



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, ustekinumab may be used as a potential alternative for treatment of a variety of inflammatory skin conditions. More importantly, ustekinumab 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 a 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.

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 (TNF α), a potent inflammatory mediator associated with various IMD, such as rheumatologic, dermatologic, and gastroen-

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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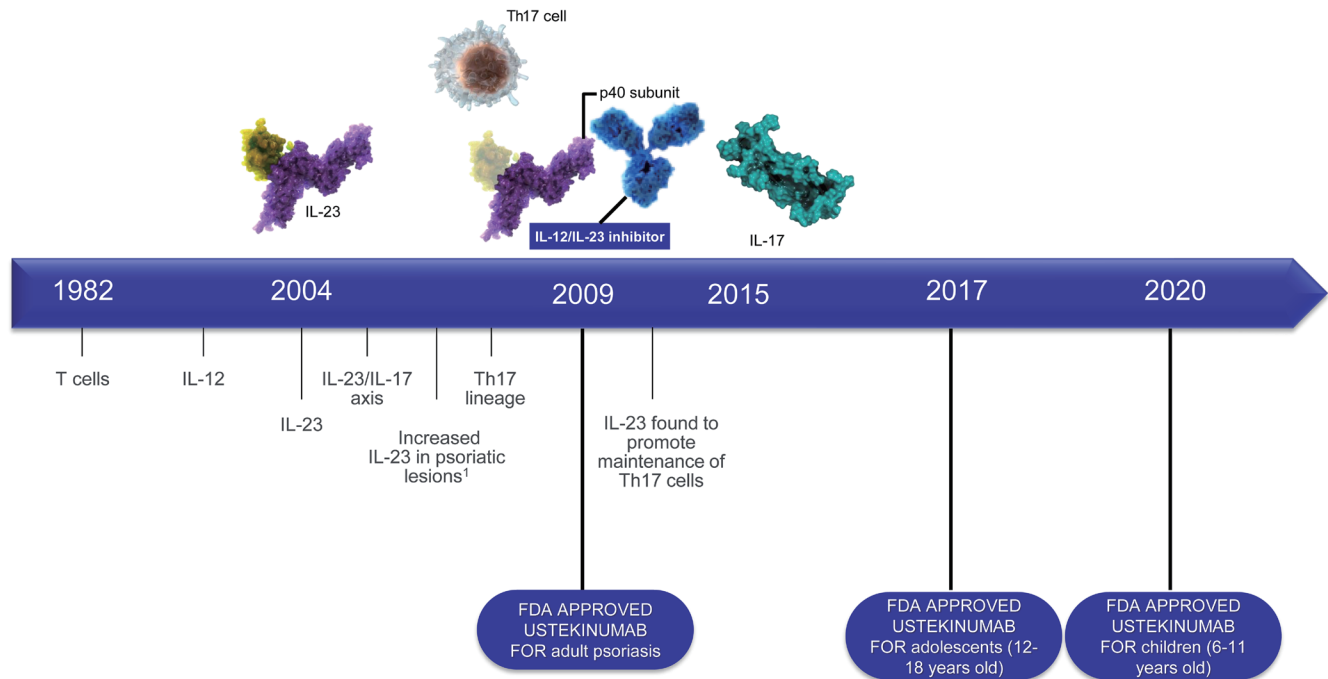


Fig. 1. Timeline of the development and approval of ustekinumab for psoriasis. FDA, Food and Drug Administration; IL, Interleukin; Th, T-helper.

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 (IL12R β 1/IL12R β 2), 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 (IL12R β 1/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, IL12R β 1. 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 TNF α -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

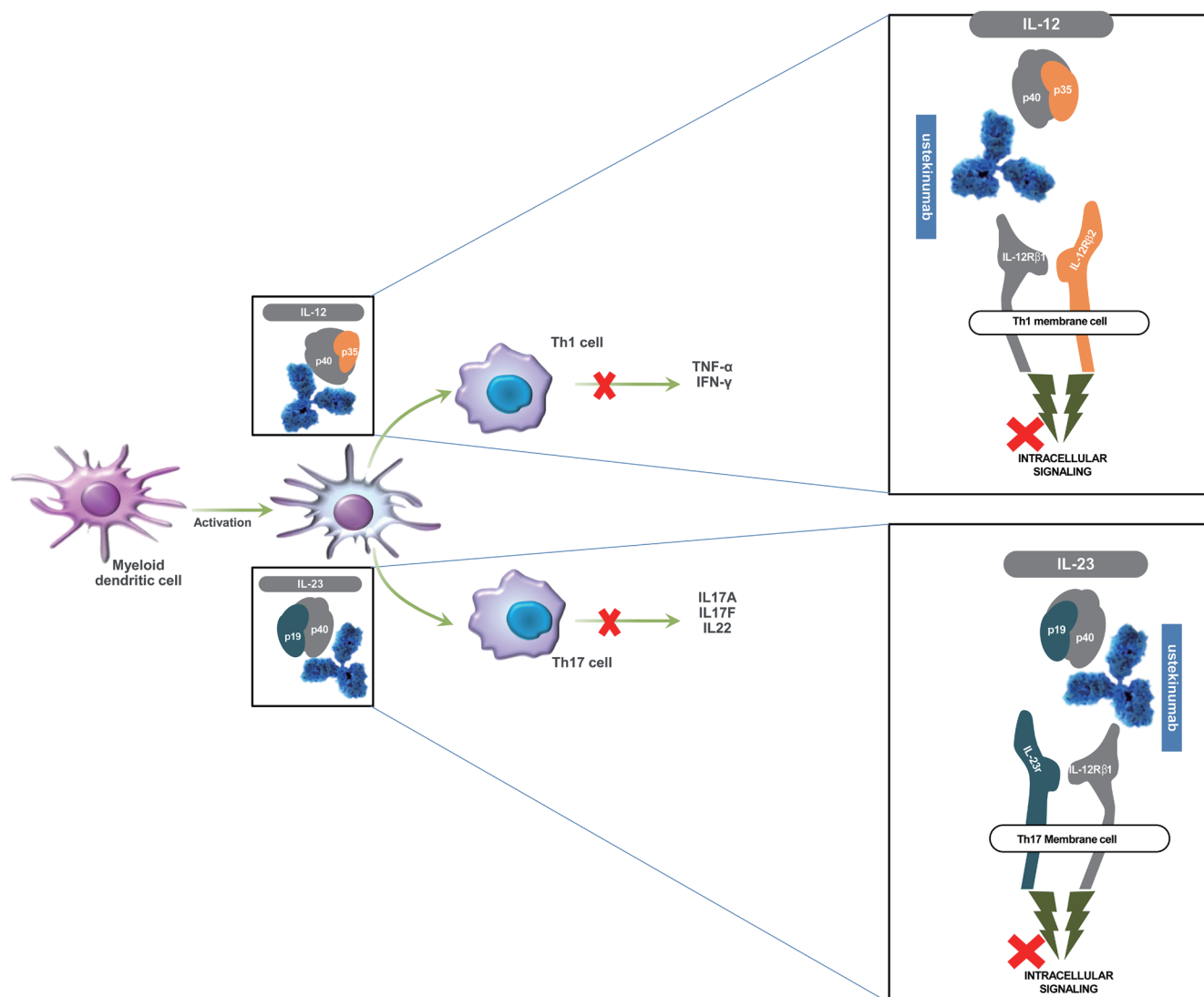


Fig. 2. The mechanisms of actions of ustekinumab in inflammatory skin diseases. IFN: Interferon; IL: Interleukin; Th: T-helper; TNF: Tumor necrosis factor.

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

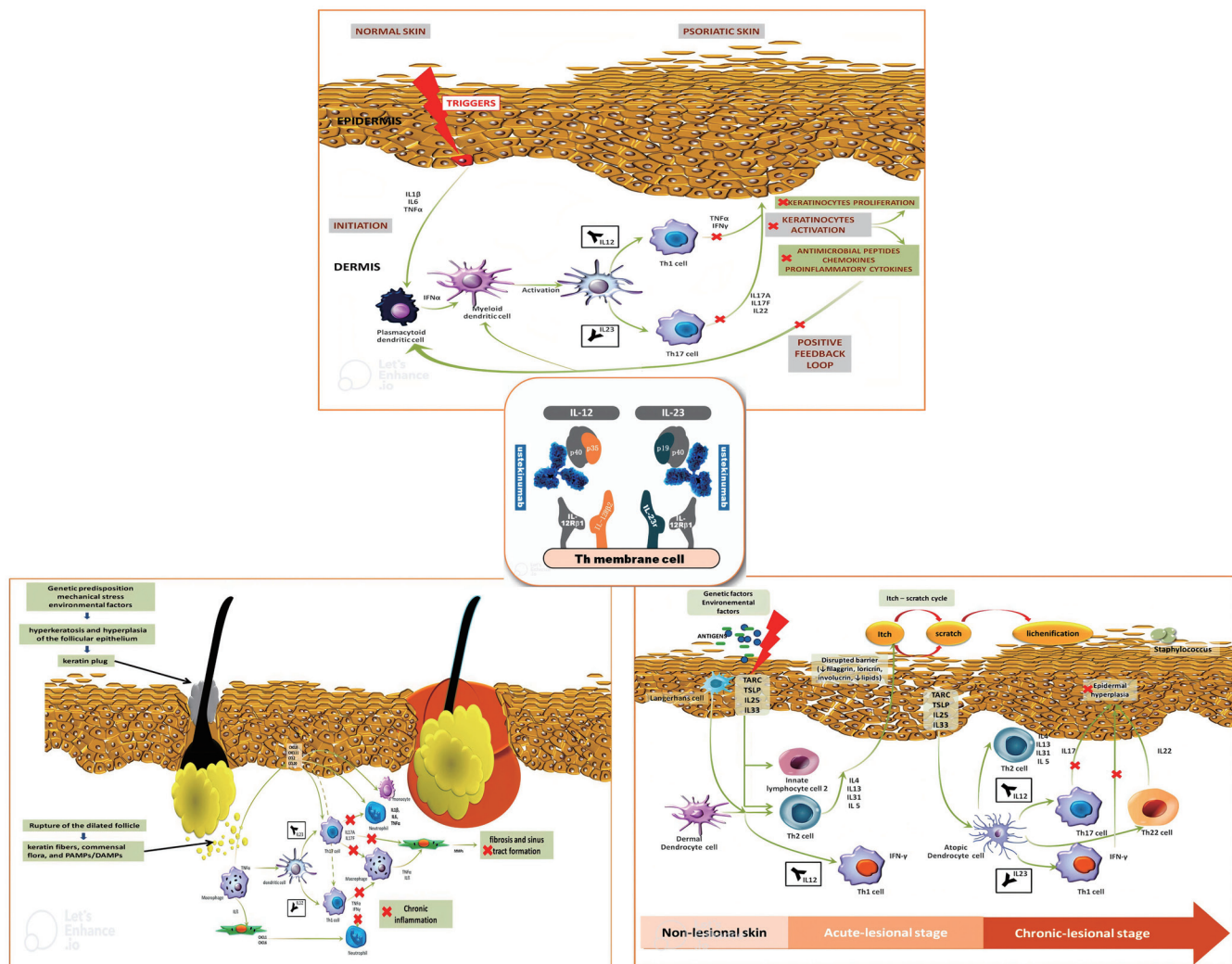


Fig. 3. Therapeutic effect of ustekinumab on psoriasis (top figure), atopic dermatitis (lower right figure), and hidradenitis suppurativa (lower left figure). IFN, interferon; IL, Interleukin; Th, T-helper; TNF, Tumor necrosis factor; TARC, thymus and activation regulated chemokine; TSLP, thymic stromal 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 a many skin diseases given its distinct and targeted mechanism of action. However, robust evi-

dence 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-TNF α	SD	Success 2/2; PASI 90	None
	Viguer ⁵³	CS	3		Anti-TNF α	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-TNF α	-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-TNF α	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-TNF α	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-TNF α	SD	Success 5/5	None
	Au ⁵⁶	open-label study	20	18–85/9M–11F	Systemic therapy, anti-TNF α	SD	Improvement 12/20, Clearance 7/20	None
	Bulai Livideanu ⁵⁷	CS	2	29 and 42/1F and 1M	CsA, MTX, Ret, phototherapy, anti-TNF α	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-TNF α	Start 90 then SD 45	Success 1/1	None
	Palacios-Alvarez ³³	CR	1	67/1M	MTX, phototherapy, Aci, anti-TNF α	SD 45	Success 1/1	None
	Saunier ⁶⁰	CR	1	53/1M	Aci, MTX, phototherapy, CsA, anti-TNF α , 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
PRP	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
	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-TNF α	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-TNF α , 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
HS	Craiglow ⁷⁶	CS	6	NA	NB-UVB, PUVA, Ret, MTX, CsA, anti-TNF α	-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
	Gulliver ⁷⁹	CS	3	30–32/1M–2F	ATBs, Ret, anti-TNF α , 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	urticaria
	Blok ³⁶	open-label study	17	20–53/4M–13F	ATBs, ISO, anti-TNFα, SCS	SD	- HISCR: 8/17; - DLQI: 07/17	
	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, liraglutide, Dap, sirolactone, anti-TNFα.	NA	Improvement 8/16	Recurrent infection
	Smith ⁸⁹	CR	1	49/1F	Anti-TNFα.	SD 90	Primary Improvement	Multifocal myositis
	Provin ⁹⁰	CR	1	17/1F	ATBs, sirolactone, 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-TNF α , 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-TNF α , 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-TNF α , colchicine, lxe, ATB,	-3 patients: 90 Q8W; -1 patient: 90 Q12W; -2 patients: 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, aminosaliclates, Mercaptopurine	-2 patients: 90 Q8W; -1 patient: 90 Q2W then Q8W; -1 patient: 90 Q4W then Q8W	Complete healing %; 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-TNF α , 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
AD	Mirouse ⁴¹	Prospective 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, hydroxychloroquine, 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
	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-Świąty ¹⁰⁹	CR	1	21/1M	None	SD 45	Exacerbation	None
	Ishuiji 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, Efa	-1 patient: SD 45; -1 patient: 45 week 0, 6, 12	Fail 2/2	None
AA	Nic Dhonncha ¹¹²	CS	10	20–50/8M–2F	phototherapy, AZA, CsA, MMF, Efa	SD 45 or 90	Significant improvements: 4/10; Fail: 6/10	None
	Saek 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
	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
Vitiligo	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; 2 patients: 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
SAPHO	Wendling ⁴⁶	CS	3	32–61/3F	Phototherapy, MTX, CsA, Anti-TNF α	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	SD 45	Significant improvement	None
					Hydroxychloroquine			
BP	Loget ⁴⁹	CR	1	88/1F	None	SD 45	Remission	None
	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
	Mazga 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-TNF α , tumor necrosis factor α inhibitor; APF, Amicrobial pustulosis of the folds; Apr, apremilast; ATB, antibiotic; AZA, azathioprine; BD, Behçet disease; BP, bullous pemphigoid; CR, case report; CS, case series; CsA, cyclosporine; Dap, dapson; Efa, efalunumab; EP, erythrodermic psoriasis; Eta, etanercept; GP, generalized psoriasis; GPP, generalized pustular psoriasis; HS, Hidradenitis suppurativa; IFX, infliximab; ISO, isotretinoin; IV IG, intravenous immunoglobulins; IV, intravenous; Ixe, ixekizumab; LP, lichen planus; MMF, mycophenolate mofetil; MTX, methotrexate; PG, pyoderma gangrenosum; PPP, palmoplantar pustulosis; 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-TNF α 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 series³² 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-TNF α 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-TNF α 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 TNF α and IL-17 are recognized as central players in HS pathogenesis.¹³² One study suggests that gene polymorphisms in IL12RB1 may be linked to some severe forms of HS.¹³³ Currently, adalimumab, a type of anti-TNF α 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 TNF α 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 TNF α , 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 dermatitis-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 miscellane-

ous 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 TNF α inhibitors.¹⁵⁸ In addition to infectious hazards, the most reported AEs of ustekinumab treatment are the risk of major adverse cardiovascular events (MACEs); a meta-analysis of RCTs in 2011 reported an increase in MACEs 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

Table 2. Skin adverse events associated with ustekinumab

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 acuminata, 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; Seborrheic keratosis; Thrombotic thrombocytopenic purpura; Sarcoidosis-like paradoxical reaction; Wells syndrome; Erythema annulare centrifugum; Cutaneous focal mucinosis; Lentigines; Spiny follicular hyperkeratosis

IgA, Immunoglobulin A.

the risk of malignancies.¹⁶¹ However, despite scarce reports of 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-TNF α 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-TNF α 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

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	<i>Bacterial infections</i> : latent tuberculosis reactivation, miliary tuberculosis, meningococcal meningitis, pneumonia, Clostridium difficile infection, Mycobacterium fortuitum ventriculoperitoneal shunt infection, perianal abscess, dental abscess, urinary tract infection, Staphylococcus aureus bacteremia with iliac artery endarteritis, Streptococcal sepsis; <i>Viral infections</i> : HSV-2 meningitis, Varicella zoster virus meningitis, acute hepatitis B, HBV reactivation, HCV reactivation, herpes simplex virus encephalitis, nasopharyngitis, Respiratory tract infections; <i>Fungal infection</i> : mycotic oesophagitis; <i>Parasitic infections</i> : 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).

References

- [1] Benson JM, Peritt D, Scallion BJ, Heavner GA, Shealy DJ, Giles-Komar JM, *et al*. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. *MAbs* 2011;3(6):535–545. doi:10.4161/mabs.3.6.17815, PMID:22123062.
- [2] Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371(9625):1665–1674. doi:10.1016/S0140-6736(08)60725-4, PMID:18486739.
- [3] Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, *et al*. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371(9625):1675–1684. doi:10.1016/S0140-6736(08)60726-6, PMID:18486740.
- [4] Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, *et al*. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis. *J Am Acad Dermatol* 2012;66(4):611–618. doi:10.1016/j.jaad.2011.09.011, PMID:22123062.

- riasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci* 2011;63(3):154–163. doi:10.1016/j.jdermsci.2011.05.005, PMID:21741220.
- [5] Young MS, Horn EJ, Cather JC. The ACCEPT study: ustekinumab versus etanercept in moderate-to-severe psoriasis patients. *Expert Rev Clin Immunol* 2011;7(1):9–13. doi:10.1586/eci.10.92, PMID:21162644.
 - [6] Rawal S, Kianian S, Guo W, Marquez J, Ayasse M, Siamas KA, *et al*. Alternative uses of ustekinumab for non-indicated dermatological conditions: a systematic review. *Arch Dermatol Res* 2022;314(6):503–514. doi:10.1007/s00403-021-02262-7, PMID:34156549.
 - [7] Hernández MV, Meineri M, Sanmartí R. Skin lesions and treatment with tumor necrosis factor alpha antagonists. *Reumatol Clin* 2013;9(1):53–61. doi:10.1016/j.reuma.2012.04.007, PMID:22766431.
 - [8] Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, *et al*. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat Med* 2015;21(7):719–729. doi:10.1038/nm.3895, PMID:26121196.
 - [9] Zundler S, Neurath MF. Interleukin-12: Functional activities and implications for disease. *Cytokine Growth Factor Rev* 2015;26(5):559–568. doi:10.1016/j.cytogfr.2015.07.003, PMID:26182974.
 - [10] Sun L, He C, Nair L, Yeung J, Egwuagu CE. Interleukin 12 (IL-12) family cytokines: Role in immune pathogenesis and treatment of CNS autoimmune disease. *Cytokine* 2015;75(2):249–255. doi:10.1016/j.cyt.2015.01.030, PMID:25796985.
 - [11] Wojkowska DW, Szpakowski P, Glabinski A. Interleukin 17A Promotes Lymphocytes Adhesion and Induces CCL2 and CXCL1 Release from Brain Endothelial Cells. *Int J Mol Sci* 2017;18(5):E1000. doi:10.3390/ijms18051000, PMID:28481289.
 - [12] Wolk K, Haugen HS, Xu W, Witte E, Waggle K, Anderson M, *et al*. IL-22 and IL-20 are key mediators of the epidermal alterations in psoriasis while IL-17 and IFN-gamma are not. *J Mol Med (Berl)* 2009;87(5):523–536. doi:10.1007/s00109-009-0457-0, PMID:19330474.
 - [13] Brembilla NC, Senra L, Boehncke WH. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. *Front Immunol* 2018;9:1682. doi:10.3389/fimmu.2018.01682, PMID:30127781.
 - [14] Chyuan IT, Lai JH. New insights into the IL-12 and IL-23: From a molecular basis to clinical application in immune-mediated inflammation and cancers. *Biochem Pharmacol* 2020;175:113928. doi:10.1016/j.bcp.2020.113928, PMID:32217101.
 - [15] Kimmel GW, Lebwohl M. Psoriasis: Overview and Diagnosis. *Evidence-Based Psoriasis* 2018;1:1–16. doi:10.1007/978-3-319-90107-7_1.
 - [16] Kimmel GW, Lebwohl M. Psoriasis: Overview and Diagnosis. In: Bhutani T, Liao W, Nakamura M (eds). *Evidence-Based Psoriasis: Diagnosis and Treatment*. Cham: Springer International Publishing; 2018:1–16. doi:10.1007/978-3-319-90107-7_1.
 - [17] Mattei PL, Corey KC, Kimball AB. Cumulative life course impairment: evidence for psoriasis. *Curr Probl Dermatol* 2013;44:82–90. doi:10.1159/000350008, PMID:23796812.
 - [18] Sarac G, Koca TT, Baglan T. A brief summary of clinical types of psoriasis. *North Clin Istanbul* 2016;3(1):79–82. doi:10.14744/nci.2016.16023, PMID:28058392.
 - [19] Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *Int J Mol Sci* 2019;20(6):E1475. doi:10.3390/ijms20061475, PMID:30909615.
 - [20] Bianchi E, Rogge L. The IL-23/IL-17 pathway in human chronic inflammatory diseases-new insight from genetics and targeted therapies. *Genes Immun* 2019;20(5):415–425. doi:10.1038/s41435-019-0067-y, PMID:31000797.
 - [21] Jeon C, Sekhon S, Yan D, Afifi L, Nakamura M, Bhutani T. Monoclonal antibodies inhibiting IL-12, -23, and -17 for the treatment of psoriasis. *Hum Vaccin Immunother* 2017;13(10):2247–2259. doi:10.1080/21645515.2017.1356498, PMID:28825875.
 - [22] Rønholdt K, Iversen L. Old and New Biological Therapies for Psoriasis. *Int J Mol Sci* 2017;18(11):2297. doi:10.3390/ijms18112297, PMID:29104241.
 - [23] Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Targeting IL-23 in psoriasis: current perspectives. *Psoriasis (Auckl)* 2018;8:1–5. doi:10.2147/PTT.S98893, PMID:29441315.
 - [24] Kimball AB, Papp KA, Wasfi Y, Chan D, Bissonnette R, Sofen H, *et al*. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study. *J Eur Acad Dermatol Venereol* 2013;27(12):1535–1545. doi:10.1111/jdv.12046, PMID:23279003.
 - [25] Chiu HY, Hui RC, Tsai TF, Chen YC, Chang Liao NF, Chen PH, *et al*. Predictors of time to relapse following ustekinumab withdrawal in patients with psoriasis who had responded to therapy: An 8-year multicenter study. *J Am Acad Dermatol* 2023;88(1):71–78. doi:10.1016/j.jaad.2019.01.035, PMID:30703455.
 - [26] Brummer GC, Hawkes JE, Duffin KC. Ustekinumab-induced remission of recalcitrant guttate psoriasis: A case series. *JAAD Case Rep* 2017;3(5):432–435. doi:10.1016/j.jdc.2017.06.015, PMID:28932788.
 - [27] Pescitelli L, Dini V, Gisondi P, Loconsole F, Piaserico S, Piccirillo A, *et al*. Erythrodermic psoriasis treated with ustekinumab: an Italian multicenter retrospective analysis. *J Dermatol Sci* 2015;78(2):149–151. doi:10.1016/j.jdermsci.2015.01.005, PMID:25681953.
 - [28] Santos-Juanes J, Coto-Segura P, Mas-Vidal A, Galache Osuna C. Ustekinumab induces rapid clearing of erythrodermic psoriasis after failure of antitumor necrosis factor therapies. *Br J Dermatol* 2010;162(5):1144–1146. doi:10.1111/j.1365-2133.2010.09669.x, PMID:20222926.
 - [29] Wang TS, Tsai TF. Clinical experience of ustekinumab in the treatment of erythrodermic psoriasis: a case series. *J Dermatol* 2011;38(11):1096–1099. doi:10.1111/j.1346-8138.2011.01224.x, PMID:21545503.
 - [30] Storan ER, O’Gorman SM, Markham T. Generalized pustular psoriasis treated with ustekinumab. *Clin Exp Dermatol* 2016;41(6):689–690. doi:10.1111/ced.12868, PMID:27333948.
 - [31] Daudén E, Santiago-et-Sánchez-Mateos D, Sotomayor-López E, García-Díez A. Ustekinumab: effective in a patient with severe recalcitrant generalized pustular psoriasis. *Br J Dermatol* 2010;163(6):1346–1347. doi:10.1111/j.1365-2133.2010.09995.x, PMID:20716216.
 - [32] Arakawa A, Ruzicka T, Prinz JC. Therapeutic Efficacy of Interleukin 12/Interleukin 23 Blockade in Generalized Pustular Psoriasis Regardless of IL36RN Mutation Status. *JAMA Dermatol* 2016;152(7):825–828. doi:10.1001/jamadermatol.2016.0751, PMID:27096382.
 - [33] Palacios-Álvarez I, Simal-Gómez G, Mas-Vidal A, Bernad-Alonso I. Treatment of acrodermatitis continua of Hallopeau with ustekinumab as monotherapy after failure of anti-TNF agents. *J Dtsch Dermatol Ges* 2018;16(5):611–613. doi:10.1111/ddg.13506, PMID:29659137.
 - [34] Cymerman RM, Cohen DE. Treatment of Acrodermatitis Continua of Hallopeau With Ustekinumab as Monotherapy. *JAMA Dermatol* 2016;152(3):346–348. doi:10.1001/jamadermatol.2015.3444, PMID:26560053.
 - [35] Husson B, Barbe C, Hegazy S, Seneschal J, Aubin F, Mahé E, *et al*. Efficacy and safety of TNF blockers and of ustekinumab in palmoplantar pustulosis and in acrodermatitis continua of Hallopeau. *J Eur Acad Dermatol Venereol* 2020;34(10):2330–2338. doi:10.1111/jdv.16265, PMID:32030802.
 - [36] Blok JL, Li K, Brodmerkel C, Horvátovich P, Jonkman MF, Horváth B. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. *Br J Dermatol* 2016;174(4):839–846. doi:10.1111/bjd.14338, PMID:26641739.
 - [37] Guenova E, Teske A, Fehrenbacher B, Hoerber S, Adamczyk A, Schaller M, *et al*. Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. *Arch Dermatol* 2011;147(10):1203–1205. doi:10.1001/archdermatol.2011.168, PMID:21680759.
 - [38] de Risi-Pugliese T, Seksik P, Bouaziz JD, Chasset F, Moguelet P, Gornet JM, *et al*. Ustekinumab treatment for neutrophilic dermatoses associated with Crohn’s disease: A multicenter retrospective study. *J Am Acad Dermatol* 2019;80(3):781–784. doi:10.1016/j.jaad.2018.06.065, PMID:30003991.
 - [39] Piqueras-García J, Sahuquillo-Torralla AJ, Torres-Navarro I, Botella-Estrada R. Pyoderma Gangrenosum With Ulcerative Colitis Successfully Treated With Ustekinumab. *Actas Dermosifiliogr (Engl Ed)* 2019;110(9):776–778. doi:10.1016/j.ad.2018.03.034, PMID:31151671.
 - [40] Petty AJ, Whitley MJ, Balaban A, Ellington K, Marano AL. Pyoderma gangrenosum induced by secukinumab in a patient with psoriasis successfully treated with ustekinumab. *JAAD Case Rep* 2020;6(8):731–733. doi:10.1016/j.jdc.2020.06.011, PMID:32715064.
 - [41] Mirose A, Barete S, Monfort JB, Resche-Rigon M, Bouyer AS, Comarmond C, *et al*. Ustekinumab for Behçet’s disease. *J Autoimmun* 2017;82:41–46. doi:10.1016/j.jaut.2017.05.002, PMID:28483439.
 - [42] Fernández-Antón Martínez MC, Alfageme Roldán F, Ciudad Blanco

- C, Suárez Fernández R. Ustekinumab in the treatment of severe atopic dermatitis: a preliminary report of our experience with 4 patients. *Actas Dermosifiliogr* 2014;105(3):312–313. doi:10.1016/j.adengl.2013.05.005, PMID:24657022.
- [43] Guttman-Yassky E, Ungar B, Noda S, Suprun M, Shroff A, Dutt R, *et al*. Extensive alopecia areata is reversed by IL-12/IL-23p40 cytokine antagonism. *J Allergy Clin Immunol* 2016;137(1):301–304. doi:10.1016/j.jaci.2015.11.001, PMID:26607705.
- [44] Aleisa A, Lim Y, Gordon S, Her MJ, Zancanaro P, Abudu M, *et al*. Response to ustekinumab in three pediatric patients with alopecia areata. *Pediatr Dermatol* 2019;36(1):e44–e45. doi:10.1111/pde.13699, PMID:30338558.
- [45] Elkady A, Bonomo L, Amir Y, Vekaria AS, Guttman-Yassky E. Effective use of ustekinumab in a patient with concomitant psoriasis, vitiligo, and alopecia areata. *JAAD Case Rep* 2017;3(6):477–479. doi:10.1016/j.jdc.2017.07.009, PMID:28971137.
- [46] Wendling D, Aubin F, Verhoeven F, Prati C. IL-23/Th17 targeted therapies in SAPHO syndrome. A case series. *Joint Bone Spine* 2017;84(6):733–735. doi:10.1016/j.jbspin.2017.05.016, PMID:28532819.
- [47] Solimani F, Pollmann R, Schmidt T, Schmidt A, Zheng X, Savai R, *et al*. Therapeutic Targeting of Th17/Tc17 Cells Leads to Clinical Improvement of Lichen Planus. *Front Immunol* 2019;10:1808. doi:10.3389/fimmu.2019.01808, PMID:31417572.
- [48] Webster G. Failure of lichen planopilaris to respond to ustekinumab. *Dermatol Online J* 2015;21(11):13030/qt30z76472. PMID:26632941.
- [49] Loget J, Plée J, Antonicelli F, Bernard P. A successful treatment with ustekinumab in a case of relapsing bullous pemphigoid associated with psoriasis. *J Eur Acad Dermatol Venereol* 2017;31(5):e228–e230. doi:10.1111/jdv.14002, PMID:27730667.
- [50] Winchester D, Duffin KC, Hansen C. Response to ustekinumab in a patient with both severe psoriasis and hypertrophic cutaneous lupus. *Lupus* 2012;21(9):1007–1010. doi:10.1177/0961203312441982, PMID:22438028.
- [51] Dahl C, Johansen C, Kragballe K, Olesen AB. Ustekinumab in the treatment of refractory chronic cutaneous lupus erythematosus: a case report. *Acta Derm Venereol* 2013;93(3):368–369. doi:10.2340/00015555-1467, PMID:23038045.
- [52] Amarnani A, Rosenthal KS, Mercado JM, Brodell RT. Concurrent treatment of chronic psoriasis and asthma with ustekinumab. *J Dermatolog Treat* 2014;25(1):63–66. doi:10.3109/09546634.2013.782095, PMID:23469809.
- [53] Viguier M, Pagès C, Aubin F, Delaporte E, Descamps V, Lok C, *et al*. Efficacy and safety of biologics in erythrodermic psoriasis: a multicentre, retrospective study. *Br J Dermatol* 2012;167(2):417–423. doi:10.1111/j.1365-2133.2012.10940.x, PMID:22413927.
- [54] Matsumoto A, Komine M, Karakawa M, Kishimoto M, Ohtsuki M. Adalimumab administration after infliximab therapy is a successful treatment strategy for generalized pustular psoriasis. *J Dermatol* 2017;44(2):202–204. doi:10.1111/1346-8138.13632, PMID:27743397.
- [55] Morales-Múnera C, Vilarrasa E, Puig L. Efficacy of ustekinumab in refractory palmoplantar pustular psoriasis. *Br J Dermatol* 2013;168(4):820–824. doi:10.1111/bjd.12150, PMID:23210683.
- [56] Au SC, Goldminz AM, Kim N, Dumont N, Michelon M, Volf E, *et al*. Investigator-initiated, open-label trial of ustekinumab for the treatment of moderate-to-severe palmoplantar psoriasis. *J Dermatolog Treat* 2013;24(3):179–187. doi:10.3109/09546634.2012.672710, PMID:22390688.
- [57] Bulai Livideanu C, Lahfa M, Mazereeuw-Hautier J, Paul C. Efficacy of ustekinumab in palmoplantar psoriasis. *Dermatology* 2010;221(4):321–323. doi:10.1159/000320961, PMID:20980724.
- [58] Bissonnette R, Nigen S, Langley RG, Lynde CW, Tan J, Fuentes-Duculan J, *et al*. Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. *J Eur Acad Dermatol Venereol* 2014;28(10):1298–1305. doi:10.1111/jdv.12272, PMID:24112799.
- [59] Adışen E, Özer İ, Temel B, Gürer MA. Ustekinumab for the treatment of acrodermatitis continua of Hallopeau refractory to anti-TNF agents. *Dermatol Ther* 2017;30(2):e12460. doi:10.1111/dth.12460, PMID:28139054.
- [60] Saunier J, Debarbieux S, Jullien D, Garnier L, Dalle S, Thomas L. Acrodermatitis continua of Hallopeau treated successfully with ustekinumab and acitretin after failure of tumour necrosis factor blockade and anakinra. *Dermatology* 2015;230(2):97–100. doi:10.1159/000367690, PMID:25471551.
- [61] Adas A, Dadban A, Arnault JP, Chaby G, Lok C. Acrodermatitis continua of Hallopeau response to optimized biological therapy. *Dermatol Online J* 2019;25(2):13030/qt93s9w1p3. PMID:30865417.
- [62] Ruiz Villaverde R, Sánchez Cano D. Successful treatment of type 1 pityriasis rubra pilaris with ustekinumab therapy. *Eur J Dermatol* 2010;20(5):630–631. doi:10.1684/ejd.2010.1004, PMID:20605773.
- [63] Byekova Y, Sami N. Successful response of refractory type I adult-onset pityriasis rubra pilaris with ustekinumab and acitretin combination therapy. *J Dermatol* 2015;42(8):830–831. doi:10.1111/1346-8138.12927, PMID:25982628.
- [64] Chowdhary M, Davila U, Cohen DJ. Ustekinumab as an alternative treatment option for chronic pityriasis rubra pilaris. *Case Rep Dermatol* 2015;7(1):46–50. doi:10.1159/000381011, PMID:25969677.
- [65] Di Stefani A, Galluzzo M, Talamonti M, Chiricozzi A, Costanzo A, Chimenti S. Long-term ustekinumab treatment for refractory type I pityriasis rubra pilaris. *J Dermatol Case Rep* 2013;7(1):5–9. doi:10.3315/jdc.2013.1127, PMID:23580907.
- [66] Eytan O, Sarig O, Sprecher E, van Steensel MA. Clinical response to ustekinumab in familial pityriasis rubra pilaris caused by a novel mutation in CARD14. *Br J Dermatol* 2014;171(2):420–422. doi:10.1111/bjd.12952, PMID:24641799.
- [67] Humme D, Beyer M, Röwert-Huber HJ, Sterry W, Philipp S. [CD30-positive anaplastic large cell T-cell lymphoma developing during immunosuppressive therapy of pityriasis rubra pilaris with ustekinumab]. *Hautarzt* 2013;64(3):190–194. doi:10.1007/s00105-012-2526-5, PMID:23322178.
- [68] Lerna VD, Ficarelli E, Zanelli M. Ineffectiveness of tumor necrosis factor- α blockers and ustekinumab in a case of type IV pityriasis rubra pilaris. *Indian Dermatol Online J* 2015;6(3):207–209. doi:10.4103/2229-5178.156410, PMID:26009720.
- [69] Lwin SM, Hsu CK, Liu L, Huang HY, Levell NJ, McGrath JA. Beneficial effect of ustekinumab in familial pityriasis rubra pilaris with a new missense mutation in CARD14. *Br J Dermatol* 2018;178(4):969–972. doi:10.1111/bjd.15462, PMID:28301045.
- [70] Paganelli A, Ciardo S, Odorici G, Pellacani G, Conti A. Efficacy of ustekinumab after failure of infliximab CT-P13 in a HLA-Cw6-positive patient affected by pityriasis rubra pilaris: monitoring with reflectance confocal microscopy (RCM) and optical coherence tomography (OCT). *J Eur Acad Dermatol Venereol* 2017;31(5):e249–e251. doi:10.1111/jdv.14009, PMID:27739122.
- [71] Wohlrab J, Kreft B. Treatment of pityriasis rubra pilaris with ustekinumab. *Br J Dermatol* 2010;163(3):655–656. doi:10.1111/j.1365-2133.2010.09855.x, PMID:20491761.
- [72] Aragón-Miguel R, Prieto-Barrios M, Calleja-Algarra A, Velasco-Tamarez V, Andres-Lencina JJ, Ortiz-Romero P, *et al*. Refractory pityriasis rubra pilaris with good response after treatment with ustekinumab. *J Dtsch Dermatol Ges* 2018;16(8):1022–1025. doi:10.1111/ddg.13550, PMID:29947473.
- [73] Feldmeyer L, Mylonas A, Demaria O, Mennella A, Yawalkar N, Laffitte E, *et al*. Interleukin 23-Helper T Cell 17 Axis as a Treatment Target for Pityriasis Rubra Pilaris. *JAMA Dermatol* 2017;153(4):304–308. doi:10.1001/jamadermatol.2016.5384, PMID:28122069.
- [74] Kalogeropoulos CI, Papathanasiou KA, Tsagkaraki I, Giannopoulos G, Bamias A, Boutati EI. A Case of Meningococcal and HSV-2 Meningitis in a Patient Being Treated with Ustekinumab for Pityriasis Rubra Pilaris. *Eur J Case Rep Intern Med* 2020;7(8):001615. doi:10.12890/2020_001615, PMID:32789127.
- [75] Napolitano M, Lembo L, Fania L, Abeni D, Didona D, Didona B. Ustekinumab treatment of pityriasis rubra pilaris: A report of five cases. *J Dermatol* 2018;45(2):202–206. doi:10.1111/1346-8138.14114, PMID:29080273.
- [76] Craiglow BG, Boyden LM, Hu R, Virtanen M, Su J, Rodriguez G, *et al*. CARD14-associated papulosquamous eruption: A spectrum including features of psoriasis and pityriasis rubra pilaris. *J Am Acad Dermatol* 2018;79(3):487–494. doi:10.1016/j.jaad.2018.02.034, PMID:29477734.
- [77] Matsuda T, Yamazaki F, Ueda-Hayakawa I, Kambe N, Okamoto H.

- Case of pityriasis rubra pilaris progressed to generalized erythroderma following blockade of interleukin-17A, but improved after blockade of interleukin-12/23 p40. *J Dermatol* 2019;46(1):70–72. doi:10.1111/1346-8138.14709, PMID:30506728.
- [78] Volc-Platzter B. CARD14-mutations in pityriasis rubra pilaris and therapeutic response to ustekinumab - a hypothesis. *J Dtsch Dermatol Ges* 2020;18(11):1312–1315. doi:10.1111/ddg.14218, PMID:32881385.
- [79] Gulliver WP, Jemec GB, Baker KA. Experience with ustekinumab for the treatment of moderate to severe hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2012;26(7):911–914. doi:10.1111/j.1468-3083.2011.04123.x, PMID:21605174.
- [80] Sharon VR, Garcia MS, Bagheri S, Goodarzi H, Yang C, Ono Y, *et al*. Management of recalcitrant hidradenitis suppurativa with ustekinumab. *Acta Derm Venereol* 2012;92(3):320–321. doi:10.2340/00015555-1229, PMID:22101775.
- [81] Baerveldt EM, Kappen JH, Thio HB, van Laar JA, van Hagen PM, Prens EP. Successful long-term triple disease control by ustekinumab in a patient with Behçet's disease, psoriasis and hidradenitis suppurativa. *Ann Rheum Dis* 2013;72(4):626–627. doi:10.1136/annrheumdis-2012-202392, PMID:24308927.
- [82] Santos-Pérez MI, García-Rodicio S, Del Olmo-Revuelto MA, Pozo-Román T. Ustekinumab for hidradenitis suppurativa: a case report. *Actas Dermosifiliogr* 2014;105(7):720–722. doi:10.1016/j.ad.2013.09.011, PMID:24308927.
- [83] Romani J, Vilarrasa E, Martorell A, Fuertes I, Ciudad C, Molina-Leyva A. Ustekinumab with Intravenous Infusion: Results in Hidradenitis Suppurativa. *Dermatology* 2020;236(1):21–24. doi:10.1159/000501075, PMID:31288233.
- [84] Scholl L, Hessam S, Garcovich S, Bechara FG. High-dosage ustekinumab for the treatment of severe hidradenitis suppurativa. *Eur J Dermatol* 2019;29(6):659–661. doi:10.1684/ejd.2019.3663, PMID:31903963.
- [85] Takeda K, Kikuchi K, Kanazawa Y, Yamasaki K, Aiba S. Ustekinumab treatment for hidradenitis suppurativa. *J Dermatol* 2019;46(12):1215–1218. doi:10.1111/1346-8138.15122, PMID:31638283.
- [86] Montero-Vilchez T, Pozo-Román T, Sánchez-Velicia L, Vega-Gutiérrez J, Arias-Santiago S, Molina-Leyva A. Ustekinumab in the treatment of patients with hidradenitis suppurativa: multicenter case series and systematic review. *J Dermatolog Treat* 2022;33(1):348–353. doi:10.1080/09546634.2020.1755008, PMID:32279593.
- [87] Sánchez-Martínez EM, García-Ruiz R, Moneva-Léniz LM, Mateu-Puchades A. Effectiveness and safety of ustekinumab in patients with hidradenitis suppurativa using intravenous induction. *Dermatol Ther* 2020;33(6):e14054. doi:10.1111/dth.14054, PMID:32700796.
- [88] Hollywood A, Murray G, Fleming S, Kirby B, Hughes R. Ustekinumab in the Management of Hidradenitis Suppurativa: A Retrospective Study. *J Drugs Dermatol* 2022;21(3):319–320. doi:10.36849/JDD.6298, PMID:35254749.
- [89] Smith J, Ezekwe N, Pourang A, Hamzavi I. Multifocal myositis and elevated creatine phosphokinase associated with the use of ustekinumab for hidradenitis suppurativa. *Br J Dermatol* 2021;184(6):1181–1182. doi:10.1111/bjd.19762, PMID:33370450.
- [90] Provini LE, Stellar JJ, Stetzer MN, Nguyen PD, Jen M. Combination hyperbaric oxygen therapy and ustekinumab for severe hidradenitis suppurativa. *Pediatr Dermatol* 2019;36(3):381–383. doi:10.1111/pde.13775, PMID:30805965.
- [91] Valenzuela-Ubiña S, Jiménez-Gallo D, Villegas-Romero I, Rodríguez-Mateos ME, Linares-Barrios M. Effectiveness of ustekinumab for moderate-to-severe hidradenitis suppurativa: a case series. *J Dermatolog Treat* 2022;33(2):1159–1162. doi:10.1080/09546634.2020.1776208, PMID:32502365.
- [92] Goldminz AM, Botto NC, Gottlieb AB. Severely recalcitrant pyoderma gangrenosum successfully treated with ustekinumab. *J Am Acad Dermatol* 2012;67(5):e237–e238. doi:10.1016/j.jaad.2012.04.045, PMID:23062936.
- [93] Cosgarea I, Lovric Z, Körber A, Dissemmond J. Successful treatment of refractory pyoderma gangrenosum with ustekinumab only after excision of renal cell carcinoma. *Int Wound J* 2016;13(5):1041–1042. doi:10.1111/iwj.12377, PMID:25294697.
- [94] Benzaquen M, Monnier J, Beaussault Y, Rouby F, Berbis P. Pyoderma gangrenosum arising during treatment of psoriasis with adalimumab: Effectiveness of ustekinumab. *Australas J Dermatol* 2017;58(4):e270–e271. doi:10.1111/ajd.12545, PMID:28660635.
- [95] Nunes G, Patita M, Fernandes V. Refractory Pyoderma Gangrenosum in a Patient With Crohn's Disease: Complete Response to Ustekinumab. *J Crohns Colitis* 2019;13(6):812–813. doi:10.1093/ecco-jcc/jjy200, PMID:30535292.
- [96] Low ZM, Mar A. Treatment of severe recalcitrant pyoderma gangrenosum with ustekinumab. *Australas J Dermatol* 2018;59(2):131–134. doi:10.1111/ajd.12744, PMID:29205260.
- [97] Greb JE, Gottlieb AB, Goldminz AM. High-dose ustekinumab for the treatment of severe, recalcitrant pyoderma gangrenosum. *Dermatol Ther* 2016;29(6):482–483. doi:10.1111/dth.12387, PMID:27502191.
- [98] Fahmy M, Ramamoorthy S, Hata T, Sandborn WJ. Ustekinumab for peristomal pyoderma gangrenosum. *Am J Gastroenterol* 2012;107(5):794–795. doi:10.1038/ajg.2012.42, PMID:22552250.
- [99] López González J, Lázaro Sáez M, Moreno Moraleda I, Hernández Martínez Á. Pyoderma gangrenosum solved by ustekinumab therapy. *Gastroenterol Hepatol* 2021;44(4):299–300. doi:10.1016/j.gastrohep.2020.06.027, PMID:33069432.
- [100] Vallerand IA, Hardin J. Ustekinumab for the treatment of recalcitrant pyoderma gangrenosum: A case report. *SAGE Open Med Case Rep* 2019;7:2050313X19845206. doi:10.1177/2050313X19845206, PMID:31080598.
- [101] Nieto D, Sendagorta E, Rueda JM, Herranz P. Successful treatment with ustekinumab and vacuum-assisted closure therapy in recalcitrant myelodysplastic syndrome-associated pyoderma gangrenosum: case report and literature review. *Clin Exp Dermatol* 2019;44(1):116–119. doi:10.1111/ced.13679, PMID:29851121.
- [102] Westerdahl JS, Nusbaum KB, Chung CG, Kaffenberger BH, Ortega-Loayza AG. Ustekinumab as adjuvant treatment for all pyoderma gangrenosum subtypes. *J Dermatolog Treat* 2022;33(4):2386–2390. doi:10.1080/09546634.2021.1937475, PMID:34057010.
- [103] Lopalco G, Fabiani C, Venerito V, Lapadula G, Iannone F, Cantarini L. Ustekinumab efficacy and safety in mucocutaneous multi-refractory Behçet's disease. *Clin Exp Rheumatol* 2017;35 Suppl 108(6):130–131. PMID:28980903.
- [104] Mirouse A, Barette S, Desbois AC, Comarmond C, Sène D, Domont F, *et al*. Long-Term Outcome of Ustekinumab Therapy for Behçet's Disease. *Arthritis Rheumatol* 2019;71(10):1727–1732. doi:10.1002/art.40912, PMID:31008548.
- [105] London J, Régent A, Dion J, Jilet L, Jachiet M, Lidove O, *et al*. Efficacy and safety of ustekinumab in Behçet disease: Results from the prospective phase 2 STELABEC trial. *J Am Acad Dermatol* 2022;87(3):681–684. doi:10.1016/j.jaad.2021.11.045, PMID:34864108.
- [106] Puya R, Alvarez-López M, Velez A, Casas Asuncion E, Moreno JC. Treatment of severe refractory adult atopic dermatitis with ustekinumab. *Int J Dermatol* 2012;51(1):115–116. doi:10.1111/j.1365-4632.2011.05195.x, PMID:22182388.
- [107] Agustí-Mejías A, Messeguer F, García R, Febrer I. Severe refractory atopic dermatitis in an adolescent patient successfully treated with ustekinumab. *Ann Dermatol* 2013;25(3):368–370. doi:10.5021/ad.2013.25.3.368, PMID:24003284.
- [108] Shroff A, Guttman-Yassky E. Successful use of ustekinumab therapy in refractory severe atopic dermatitis. *JAAD Case Rep* 2015;1(1):25–26. doi:10.1016/j.jdcr.2014.10.007, PMID:27075132.
- [109] Lis-Święty A, Skrzypek-Salamon A, Arasiewicz H, Brzezińska-Wcisło L. Atopic dermatitis exacerbated with ustekinumab in a psoriatic patient with childhood history of atopy. *Allergol Int* 2015;64(4):382–383. doi:10.1016/j.alit.2015.06.003, PMID:26433537.
- [110] Ishiui Y, Umezawa Y, Asahina A, Fukuta H, Aizawa N, Yanaba K, *et al*. Exacerbation of atopic dermatitis symptoms by ustekinumab in psoriatic patients with elevated serum immunoglobulin E levels: Report of two cases. *J Dermatol* 2018;45(6):732–734. doi:10.1111/1346-8138.14295, PMID:29569296.
- [111] Samorano LP, Hanifin JM, Simpson EL, Leshem YA. Inadequate response to ustekinumab in atopic dermatitis - a report of two patients. *J Eur Acad Dermatol Venereol* 2016;30(3):522–523. doi:10.1111/jdv.12918, PMID:25510643.
- [112] Nic Dhoncha E, Clowry J, Dunphy M, Buckley C, Field S, Paul L. Treatment of severe atopic dermatitis with ustekinumab: a case series of 10 patients. *Br J Dermatol* 2017;177(6):1752–1753. doi:10.1111/bjd.15262, PMID:28005276.

- [113] Saeki H, Kabashima K, Tokura Y, Murata Y, Shiraishi A, Tamamura R, *et al*. Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study. *Br J Dermatol* 2017;177(2):419–427. doi:10.1111/bjd.15493, PMID:28338223.
- [114] Wlodek C, Hewitt H, Kennedy CT. Use of ustekinumab for severe refractory atopic dermatitis in a young teenager. *Clin Exp Dermatol* 2016;41(6):625–627. doi:10.1111/ced.12847, PMID:27079289.
- [115] Khattri S, Brunner PM, Garcet S, Finney R, Cohen SR, Oliva M, *et al*. Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis. *Exp Dermatol* 2017;26(1):28–35. doi:10.1111/exd.13112, PMID:27304428.
- [116] Weiss D, Schaschinger M, Ristl R, Gruber R, Kopp T, Stingl G, *et al*. Ustekinumab treatment in severe atopic dermatitis: Down-regulation of T-helper 2/22 expression. *J Am Acad Dermatol* 2017;76(1):91–97.e3. doi:10.1016/j.jaad.2016.07.047, PMID:27745907.
- [117] Firinu D, Murgia G, Lorrai MM, Barca MP, Peralta MM, Manconi PE, *et al*. Biological treatments for SAPHO syndrome: an update. *Inflamm Allergy Drug Targets* 2014;13(3):199–205. doi:10.2174/187152811366140520100402, PMID:24846337.
- [118] Knisley RR, Petropolis AA, Mackey VT. Lichen planus pemphigoides treated with ustekinumab. *Cutis* 2017;100(6):415–418. PMID:29360890.
- [119] Majima Y, Yagi H, Tateishi C, Groth S, Schmidt E, Zillikens D, *et al*. A successful treatment with ustekinumab in a case of antilaminin-γ1 pemphigoid associated with psoriasis. *Br J Dermatol* 2013;168(6):1367–1369. doi:10.1111/bjd.12163, PMID:23252972.
- [120] De Souza A, Ali-Shaw T, Strober BE, Franks AG Jr. Successful treatment of subacute lupus erythematosus with ustekinumab. *Arch Dermatol* 2011;147(8):896–898. doi:10.1001/archdermatol.2011.185, PMID:21844448.
- [121] Varada S, Gottlieb AB, Merola JF, Saraiya AR, Tintile SJ. Treatment of coexistent psoriasis and lupus erythematosus. *J Am Acad Dermatol* 2015;72(2):253–260. doi:10.1016/j.jaad.2014.10.038, PMID:25486913.
- [122] Mazgaj M, Picard-Dahan C, Deschamps L, Marinho E, Estève E, Descamps V. Successful ustekinumab treatment in a patient with psoriasis and subacute cutaneous lupus erythematosus. *Int J Dermatol* 2020;59(4):e118–e120. doi:10.1111/ijd.14773, PMID:31957866.
- [123] Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet* 2021;397(10281):1301–1315. doi:10.1016/S0140-6736(20)32549-6, PMID:33812489.
- [124] Chalmers RJ, O'Sullivan T, Owen CM, Griffiths CE. Interventions for guttate psoriasis. *Cochrane Database Syst Rev* 2000;(2):CD001213. doi:10.1002/14651858.CD001213, PMID:10796758.
- [125] Castiñeiras I, Fernández-Díaz L, Juárez Y, Lueiro M. Sustained efficacy of ustekinumab in refractory erythrodermic psoriasis after failure of antitumor necrosis factor therapies. *J Dermatol* 2012;39(8):730–731. doi:10.1111/j.1346-8138.2011.01499.x, PMID:22364316.
- [126] Stinco G, Piccirillo A, Errichetti E, Bergamo S, Patrone P. Treatment of recalcitrant erythrodermic psoriasis with ustekinumab. *Eur J Dermatol* 2014;24(3):387–390. doi:10.1684/ejd.2014.2325, PMID:24721883.
- [127] Freitas E, Rodrigues MA, Torres T. Diagnosis, Screening and Treatment of Patients with Palmoplantar Pustulosis (PPP): A Review of Current Practices and Recommendations. *Clin Cosmet Investig Dermatol* 2020;13:561–578. doi:10.2147/CCID.S240607, PMID:32884319.
- [128] de Unamuno-Bustos B, Ballester-Sánchez R, Oliver-Martínez V, Alegre de Miquel V. [Ustekinumab for the treatment of palmar-plantar pustulosis]. *Actas Dermosifiliogr* 2011;102(10):833–835. doi:10.1016/j.ad.2011.03.026, PMID:21798490.
- [129] Roenneberg S, Biedermann T. Pityriasis rubra pilaris: algorithms for diagnosis and treatment. *J Eur Acad Dermatol Venereol* 2018;32(6):889–898. doi:10.1111/jdv.14761, PMID:29247481.
- [130] Kromer C, Sabat R, Celis D, Mössner R. Systemic therapies of pityriasis rubra pilaris: a systematic review. *J Dtsch Dermatol Ges* 2019;17(3):243–259. doi:10.1111/ddg.13718, PMID:30520557.
- [131] No Title. In: International Symposium on Hidradenitis Suppurativa Advances. Hidradenitis Suppurativa Foundation; 2009. San Diego, California 92129. www.hs-foundation.org.
- [132] Goldberg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol* 2020;82(5):1045–1058. doi:10.1016/j.jaad.2019.08.090, PMID:31604104.
- [133] Saunte DML, Jemec GBE. Hidradenitis Suppurativa: Advances in Diagnosis and Treatment. *JAMA* 2017;318(20):2019–2032. doi:10.1001/jama.2017.16691, PMID:29183082.
- [134] Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, *et al*. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. *N Engl J Med* 2016;375(5):422–434. doi:10.1056/NEJMoa1504370, PMID:27518661.
- [135] Prat L, Bouaziz JD, Wallach D, Vignon-Pennamen MD, Bagot M. Neutrophilic dermatoses as systemic diseases. *Clin Dermatol* 2014;32(3):376–388. doi:10.1016/j.clindermatol.2013.11.004, PMID:24767185.
- [136] Cohen PR. Neutrophilic dermatoses: a review of current treatment options. *Am J Clin Dermatol* 2009;10(5):301–312. doi:10.2165/11310730-000000000-00000, PMID:19658442.
- [137] Molinelli E, Brisigotti V, Paolinelli M, Offidani A. Novel Therapeutic Approaches and Targets for the Treatment of Neutrophilic Dermatoses, Management of Patients with Neutrophilic Dermatoses and Future Directions in the Era of Biologic Treatment. *Curr Pharm Biotechnol* 2021;22(1):46–58. doi:10.2174/1389201021666200503050803, PMID:32359335.
- [138] Heard M, Zhang M, Jorizzo JL. A case of bowel-associated dermatosis-arthritis syndrome treated with ustekinumab: The importance of targeting underlying gastrointestinal disease. *JAAD Case Rep* 2020;6(6):506–508. doi:10.1016/j.jdc.2020.04.001, PMID:32490110.
- [139] Alpsoy E, Zouboulis CC, Ehrlich GE. Mucocutaneous lesions of Behçet's disease. *Yonsei Med J* 2007;48(4):573–585. doi:10.3349/ymj.2007.48.4.573, PMID:17722228.
- [140] Alibaz-Oner F, Direskeneli H. Advances in the Treatment of Behçet's Disease. *Curr Rheumatol Rep* 2021;23(6):47. doi:10.1007/s11926-021-01011-z, PMID:34014377.
- [141] Waldman AR, Ahluwalia J, Udokoff J, Borok JF, Eichenfield LF. Atopic Dermatitis. *Pediatr Rev* 2018;39(4):180–193. doi:10.1542/pir.2016-0169, PMID:29610426.
- [142] Johnson BB, Franco AI, Beck LA, Prezzano JC. Treatment-resistant atopic dermatitis: challenges and solutions. *Clin Cosmet Investig Dermatol* 2019;12:181–192. doi:10.2147/CCID.S163814, PMID:30962700.
- [143] Pan Y, Xu L, Qiao J, Fang H. A systematic review of ustekinumab in the treatment of atopic dermatitis. *J Dermatolog Treat* 2018;29(6):539–541. doi:10.1080/09546634.2017.1406894, PMID:29164954.
- [144] Pratt CH, King LE Jr, Messenger AG, Christiano AM, Sundberg JP. Alopecia areata. *Nat Rev Dis Primers* 2017;3:17011. doi:10.1038/nrdp.2017.11, PMID:28300084.
- [145] Pourang A, Mesinkovska NA. New and Emerging Therapies for Alopecia Areata. *Drugs* 2020;80(7):635–646. doi:10.1007/s40265-020-01293-0, PMID:32323220.
- [146] Ortolan LS, Kim SR, Crofts S, Liu LY, Craiglow BG, Wambier C, *et al*. IL-12/IL-23 neutralization is ineffective for alopecia areata in mice and humans. *J Allergy Clin Immunol* 2019;144(6):1731–1734.e1. doi:10.1016/j.jaci.2019.08.014, PMID:31470035.
- [147] Speeckaert R, Lambert J, van Geel N. Learning From Success and Failure: Biologics for Non-approved Skin Diseases. *Front Immunol* 2019;10:1918. doi:10.3389/fimmu.2019.01918, PMID:31440261.
- [148] Méry-Bossard L, Bagny K, Chaby G, Khemis A, Maccari F, Marotte H, *et al*. New-onset vitiligo and progression of pre-existing vitiligo during treatment with biological agents in chronic inflammatory diseases. *J Eur Acad Dermatol Venereol* 2017;31(1):181–186. doi:10.1111/jdv.13759, PMID:27291924.
- [149] Gedikli OK, Kilic G. New-onset vitiligo as an unusual cutaneous reaction under ustekinumab therapy in patients with psoriatic arthritis. *Acta Reumatol Port* 2020;45(4):301–303. PMID:33420768.
- [150] Daoussis D, Konstantopoulou G, Kraniotis P, Sakkas L, Liossis SN. Biologics in SAPHO syndrome: A systematic review. *Semin Arthritis Rheum* 2019;48(4):618–625. doi:10.1016/j.semarthrit.2018.04.003, PMID:29773231.
- [151] Le Guern A, Alkeraye S, Vermersch-Langlin A, Coupe P, Vonarx M. Bullous pemphigoid during ustekinumab therapy. *JAAD Case Rep* 2015;1(6):359–360. doi:10.1016/j.jdc.2015.07.014, PMID:27051780.
- [152] van Vollenhoven RF, Hahn BH, Tsokos GC, Wagner CL, Lipsky P, Touma Z, *et al*. Efficacy and safety of ustekinumab, an IL-12 and IL-23

- inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet* 2018;392(10155):1330–1339. doi:10.1016/S0140-6736(18)32167-6, PMID:30249507.
- [153] Tierney E, Kirthi S, Ramsay B, Ahmad K. Ustekinumab-induced subacute cutaneous lupus. *JAAD Case Rep* 2019;5(3):271–273. doi:10.1016/j.jdc.2019.01.015, PMID:30891478.
- [154] Rolston VS, Kimmel J, Popov V, Bosworth BP, Hudesman D, Malter LB, *et al*. Ustekinumab Does Not Increase Risk of Adverse Events: A Meta-Analysis of Randomized Controlled Trials. *Dig Dis Sci* 2021;66(5):1631–1638. doi:10.1007/s10620-020-06344-w, PMID:32445049.
- [155] Qian Y, Kang Z, Liu C, Li X. IL-17 signaling in host defense and inflammatory diseases. *Cell Mol Immunol* 2010;7(5):328–333. doi:10.1038/cmi.2010.27, PMID:20514051.
- [156] Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC. Comparative risk of serious infections among real-world users of biologics for psoriasis or psoriatic arthritis. *Ann Rheum Dis* 2020;79(2):285–291. doi:10.1136/annrheumdis-2019-216102, PMID:31672774.
- [157] Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, *et al*. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol* 2015;14(7):706–714. PMID:26151787.
- [158] Cho SI, Kang S, Kim YE, Lee JY, Jo SJ. Ustekinumab does not increase tuberculosis risk: Results from a national database in South Korea. *J Am Acad Dermatol* 2020;82(5):1243–1245. doi:10.1016/j.jaad.2019.12.033, PMID:31866266.
- [159] Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, *et al*. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a meta-analysis of randomized controlled trials. *JAMA* 2011;306(8):864–871. doi:10.1001/jama.2011.1211, PMID:21862748.
- [160] Poizeau F, Nowak E, Kerbrat S, Le Nautout B, Droitcourt C, Drici MD, *et al*. Association Between Early Severe Cardiovascular Events and the Initiation of Treatment With the Anti-Interleukin 12/23p40 Antibody Ustekinumab. *JAMA Dermatol* 2020;156(11):1208–1215. doi:10.1001/jamadermatol.2020.2977, PMID:32902568.
- [161] Santos-Juanes J, Coto P, Galache F C. Ustekinumab. Neoplasias y otros aspectos de seguridad Ustekinumab. Neoplasms and Other Safety Aspects. *Actas Dermo-Sifiliográficas* 2012;103(Suppl 2):39–44. doi:10.1016/S0001-7310(12)70007-8.