliary events	Acute hepatitis, elevated alanine transferase levels, fatty liver infiltration, diverticulitis, retroperitoneal fibrosis, pancreatitis
Musculoskeletal events	Paradoxical psoriatic arthritis, arthralgia, multifocal myositis, polymyositis, myasthenia gravis
Renal adverse events	Lupus nephritis, new-onset autoantibody-mediated nephritis, nephrotic syndrome, IgA nephropathy, focal segmental glomerulosclerosis
Nervous system events	Headache, neuropathic pain, memory loss, parkinsonism, benign intracranial hypertension, posterior reversible encephalopathy syndrome, demyelination, limbic encephalitis, Facial palsy, reversible cerebral vasoconstriction syndrome, ischaemic stroke, Guillain-Barré syndrome, peripheral neuropathy
Respiratory adverse events	Noninfectious pneumonia, bronchospasm crisis, pneumothorax, sarcoidosis
Urogenital and obstetric events	Urolithiasis; Epididymo-orchitis, erectile dysfunction; Foetal death and miscarriage;
Other systemic events	-Monoclonal gammopathy of undetermined significance; Autoimmune thyroiditis

HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HSV-2, Herpes Simplex Virus-2.

other dermatological conditions, but there are few clinical trials to evaluate the therapeutic efficacy and safety of ustekinumab for these disorders.

This review highlights the significant progression during the past decade on the optimal use of ustekinumab for skin diseases beyond its labeled indications. However, there are some limitations, like the lack of RCTs and the limited amount of available data, especially regarding the off-label use of the biological drug. Further studies with larger cohorts of patients and robust designs are warranted to investigate ustekinumab's efficacy, safety, and long-term effects in off-label uses for other skin diseases.

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Conflict of interest

Dr. Hakim Rahmoune has been an editorial board member of *Journal of Exploratory Research in Pharmacology* since June 2017. The authors have no other conflict of interests to declare.

Author contributions

Contributed to study concept and design (ASC, NB, and HR), acquisition of the data (ASC and HR), data analysis (ASC), drafting of the manuscript (ASC and HR), critical revision of the manuscript (NB and HR), and supervision (ASC).

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