Dermatology Practical & Conceptual

Management of Infections in Psoriatic Patients Treated with Systemic Therapies: A Lesson from the Immunopathogenesis of Psoriasis

Anna Balato[1], Emanuele Scala[2,3], Kilian Eyerich[2,3,4], Nicolò Costantino Brembilla[5], Andrea Chiricozzi[6], Robert Sabat[7,8], Kamran Ghoreschi[9]

1 Dermatology Unit, University of Campania, Naples, Italy
2 Division of Dermatology and Venereology, Department of Medicine Solna, and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden
3 Department of Dermatology and Venereology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
4 Department of Dermatology and Venereology, Unit of Dermatology, Karolinska University Hospital, Stockholm, Sweden
5 Department of Pathology and Immunology, University of Geneva, Geneva, Switzerland
6 Institute of Dermatology, Catholic University, Rome, Italy
7 Interdisciplinary Group of Molecular Immunopathology, Dermatology/Medical Immunology, Charité–Universitätsmedizin, Berlin, Germany
8 Psoriasis Research and Treatment Center, Department of Dermatology and Allergy and Institute of Medical Immunology, Charité–Universitätsmedizin, Berlin, Germany
9 Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin, Berlin, Germany

Key words: psoriasis, infection, prevention, management, covid-19

Citation: Balato A, Scala E, Eyerich K, et al. Management Of Infections In Psoriatic Patients Treated With Systemic Therapies: A Lesson From The Immunopathogenesis Of Psoriasis. *Dermatol Pract Concept.* 2023;13(1):e2023016. DOI: https://doi.org/10.5826/dpc.1301a16

Accepted: May 30, 2022; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Emanuele Scala, PhD, Division of Dermatology and Venereology, Department of Medicine Solna, and Center for Molecular Medicine, Karolinska Institutet, 17176 Stockholm, Sweden. Email: emanuele.scala@ki.se

ABSTRACT Modern treatments continue to be developed based on identifying targets within the innate and adaptive immune pathways associated with psoriasis. Whilst there is a sound biologic rationale for increased risk of infection following treatment with immunomodulators, the clinical evidence is confounded by these agents being used in patients affected with several comorbidities. In an era characterized by an ever greater and growing risk of infections, it is necessary to always be updated on this risk. In this mini-review, we will discuss recent updates in psoriasis immunopathogenesis as a rationale for systemic therapy, outline the risk of infections linked to the disease itself and systemic therapy as well, and provide an overview of the prevention and management of infections.

Introduction

In the last decade, our understanding of psoriasis pathogenesis made significant steps forwards leading to the development of multiple game-changer therapies [1]. Although we can confidently say that the horizon is now a little brighter, we cannot argue that "the whole job" has been done. The advent of therapies targeting specific components of the immune response has highlighted the possible association of infections with psoriasis. Whilst there is a sound biologic rationale for increased risk of infection following treatment with immunomodulators, the clinical evidence is confounded by these agents being used in moderate-to-severe psoriasis in association with several comorbidities. In this article, we summarize the available information on the risk of infections, including the respiratory ones, linked to psoriasis and immunomodulators as well. Lastly, we provide an overview of the prevention and management of infections in psoriatic patients on immunomodulatory therapies.

Immunopathogenesis of Psoriasis: An Update

Psoriasis has been primarily defined as an autoimmune, T-cell-mediated disease with dysregulated inflammatory response that is composed of both innate and adaptive immunity [1-4]. Other factors such as environmental ones and genetic susceptibility are also involved [4,5]. Several gene loci are associated with psoriasis, such as HLA-Cw6 and PSORS1-9, providing initial evidence of a possibly (auto) immune component [6,7]. However, ~ 60 loci identified contain genes involved in the immune system at large and the interleukin (IL)-23/T helper (Th)17 pathway in particular [8,9]. IL-17A is the most studied cytokine of the psoriatic IL-23/Th17 cell pathogenic axis and is claimed to be directly responsible for the development of the psoriatic lesion [10,11]. It does not act as a single cytokine but exerts its function in a complex cytokine network which includes IL-19, IL-22, IL-23, tumor necrosis factor (TNF)-α and several IL-1 family members [12-15]. IL-17A is not exclusively produced by Th17 cells in the lesion, but possibly also by several other cells: such as γδ T cells, type 3 innate lymphoid cells (ILC3s) and invariant natural killer (iNK)T cells, and other thymus-independent cells, including mast cells and neutrophils [16-19]. Besides IL-17A, the immune-derived IL-17F, the epithelial-derived IL-17C and IL-17E, have all been shown to independently participate in psoriasiform inflammation in murine models [20-22]. Interestingly, the inhibition of the IL-17A/IL-23 axis might potentially lead to the enhancement of other IL-17 cytokine members, particularly the epithelial-derived cytokines. A better assessment of the different sources and the possible IL-17 substitute cytokines is critical to better understand the mechanism of action of the current IL-23/IL-17-targeted therapies, possibly helping to explain unwanted effects or secondary loss of efficacy.

Psoriasis and Skin Infection

Psoriatic lesions show a disturbed skin barrier function, similar to the affected skin of patients with atopic dermatitis (AD) [23-24]. This altered epidermal barrier facilitates the penetration of bacteria and viruses into the skin and should lead to an increased incidence of cutaneous infections. However, the frequency of skin infections is impressively underrepresented in patients with psoriasis [25, 26]. The main reason for this clinical observation is the specific increase in the levels of antimicrobial peptides (AMPs) and antiviral peptides (AVPs) within the epidermis of psoriatic lesions [14, 27-29]. Correspondingly, the enhancement of AMPs and AVPs in the affected skin of AD patients is only minimal and these patients often suffer from bacterial and viral skin infections. The mostly up-regulated AMPs in psoriatic skin are human β-defensin (HBD)-2, S100A7 (psoriasin) and to a lesser extent HBD-3, S100A8 (calgranulin A), S100A9 (calgranulin B), and lipocalin (LCN)-2 [27, 30-32]. The spectrum of affected microbes differs among the diverse AMPs. For example, S100A7 is primarily an *E. coli*-killing antimicrobial peptide, whereas HBD-3 exhibits a broad spectrum of antimicrobial activity against various Gram□negative and Gram□positive bacteria as well as fungi [33]. AMPs inhibit propagation and kill microbes through various mechanisms such as destabilization of their membrane or sequestrating metal ions [33, 34]. Most of the AMPs are constitutively expressed at low levels in keratinocytes and might be strongly up-regulated by cytokines under inflammatory conditions. The powerful inducers of AMPs in epithelial cells are IL-17 and IL-22 [31, 35]. However, the synergistic action of both cytokines is essential for the strong induction of AMPs in keratinocytes [36, 37]. In psoriatic lesions, this effect might be amplified by TNF-α, interferon (IFN)-γ, IL-19, and IL-36s [15, 37-39]. Interestingly, the joint action of IL-22 and TNF-α seems to be relevant for the maintenance of epidermal integrity during infection with *Candida albicans* [38]. The up-regulated AVPs in psoriatic lesions comprise OAS2, BST2 (tetherin), MX1, and ISG15 [29]. The main driver for this increase is IL-29, a member of the IL-10-IFN family of cytokines [40]. In psoriatic lesions, IL-29 is produced by Th17 cells [29]. It directly acts on keratinocytes via the transmembrane receptor complex composed of IL-28R1 and IL-10R2 and activates intracellular JAK-STAT signaling. Interestingly, IL-10R2 is also a part of the IL-22 receptor complex [41]. The AVP-inducing effect of IL-29 can be only minimally amplified by IFN-γ in keratinocytes [40]. An overview of the main psoriasis signature cytokines and their effects on infections is shown in Table 1.

Table 1. Psoriasis signature cytokines and their effects on infections.

Cytokines	Cellular sources	Findings
IL-12	DCs, monocytes, macrophages, neutrophils, B cells and KCs	Enhances HBD-2 production in KCs, and the antimicrobial activity of macrophages
IL-17A	Th17 cells, ILC3s, mast cells, neutrophils, CD8+ T cells, γδ T cells, NK cells, iNKT cells, and LTi cells	Induces the production of AMPs (HBD-2, LL-37, LCN-2, and S100A7-9) in KCs, neutrophil recruitment, and immunity to extracellular pathogens
IL-17C	Prostate and fetal kidney cells, KCs, colonic epithelial cells, and lung epithelial cells	Enhances epithelial host defense (HBD-2/-3, and S100A7-9) in an autocrine/paracrine manner
IL-17E	Intraepithelial lymphocytes, lung epithelial cells, alveolar macrophages, eosinophils, basophils, NKT cells, Th2 cells, mast cells, and cells of the gastrointestinal tract and uterus	Promotes innate cell recruitment and activation. Provides immunity to extracellular pathogens
IL-17F	Th17 cells, mast cells, neutrophils, CD8+ T cells, γδ T cells, NK cells, NKT cells, and LTi cells	Synergistically cooperates with IL-17A and IL-22 for the induction of AMPs in KCs. Provides immunity to extracellular pathogens and is involved in neutrophil recruitment
IL-19	Monocytes, DCs and KCs	Increases the production of AMPs (S100A7-9) in KCs and amplifies IL-17A activity.
IL-21	Th17 cells, Th1* cells, Th2 cells, CD8+ T cells, and NKT cells	Enhances the antimicrobial activity of macrophages, and maintains the CD8+ T cell effector activity during the infection
IL-22	Th22 cells, Th17 cells, Th1 cells, CD8+ T cells, γδ T cells, ILC3s, NKT cells, LTi cells, alveolar macrophages*, and neutrophils*	Increases the expression of HBD-2/-3, and S100A7-9 in KCs, and reinforces TNF-α activity
IL-23	DCs, macrophages, and psoriatic KCs	Induces HBD-2 expression in KCs, and optimizes the antimicrobial activity of macrophages
IL-26	Th17 cells, Th1 cells, epithelial cells, NK cells, alveolar macrophages, and macrophage-like synoviocytes	Exerts antiviral and antimicrobial actions, as well as regulates the expression of HBD-2/-3
IL-29 (alternative name INFλ)	Th17 cells, DCs, macrophages, mast cells, and alveolar cells	Induces the production of antiviral proteins (MX1, BST2, ISG15, and OAS2) in KCs
IL-36s	KCs, macrophages, monocytes, DCs, and lymphocytes	Promote viral resistance, and the production of AMPs in KCs
TNF-α	Macrophages, monocytes, DCs, NK cells, T cells, B cells, and KCs	Induces the production of S100A7 and HBD-2/-3, as well as antimicrobial chemokines CXCL-9/-10/-11 in KCs

**Controversial among researchers. AMPs* antimicrobial peptides, *DCs* dendritic cells, *ILC3s* type 3 innate lymphoid cells, *KCs* keratinocytes, *LTi* lymphoid tissue inducer, *iNKT* invariant natural killer T cells, *Th* T helper. Data from multiple sources [12-15, 20-22, 29, 31, 35-41, 81-98]

Psoriasis and Respiratory Infections

Lower respiratory tract infections including pneumonia are the most frequent types of serious infections among psoriasis patients as documented by numerous registries [42, 43]. The incidence of pneumonia seems to be even increased among psoriasis patients compared to those without psoriasis [44,45]. However, it is not definitely clear to what extent this increase is related, either to psoriasis itself, its concomitant disorders, or its treatment [44]. In fact, psoriasis patients frequently suffer from diabetes mellitus, hyperlipidemia, and hypertension, are smokers, and have elevated body mass index (BMI), which can make them vulnerable to infectious diseases [25,46].

Systemic Therapies and Infection Risk, Including SARS-CoV-2

The conventional systemic therapies for plaque psoriasis include cyclosporine, methotrexate, and oral retinoids [47]. Cyclosporine is a calcineurin inhibitor broadly suppressing T cells; methotrexate, and retinoids have multiple effects on several immune cells. More recently, 2 small-molecule drugs

have been approved for the treatment of plaque psoriasis: apremilast, an oral phosphodiesterase (PDE)-4 inhibitor, and dimethyl fumarate [48,49]. Both molecules impact the NF-kB complex and have broad functions on the immune system. Modern biological therapies, such as anti-TNF-α, anti-IL-12/23, anti-IL-17, and anti-IL-23 antibodies, are designed to block specific molecular steps important in the pathogenesis of psoriasis. Namely, anti-TNF-α agents neutralize TNF-α which has a dual role as an upstream mediator of T cell differentiation into Th1, Th17 and Th22 cells, as well as a pro-inflammatory mediator synergistic with IL-17A, IL-17F, and IL-22 [50]. The anti-IL-12/23 agent targets the P40 subunit shared by IL-12 and IL-23 preventing their interaction with the receptor and thereby blocking Th1/Th17 immunity [1,50]. This was further developed into biologics neutralizing only IL-23 via the p19 subunit, thereby only blocking Th17 immunity [1]. Finally, direct interaction with IL-17A and/or other members of the IL-17 family is a successful strategy realized through IL-17A, IL-7RA, or bispecific IL-17A/F targeting.

However, analysis of the population-based electronic medical record database from the UK on approximately 200,000 patients with psoriasis indicates that patients with moderate-to-severe disease that receive immunosuppressive therapies do have an increased risk for opportunistic infections and reactivation of varicella-zoster virus [51]. Furthermore, analyzing data from psoriasis patients treated with biologic (n=2258) or non-biologic systemic agents (n=3631) demonstrated that systemic therapies with biologics significantly increase the overall risk for serious infection [52]. The extent of impairment and the type of infection are related to the mode of action of individual drugs or drug groups [1]. For instance, TNF-α antagonists can lead to the reactivation of latent tuberculosis and IL-17 neutralization may result in mucocutaneous candidiasis [1]. However, it should be noted, there is no signal for increased risk of invasive fungal disease due to anti-IL-17 therapy [53]. Cases of opportunistic infections like atypical histoplasmosis or toxoplasmosis have been mainly reported in connection with blocking TNF-α or IL-12/IL-23 p40 [53,54]. Accordingly, the evaluation of registry data primarily notes the association of the use of infliximab, a chimeric monoclonal anti-TNF-α antibody, with increased incidence of pneumonia [44,45]. Furthermore, while neutralizing TNF-α or IL-17 has been associated with such a risk, there is no evidence that blocking IL-23 increases the risk of respiratory tract infections [55]. Despite the relevant concomitant disorders such as obesity, hypertension, and diabetes, recent data accumulated during the Covid-19 pandemic indicate that patients with psoriasis with or without systemic treatment are neither at higher risk for infection with SARS-CoV-2 nor show more severe symptoms [56]. This might be caused by the fact that cytokines, such as IL-1β and IL-6, which may play a pathogenic role in the severe/fatal course of Covid-19 infection are only moderately expressed in psoriatic lesions and do not play an important role in psoriasis pathogenesis compared to other inflammatory skin diseases [57,58]. Importantly, the incidence of Covid-19 infection, Covid-19-related hospitalization, and Covid-19-related death do not seem to be elevated among psoriasis patients treated with biologics [60,61]. The disease course in most patients with biological treatment was even milder, indicating that the anti-cytokine therapy may be beneficial in preventing a severe cytokine storm [59,62]. A schematization of the risks and benefits of cytokine-blocking therapies in psoriasis is displayed in Figure 1.

Prevention and Management of Infections in Psoriatic Patients Treated With Systemic Therapies

As any patient with moderate to severe psoriasis may progress to immunomodulatory therapies, it is important that their immunizations are up to date. Two general strategies have been suggested: screening for infection prior to therapy initiation as well as providing protection through vaccination. As for the first strategy, guidelines suggest tuberculosis screening before starting all biological therapies [63,64]. However, data from clinical trials and post-marketing surveillance with IL-23 and IL-17 inhibitors suggest that they are not crucial to tuberculosis reactivation [65]. Furthermore, screening for *Candida* infections, hepatitis, human immunodeficiency virus (HIV), and other chronic infections is generally recommended. As for the latter, vaccination is a proven strategy to reduce infections. In view of this, dermatologists can play an important role in educating patients about immunizations. To prevent severe infections, it is suggested that psoriatic patients receive their complete recommended vaccinations (especially live vaccines) before initiating biological therapy [66]. In short, the medical board of the National Psoriasis Foundation recommends that all patients with moderate-to-severe psoriasis have an assessment of their immunization status, including immunization or disease history for varicella zoster, *Haemophilus influenzae*, tetanus, pertussis, hepatitis A and B, human papillomavirus (HPV), influenza, *Neisseria meningitides*, and *Streptococcus pneumoniae* during initial workup [67]. Notably, vaccines such as *Mycobacterium vaccae*, live attenuated varicella zoster virus and Leishmania amastigotes have been reported to be effective during psoriasis treatment [68-70] even though these data need to be confirmed in larger and controlled clinical trials. Lastly, vaccination against SARS-CoV-2 is recommended in patients with psoriasis, even in those under biological therapy [71].

Hence, it is clear now that immune pathways involved in psoriasis pathogenesis contribute to host defense against certain pathogens, thus a possible consequence is represented

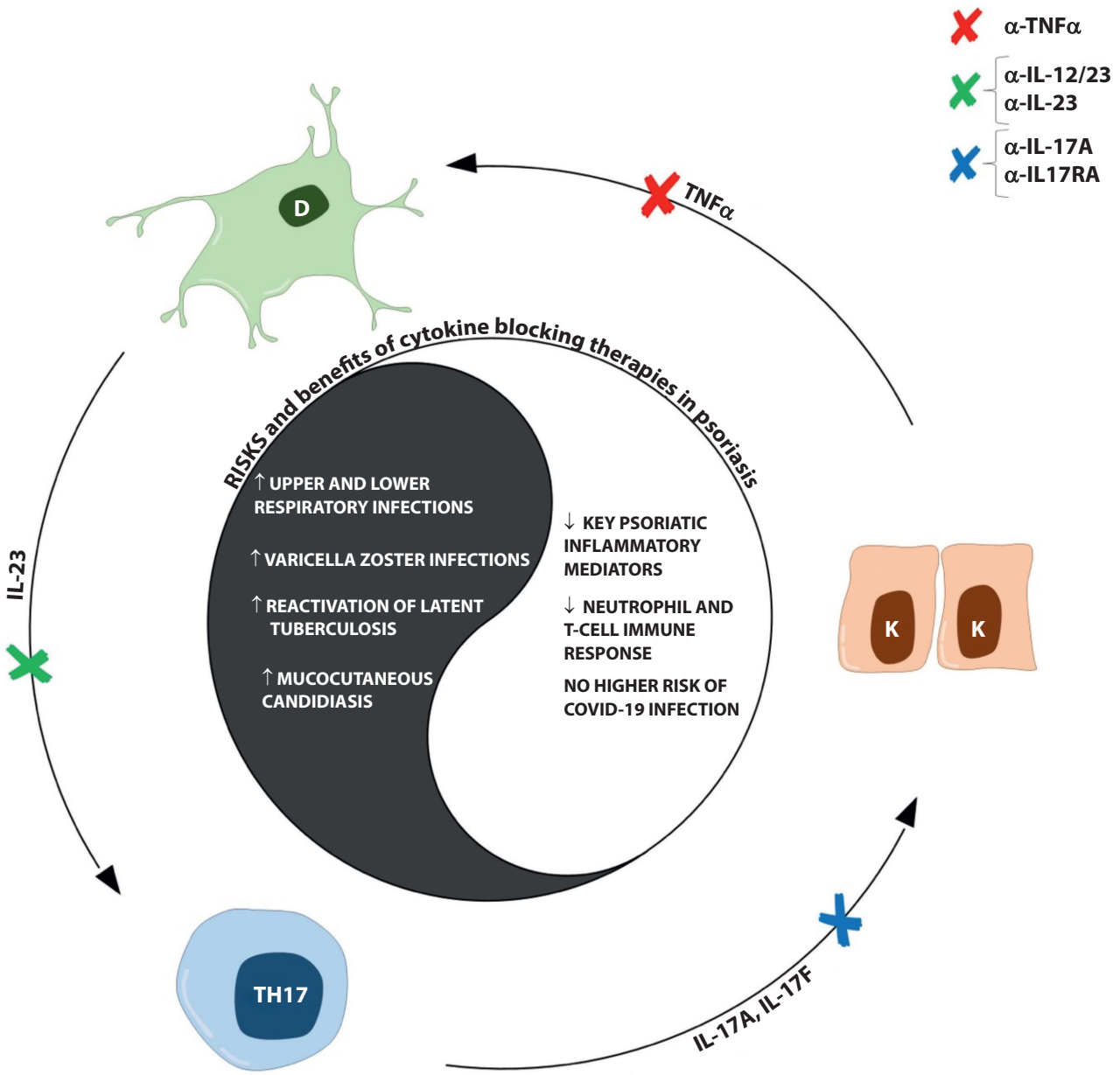

Figure 1. Schematization of risks and benefits of cytokine blocking therapies in psoriasis. *D* dendritic cell, *IL* interleukin, *K* keratinocyte, *Th* T helper, *TNF* tumor necrosis factor.

by the fact that a selective inhibition might predispose to specific infections. Nevertheless, some biologic agents and novel small molecule drugs (i.e., apremilast) appeared to be safer or at least not associated with significant increases in the risk of serious infections, compared to conventional nonbiologic systemic compounds [72]. Mild to moderate infections (i.e., upper respiratory tract infections) or minor surgery (i.e., skin surgery, dental procedures) do not usually cause treatment discontinuation where it would otherwise be continued. Delayed starting or interruption of immunomodulatory therapies is recommended in case of clinically meaningful active infection (severe signs and symptoms requiring systemic oral or intramuscular antibiotic, antiviral, or antifungal therapy) or serious infection requiring hospitalization or intravenous antibiotic, antiviral, or antifungal therapy. Evaluating the risk-benefit ratio for recurrent serious infections, therapy can be restarted once infection has been fully resolved, empirically after 2-4 weeks from the resolution of the infectious event [73]. Analogous therapeutic management during the SARS-CoV-2 pandemic has been suggested [74,75]. In the event of SARS-CoV-2 infection, psoriasis treatments should be suspended and resumed after complete resolution of COVID-19 symptoms and SARS-CoV-2 negativization. On the contrary, in those asymptomatic SARS-CoV-2+ patients with high-need-to-treat psoriasis, as well as in psoriasis patients who have had a severe hospital course or the persistence of 1 or more symptoms of COVID-19, beyond the acute phase of the illness, the decision to restart treatment

Table 2. Infectious diseases to consider for selecting biological and new small-molecule therapies.

Class of agents	Drug	HCV	HBV	HIV	Latent TB	CMCC
Anti-TNF-α	Etanercept Adalimumab Infliximab Certolizumab Golimumab	Preferred	Not preferred	Preferred	Not preferred	Preferred
Anti-IL-12/23	Ustekinumab	Preferred	Preferred	Preferred	Preferred	Preferred
Anti-IL-17A	Secukinumab Ixekizumab	Preferred	Likely safe/Not enough data	Likely safe/Not enough data	Preferred	Not preferred
Anti-IL-17RA	Brodalumab	Preferred	Likely safe/Not enough data	Likely safe/Not enough data	Preferred	Not preferred
Anti-IL-23	Guselkumab Tildrakizumab Risankizumab	Preferred	Not enough data	Not enough data	Preferred	Preferred
Oral novel small molecule	Apremilast	Preferred	Not enough data	Not enough data	Preferred	Preferred

CMCC chronic mucocutaneous candidiasis, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *IL* interleukin, *RA* receptor A, *TB* tuberculosis, *TNF* tumor necrosis factor. Data from several sources [99-101].

should be taken on a case-by-case basis [76,77]. Similar to active serious infections, in case of major surgery (i.e., under general anesthesia with exposure of large body areas, internal organ surgery), guidelines recommend treatment interruption, evaluating case-by-case patient characteristics, the risk of infection, the risk of psoriasis worsening and consultation with the surgeon [78]. Therapy restart can be considered after full recovery. Nevertheless, real-life data on perioperative management are limited and do not provide strong evidence of peri- or post-operative complications due to continuous treatment with biologic agents or apremilast [78-80]. Infectious diseases to consider for selecting biological and new small-molecule therapies are listed in Table 2.

Conclusion

In an era characterized by an ever greater and growing risk of infections, but at the same time by increasingly specific and advanced immune-mediated therapies, it is necessary to always be updated on the risk of such infections and on the ability to manage them. Currently, we are witnessing a revolution in the treatment of psoriasis where the starting point is the translational approach, and we firmly believe that by following this path we can reach a wider knowledge that will help us in preventing and treating properly infections associated with psoriasis.

References

1. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet*. 2021;397(10275):754-766. doi:10.1016/S0140-6736(21)00184-7
2. Boehncke WH, Schön MP. Psoriasis. *Lancet*. 2015;386(9997):983-994. doi:10.1016/S0140-6736(14)61909-7
3. Nickoloff BJ, Qin JZ, Nestle FO. Immunopathogenesis of psoriasis. *Clin Rev Allergy Immunol*. 2007;33(1-2):45-56. doi:10.1007/s12016-007-0039-2
4. Cai Y, Fleming C, Yan J. New insights of T cells in the pathogenesis of psoriasis. *Cell Mol Immunol*. 2012;9(4):302-309. doi:10.1038/cmi.2012.15
5. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of Psoriasis: A comprehensive review. *J Autoimmun*. 2015;64:66-73. doi:10.1016/j.jaut.2015.07.008
6. Elder JT. Genome-wide association scan yields new insights into the immunopathogenesis of psoriasis. *Genes Immun*. 2009;10(3):201-209. doi:10.1038/gene.2009.11
7. Capon F. The Genetic Basis of Psoriasis. *Int J Mol Sci*. 2017;18(12):2526. Published 2017 Nov 25. doi:10.3390/ijms18122526
8. 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
9. Ray-Jones H, Eyre S, Barton A, Warren RB. One SNP at a Time: Moving beyond GWAS in Psoriasis. *J Invest Dermatol*. 2016;136(3):567-573. doi:10.1016/j.jid.2015.11.025
10. Li B, Huang L, Lv P, et al. The role of Th17 cells in psoriasis. *Immunol Res*. 2020;68(5):296-309. doi:10.1007/s12026-020-09149-1
11. Martin DA, Towne JE, Kricorian G, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J Invest Dermatol*. 2013;133(1):17-26. doi:10.1038/jid.2012.194
12. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, et al. Integrative responses to IL-17 and TNF-α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *J Invest Dermatol*. 2011;131(3):677-687. doi:10.1038/jid.2010.340
13. Carrier Y, Ma HL, Ramon HE, et al. Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications

in psoriasis pathogenesis. *J Invest Dermatol*. 2011;131(12): 2428-2437. doi:10.1038/jid.2011.234
14. Wolk K, Kunz S, Witte E, Friedrich M, Asadullah K, Sabat R. IL-22 increases the innate immunity of tissues. *Immunity*. 2004;21(2):241-254. doi:10.1016/j.immuni.2004.07.007
15. Witte E, Kokolakis G, Witte K, et al. IL-19 is a component of the pathogenetic IL-23/IL-17 cascade in psoriasis. *J Invest Dermatol*. 2014;134(11):2757-2767. doi:10.1038/jid.2014.308
16. Brembilla NC, Stalder R, Senra L, Boehncke WH. IL-17A localizes in the exocytic compartment of mast cells in psoriatic skin. *Br J Dermatol*. 2017;177(5):1458-1460. doi:10.1111/bjd.15358
17. Gaffen SL. Recent advances in the IL-17 cytokine family. *Curr Opin Immunol*. 2011;23(5):613-619. doi:10.1016/j.coi.2011.07.006
18. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol*. 2014;14(9):585-600. doi:10.1038/nri3707
19. Keijsers RRMC, Hendriks AGM, van Erp PEJ, et al. In vivo induction of cutaneous inflammation results in the accumulation of extracellular trap-forming neutrophils expressing RORγt and IL-17. *J Invest Dermatol*. 2014;134(5):1276-1284. doi:10.1038/jid.2013.526
20. Brembilla NC, Senra L, Boehncke WH. The IL-17 Family of Cytokines in Psoriasis: IL-17A and Beyond. *Front Immunol*. 2018;9:1682. Published 2018 Aug 2. doi:10.3389/fimmu.2018.01682
21. Senra L, Mylonas A, Kavanagh RD, et al. IL-17E (IL-25) Enhances Innate Immune Responses during Skin Inflammation. *J Invest Dermatol*. 2019;139(8):1732-1742.e17. doi:10.1016/j.jid.2019.01.021
22. Johnston A, Fritz Y, Dawes SM, et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. *J Immunol*. 2013;190(5):2252-2262. doi:10.4049/jimmunol.1201505
23. Montero-Vilchez T, Segura-Fernández-Nogueras MV, Pérez-Rodríguez I, et al. Skin Barrier Function in Psoriasis and Atopic Dermatitis: Transepidermal Water Loss and Temperature as Useful Tools to Assess Disease Severity. *J Clin Med*. 2021;10(2):359. Published 2021 Jan 19. doi:10.3390/jcm10020359
24. Stawczyk-Macieja M, Szczerkowska-Dobosz A, Rębała K, Purzycka-Bohdan D. Genetic background of skin barrier dysfunction in the pathogenesis of psoriasis vulgaris. *Postepy Dermatol Alergol*. 2015;32(2):123-126. doi:10.5114/pdia.2014.44003
25. Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol*. 1995;32(6):982-986. doi:10.1016/0190-9622(95)91336-x
26. Christophers E, Henseler T. Contrasting disease patterns in psoriasis and atopic dermatitis. *Arch Dermatol Res*. 1987;279 Suppl:S48-S51. doi:10.1007/BF00585919
27. Schröder JM, Harder J. Human beta-defensin-2. *Int J Biochem Cell Biol*. 1999;31(6):645-651. doi:10.1016/s1357-2725(99)00013-8
28. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*. 2002;347(15):1151-1160. doi:10.1056/NEJMoa021481
29. Wolk K, Witte K, Witte E, et al. IL-29 is produced by T(H)17 cells and mediates the cutaneous antiviral competence in psoriasis. *Sci Transl Med*. 2013;5(204):204ra129. doi:10.1126/scitranslmed.3006245
30. Gläser R, Harder J, Lange H, Bartels J, Christophers E, Schröder JM. Antimicrobial psoriasin (S100A7) protects human skin from Escherichia coli infection. *Nat Immunol*. 2005;6(1):57-64. doi:10.1038/ni1142
31. Wolk K, Witte E, Wallace E, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. *Eur J Immunol*. 2006;36(5):1309-1323. doi:10.1002/eji.200535503
32. Mallbris L, O'Brien KP, Hulthén A, et al. Neutrophil gelatinase-associated lipocalin is a marker for dysregulated keratinocyte differentiation in human skin. *Exp Dermatol*. 2002;11(6):584-591. doi:10.1034/j.1600-0625.2002.110611.x
33. Schröder JM. Antimicrobial peptides in healthy skin and atopic dermatitis. *Allergol Int*. 2011;60(1):17-24. doi:10.2332/allergolint.10-RAI-0292
34. Wang G. Human antimicrobial peptides and proteins. *Pharmaceuticals* (Basel). 2014;7(5):545-594. Published 2014 May 13. doi:10.3390/ph7050545
35. Kao CY, Chen Y, Thai P, et al. IL-17 markedly up-regulates beta-defensin-2 expression in human airway epithelium via JAK and NF-kappaB signaling pathways. *J Immunol*. 2004;173(5):3482-3491. doi:10.4049/jimmunol.173.5.3482
36. Liang SC, Tan XY, Luxenberg DP, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med*. 2006;203(10):2271-2279. doi:10.1084/jem.20061308
37. Wolk K, Warszawska K, Hoeflich C, et al. Deficiency of IL-22 contributes to a chronic inflammatory disease: pathogenetic mechanisms in acne inversa. *J Immunol*. 2011;186(2):1228-1239. doi:10.4049/jimmunol.0903907
38. Eyerich S, Wagener J, Wenzel V, et al. IL-22 and TNF-α represent a key cytokine combination for epidermal integrity during infection with Candida albicans. *Eur J Immunol*. 2011;41(7):1894-1901. doi:10.1002/eji.201041197
39. Johnston A, Xing X, Guzman AM, et al. IL-1F5, -F6, -F8, and -F9: a novel IL-1 family signaling system that is active in psoriasis and promotes keratinocyte antimicrobial peptide expression. *J Immunol*. 2011;186(4):2613-2622. doi:10.4049/jimmunol.1003162
40. Witte K, Witte E, Sabat R, Wolk K. IL-28A, IL-28B, and IL-29: promising cytokines with type I interferon-like properties. *Cytokine Growth Factor Rev*. 2010;21(4):237-251. doi:10.1016/j.cytogfr.2010.04.002
41. Sabat R, Ouyang W, Wolk K. Therapeutic opportunities of the IL-22-IL-22R1 system. *Nat Rev Drug Discov*. 2014;13(1):21-38. doi:10.1038/nrd4176
42. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of Serious Infection With Biologic and Systemic Treatment of Psoriasis: Results From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *JAMA Dermatol*. 2015;151(9):961-969. doi:10.1001/jamadermatol.2015.0718
43. Yiu ZZN, Sorbe C, Lunt M, et al. Development and validation of a multivariable risk prediction model for serious infection in patients with psoriasis receiving systemic therapy. *Br J Dermatol*. 2019;180(4):894-901. doi:10.1111/bjd.17421
44. Kao LT, Lee CZ, Liu SP, Tsai MC, Lin HC. Psoriasis and the risk of pneumonia: a population-based study. *PLoS One*. 2014;9(12):e116077. Published 2014 Dec 26. doi:10.1371/journal.pone.0116077
45. Svedbom A, Mallbris L, Ståhle M. Risk of respiratory infection in patients with plaque psoriasis. *J Am Acad Dermatol*. 2021;85(4):1013-1015. doi:10.1016/j.jaad.2020.12.083
46. Kojanova M, Fialova J, Cetkovska P, et al. Characteristics and risk profile of psoriasis patients included in the Czech national

registry BIOREP and a comparison with other registries. *Int J Dermatol*. 2017;56(4):428-434. doi:10.1111/ijd.13543
47. Nast A, Gisondi P, Ormerod AD, et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *J Eur Acad Dermatol Venereol*. 2015;29(12):2277-2294. doi:10.1111/jdv.13354
48. Balak DMW, Gerdes S, Parodi A, Salgado-Boquete L. Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature. *Dermatol Ther* (Heidelb). 2020;10(4):589-613. doi:10.1007/s13555-020-00409-4
49. Mrowietz U, Sorbe C, Reich K, et al. Fumaric acid esters for the treatment of psoriasis in Germany: characterising patients in routine care. *Eur J Dermatol*. 2020;30(1):41-48. doi:10.1684/ejd.2020.3709
50. Balato A, Scala E, Balato N, et al. Biologics that inhibit the Th17 pathway and related cytokines to treat inflammatory disorders. *Expert Opin Biol Ther*. 2017;17(11):1363-1374. doi:10.1080/14712598.2017.1363884
51. Takeshita J, Shin DB, Ogdie A, Gelfand JM. Risk of Serious Infection, Opportunistic Infection, and Herpes Zoster among Patients with Psoriasis in the United Kingdom. *J Invest Dermatol*. 2018;138(8):1726-1735. doi:10.1016/j.jid.2018.01.039
52. Dobry AS, Quesenberry CP, Ray GT, Geier JL, Asgari MM. Serious infections among a large cohort of subjects with systemically treated psoriasis. *J Am Acad Dermatol*. 2017;77(5):838-844. doi:10.1016/j.jaad.2017.07.047
53. Lee MP, Wu KK, Lee EB, Wu JJ. Risk for deep fungal infections during IL-17 and IL-23 inhibitor therapy for psoriasis. *Cutis*. 2020;106(4):199-205. doi:10.12788/cutis.0088
54. Wood KL, Hage CA, Knox KS, et al. Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. *Am J Respir Crit Care Med*. 2003;167(9):1279-1282. doi:10.1164/rccm.200206-563OC
55. Syed MN, Shin DB, Wan MT, Winthrop KL, Gelfand JM. The risk of respiratory tract infections in patients with psoriasis treated with interleukin 23 pathway-inhibiting biologics: A meta-estimate of pivotal trials relevant to decision making during the COVID-19 pandemic. *J Am Acad Dermatol*. 2020;83(5):1523-1526. doi:10.1016/j.jaad.2020.06.1014
56. Carugno A, Gambini DM, Raponi F, et al. COVID-19 and biologics for psoriasis: A high-epidemic area experience-Bergamo, Lombardy, Italy. *J Am Acad Dermatol*. 2020;83(1):292-294. doi:10.1016/j.jaad.2020.04.165
57. Witte-Händel E, Wolk K, Tsaousi A, et al. The IL-1 Pathway Is Hyperactive in Hidradenitis Suppurativa and Contributes to Skin Infiltration and Destruction. *J Invest Dermatol*. 2019;139(6):1294-1305. doi:10.1016/j.jid.2018.11.018
58. Sabat R, Wolk K, Loyal L, Döcke WD, Ghoreschi K. T cell pathology in skin inflammation. *Semin Immunopathol*. 2019;41(3):359-377. doi:10.1007/s00281-019-00742-7
59. Solimani F, Meier K, Ghoreschi K. Janus kinase signaling as risk factor and therapeutic target for severe SARS-CoV-2 infection. *Eur J Immunol*. 2021;51(5):1071-1075. doi:10.1002/eji.202149173
60. Gisondi P, Talamonti M, Chiricozzi A, et al. Treat-to-Target Approach for the Management of Patients with Moderate-to-Severe Plaque Psoriasis: Consensus Recommendations. *Dermatol Ther* (Heidelb). 2021;11(1):235-252. doi:10.1007/s13555-020-00475-8
61. Piaserico S, Gisondi P, Cazzaniga S, Naldi L. Lack of Evidence for an Increased Risk of Severe COVID-19 in Psoriasis Patients on Biologics: A Cohort Study from Northeast Italy. *Am J Clin Dermatol*. 2020;21(5):749-751. doi:10.1007/s40257-020-00552-w
62. Talamonti M, Galluzzo M, Chiricozzi A, et al. Characteristic of chronic plaque psoriasis patients treated with biologics in Italy during the COVID-19 Pandemic: Risk analysis from the PSO-BIO-COVID observational study. *Expert Opin Biol Ther*. 2021;21(2):271-277. doi:10.1080/14712598.2021.1853698
63. Smith CH, Yiu ZZN, Bale T, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. *Br J Dermatol*. 2020;183(4):628-637. doi:10.1111/bjd.19039
64. Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep*. 2020;69(1):1-11. Published 2020 Feb 14. doi:10.15585/mmwr.rr6901a1
65. Nogueira M, Warren RB, Torres T. Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis - time for a paradigm change. *J Eur Acad Dermatol Venereol*. 2021;35(4):824-834. doi:10.1111/jdv.16866
66. Papp KA, Haraoui B, Kumar D, et al. Vaccination Guidelines for Patients With Immune-Mediated Disorders on Immunosuppressive Therapies. *J Cutan Med Surg*. 2019;23(1):50-74. doi:10.1177/1203475418811335
67. Wine-Lee L, Keller SC, Wilck MB, Gluckman SJ, Van Voorhees AS. From the Medical Board of the National Psoriasis Foundation: Vaccination in adult patients on systemic therapy for psoriasis. *J Am Acad Dermatol*. 2013;69(6):1003-1013. doi:10.1016/j.jaad.2013.06.046
68. Balagon MV, Walsh DS, Tan PL, et al. Improvement in psoriasis after intradermal administration of heat-killed Mycobacterium vaccae. *Int J Dermatol*. 2000;39(1):51-58. doi:10.1046/j.1365-4362.2000.00862.x
69. O'Daly JA, Gleason J, Lezama R, Rodriguez PJ, Silva E, Indriago NR. Antigens from Leishmania amastigotes inducing clinical remission of psoriatic arthritis. *Arch Dermatol Res*. 2011;303(6):399 PubMed -415. doi: 10.1007/s00403-011-1133-0.
70. El-Darouti MA, Hegazy RA, Abdel Hay RM, Rashed LA. Study of T helper (17) and T regulatory cells in psoriatic patients receiving live attenuated varicella vaccine therapy in a randomized controlled trial. *Eur J Dermatol*. 2014;24(4):464-469. doi:10.1684/ejd.2014.2377
71. Diotallevi F, Campanati A, Radi G, et al. Vaccination against SARS-CoV-2 and psoriasis: the three things every dermatologist should know. *J Eur Acad Dermatol Venereol*. 2021;35(7):e428-e430. doi:10.1111/jdv.17256
72. Dávila-Seijo P, Dauden E, Descalzo MA, et al. Infections in Moderate to Severe Psoriasis Patients Treated with Biological Drugs Compared to Classic Systemic Drugs: Findings from the BIOBADADERM Registry. *J Invest Dermatol*. 2017;137(2):313-321. doi:10.1016/j.jid.2016.08.034
73. Rademaker M, Agnew K, Anagnostou N, et al. Psoriasis and infection. A clinical practice narrative. *Australas J Dermatol*. 2019;60(2):91-98. doi:10.1111/ajd.12895
74. Talamonti M, Galluzzo M, Chiricozzi A, et al. Management of biological therapies for chronic plaque psoriasis during COVID-19 emergency in Italy. *J Eur Acad Dermatol Venereol*. 2020;34(12):e770-e772. doi:10.1111/jdv.16841
75. Gelfand JM, Armstrong AW, Bell S, et al. National Psoriasis Foundation COVID-19 Task Force guidance for management of psoriatic disease during the pandemic: Version 2-Advances

in psoriatic disease management, COVID-19 vaccines, and COVID-19 treatments. *J Am Acad Dermatol*. 2021;84(5): 1254-1268. doi:10.1016/j.jaad.2020.12.058

76. Gisondi P, PIaserico S, Bordin C, Alaibac M, Girolomoni G, Naldi L. Cutaneous manifestations of SARS-CoV-2 infection: a clinical update. *J Eur Acad Dermatol Venereol*. 2020;34(11):2499-2504. doi:10.1111/jdv.16774
77. Gadarowski MB, Balogh EA, Bashyam AM, Feldman SR. Examining recommendations for the use of biologics and other systemic therapies during COVID-19: a review and comparison of available dermatology guidelines and patient registries [published online ahead of print, 2020 Oct 30]. *J Dermatolog Treat*. 2020;1-5. doi:10.1080/09546634.2020.1808154
78. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: treatment and monitoring recommendations. *J Eur Acad Dermatol Venereol*. 2020;34(11):2461-2498. doi:10.1111/jdv.16915
79. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *J Rheumatol*. 2007;34(4):689-695.
80. Pappas DA, Giles JT. Do antitumor necrosis factor agents increase the risk of postoperative orthopedic infections?. *Curr Opin Rheumatol*. 2008;20(4):450-456. doi:10.1097/BOR.0b013e3282fcc345
81. Aragane Y, Riemann H, Bhardwaj RS, et al. IL-12 is expressed and released by human keratinocytes and epidermoid carcinoma cell lines. *J Immunol*. 1994;153(12):5366-5372.
82. Hamza T, Barnett JB, Li B. Interleukin 12 a key immunoregulatory cytokine in infection applications. *Int J Mol Sci*. 2010;11(3):789-806. Published 2010 Feb 26. doi:10.3390/ijms11030789
83. Kanda N, Watanabe S. IL-12, IL-23, and IL-27 enhance human beta-defensin-2 production in human keratinocytes. *Eur J Immunol*. 2008;38(5):1287-1296. doi:10.1002/eji.200738051
84. Furue M, Furue K, Tsuji G, Nakahara T. Interleukin-17A and Keratinocytes in Psoriasis. *Int J Mol Sci*. 2020;21(4):1275. Published 2020 Feb 13. doi:10.3390/ijms21041275
85. Pappu R, Ramirez-Carrozzi V, Sambandam A. The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases. *Immunology*. 2011;134(1):8-16. doi:10.1111/j.1365-2567.2011.03465.x
86. Kusagaya H, Fujisawa T, Yamanaka K, et al. Toll-like receptor-mediated airway IL-17C enhances epithelial host defense in an autocrine/paracrine manner. *Am J Respir Cell Mol Biol*. 2014;50(1):30-39. doi:10.1165/rcmb.2013-0130OC
87. Ramirez-Carrozzi V, Sambandam A, Luis E, et al. IL-17C regulates the innate immune function of epithelial cells in an autocrine manner. *Nat Immunol*. 2011;12(12):1159-1166. Published 2011 Oct 12. doi:10.1038/ni.2156
88. Xu M, Lu H, Lee YH, et al. An Interleukin-25-Mediated Autoregulatory Circuit in Keratinocytes Plays a Pivotal Role in Psoriatic Skin Inflammation. *Immunity*. 2018;48(4):787-798.e4. doi:10.1016/j.immuni.2018.03.019
89. Ha HL, Wang H, Claudio E, Tang W, Siebenlist U. IL-20-Receptor Signaling Delimits IL-17 Production in Psoriatic Inflammation. *J Invest Dermatol*. 2020;140(1):143-151.e3. doi:10.1016/j.jid.2019.06.127
90. Brandt K, Singh PB, Bulfone-Paus S, Rückert R. Interleukin-21: a new modulator of immunity, infection, and cancer. *Cytokine Growth Factor Rev*. 2007;18(3-4):223-232. doi:10.1016/j.cytogfr.2007.04.003
91. Elsaesser H, Sauer K, Brooks DG. IL-21 is required to control chronic viral infection [published correction appears in Science. 2009 Aug 21;325(5943):946]. *Science*. 2009;324(5934): 1569-1572. doi:10.1126/science.1174182
92. Chan TC, Hawkes JE, Krueger JG. Interleukin 23 in the skin: role in psoriasis pathogenesis and selective interleukin 23 blockade as treatment. *Ther Adv Chronic Dis*. 2018;9(5): 111-119. doi:10.1177/2040622318759282
93. Sun R, Abraham C. IL23 Promotes Antimicrobial Pathways in Human Macrophages, Which Are Reduced With the IBD-Protective IL23R R381Q Variant. *Cell Mol Gastroenterol Hepatol*. 2020;10(4):673-697. doi:10.1016/j.jcmgh.2020.05.007
94. Stephen-Victor E, Fickenscher H, Bayry J. IL-26: An Emerging Proinflammatory Member of the IL-10 Cytokine Family with Multifaceted Actions in Antiviral, Antimicrobial, and Autoimmune Responses. *PLoS Pathog*. 2016;12(6):e1005624. Published 2016 Jun 23. doi:10.1371/journal.ppat.1005624
95. Scala E, Di Caprio R, Cacciapuoti S, et al. A new T helper 17 cytokine in hidradenitis suppurativa: antimicrobial and proinflammatory role of interleukin-26. *Br J Dermatol*. 2019; 181(5):1038-1045. doi:10.1111/bjd.17854
96. Murrieta-Coxca JM, Rodríguez-Martínez S, Cancino-Diaz ME, Markert UR, Favaro RR, Morales-Prieto DM. IL-36 Cytokines: Regulators of Inflammatory Responses and Their Emerging Role in Immunology of Reproduction. *Int J Mol Sci*. 2019;20(7):1649. Published 2019 Apr 3. doi:10.3390/ijms20071649
97. Wang P, Gamero AM, Jensen LE. IL-36 promotes anti-viral immunity by boosting sensitivity to IFN-α/β in IRF1 dependent and independent manners. *Nat Commun*. 2019;10(1):4700. Published 2019 Oct 16. doi:10.1038/s41467-019-12318-y
98. Ogawa E, Sato Y, Minagawa A, Okuyama R. Pathogenesis of psoriasis and development of treatment. *J Dermatol*. 2018;45(3):264-272. doi:10.1111/1346-8138.14139
99. Lambert JLW, Segaert S, Ghislain PD, et al. Practical recommendations for systemic treatment in psoriasis in case of coexisting inflammatory, neurologic, infectious or malignant disorders (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 2). *J Eur Acad Dermatol Venereol*. 2020;34(9): 1914-1923. doi:10.1111/jdv.16683
100. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Psoriasis comorbidities and preferred systemic agents. *J Am Acad Dermatol*. 2019;80(1):27-40. doi:10.1016/j.jaad.2018.06.057
101. Blauvelt A, Lebwohl MG, Bissonnette R. IL-23/IL-17A Dysfunction Phenotypes Inform Possible Clinical Effects from Anti-IL-17A Therapies. *J Invest Dermatol*. 2015;135(8): 1946-1953. doi:10.1038/jid.2015.144