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Increased Fungal Infections while using Emerging Therapies (Biologics and Small-molecule Inhibitors) for Treating Skin Diseases: A Review

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Biologics, such as tumor necrosis factor-α and interleukin inhibitors, are commonly used for treating immunological skin diseases, including psoriasis, psoriatic arthritis, and atopic dermatitis. The cluster of differentiation inhibitors and immune checkpoint inhibitors has also been used for treating bullous disorders and melanoma, respectively. Other small-molecule inhibitors, such as JAK inhibitors, have been introduced for treating atopic dermatitis and alopecia areata. Hence, given the importance of cytokines and small molecules in antifungal immunity, using these new treatments are proposed to increase the risk of fungal infections. Thus, this review presents an overview of the reported incidences and possible mechanisms of fungal infections related to the use of biologics, including small-molecule inhibitors used for dermatological treatments.

Key Words: Fungus, IL-17 inhibitors, TNF-α inhibitors

1. INTRODUCTION

New treatments for immune-mediated skin diseases has led to the so-called biologics era. However, although the efficacy and safety of most biologics have been proven, sporadic cases of serious fungal infections related to the use of tumor necrosis factor (TNF)-α inhibitors during the treatment of certain diseases, such as rheumatoid arthritis, have steadily been reported[1-3]. TNF-α inhibitors have also been used to treat psoriasis and psoriatic arthritis at similar doses as those used for rheumatoid arthritis. Moreover, indications for the use of these new drugs, such as JAK inhibitors, which were first approved for treating rheumatologic diseases, are being expanded to other immunologic skin diseases, including atopic dermatitis and alopecia areata.

Therefore, this article reviews the reported incidences of fungal infections and their possible mechanisms according to the types of biologics and small-molecule inhibitors used during dermatological treatments, including their fungal sources. Table 1 summarizes the commonly used drugs, including TNF inhibitors, interleukin (IL) inhibitors, small-molecule inhibitors, the cluster of differentiation (CD) inhibitors, and immune checkpoint inhibitors for treating skin diseases. Table 2 summarizes the possible mechanism associated with fungal infection and susceptible fungal infection according to the biologics and small molecule inhibitors.

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Table 1. Emerging immune-mediated drugs in the dermatologic area

Classification	Drugs	Indication
TNF inhibitors	Etanercept, infliximab, adalimumab, golimumab, and certolizumab	Psoriasis, psoriatic arthritis
Interleukin inhibitors		
IL-17 inhibitors	Brodalumab, secukinumab, and ixekizumab	Psoriasis, psoriatic arthritis
IL-12/23 inhibitors	Ustekinumab, guselkumab, risankizumab, and tildrakizumab	Psoriasis, psoriatic arthritis
IL-4 inhibitors	Dupilumab	Atopic dermatitis
CD20 inhibitors	Rituximab	Pemphigus
JAK inhibitors	Tofacitinib, baricitinib, ruxolitinib, upadacitinib, and abrocitinib	Alopecia areata, atopic dermatitis, vitiligo, psoriasis, psoriatic arthritis
Immune checkpoint inhibitors	Ipilimumab: anti-CTLA-4 antibody Pembrolizumab, nivolumab: PD-1 inhibitors	Melanoma

2. FUNGAL INFECTIONS ACCORDING TO BIOLOGICS

2.1. TNF-α inhibitors

TNF-α inhibitors are used to treat autoimmune diseases, such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases. Hence, drugs, such as etanercept, infliximab, adalimumab, golimumab, and certolizumab, are TNF-α inhibitors. The blockade of TNF-α exerts an antiinflammatory effect by reducing cytokine production and inducing the impairment of monocyte recruitment[1]. Simultaneously, TNF also influences the recognition of fungal antigens, phagocytosis during fungal removal, and granuloma formation[4]. Thus, the blockade of TNF-α can be a double-edged sword, thereby increasing the risk of viral, bacterial, and fungal infections.

In patients treated with TNF-α inhibitors, the prevalence of serious fungal infections differed among patients with different diseases. Interestingly, patients with rheumatoid arthritis showed higher infection rates than those with Crohn's disease or severe psoriasis and psoriatic arthritis. Nevertheless, the dosage and interval of treatment with TNF-α inhibitors were the same between the different disease groups[5-8]. For TNF-α inhibitor users diagnosed with Crohn's disease, TNF-α inhibitors did not raise the risk of serious infections, even with concomitant use of immunomodulators or steroids[8]. However, in rheumatoid arthritis patients, the risk of serious infections with TNF-α inhibitors increased dose-dependently[6]. Additionally, rheumatoid arthritis patients with concomitant use of disease-modifying antirheumatic drugs or high-dose systemic corticosteroids recorded increased susceptibility to opportunistic or serious infections. Hence, rheumatoid arthritis itself is proposed to be a risk factor for other serious infections compared with Crohn's disease or psoriasis.

2.2. IL-17 inhibitors

IL-17 inhibitors include brodalumab, secukinumab, and ixekizumab. They are used for treating psoriasis, psoriatic arthritis, and rheumatoid arthritis[9]. IL-17 influences the innate immune defense. IL-17 also facilitates neutrophil recruitment to the skin from systemic circulations by stimulating the expression of neutrophil-recruiting chemokines (e.g., CXCL1 and CXCL5). Additionally, IL-17A contributes to mucocutaneous host defenses against fungal infections, especially candidiasis[10]. Hence, patients with an inborn deficiency of IL-17 experience chronic mucocutaneous *Candida* infections[11]. Furthermore, a study by Burstein et al. supported the causal relationship between IL-17 inhibitors and dermatophytosis in that IL-17-deficient mouse was found not to develop protective skin barrier functions against *Microsporum canis*[12]. Another study has shown that IL-17 also participated in the defense against endemic mycoses, such as histoplasmosis and coccidioidomycosis[13]. Literature has also shown that approximately 50% of patients diagnosed with adult T-cell leukemia and lymphoma develop cutaneous fungal infections[14], which is proposed to result from decreased serum IL-17 levels.

Psoriatic patients treated with secukinumab, an anti-IL-17A monoclonal antibody, developed oral, esophageal, skin,

Table 2. Possible mechanism associated with fungal infection and susceptible fungal infection according to the biologics and small molecule inhibitors

Classification	Possible mechanism	Susceptible fungal infection
TNF-α inhibitors	Blockade of TNF-α reduces the recognition of fungal antigens, phagocytosis, the removal of fungi, and granuloma formation	TNF-α inhibitors has been associated with an increased incidence of opportunistic infections, including *Candida* and *Aspergillus* infections The prevalence of serious fungal infections differed among patients with different diseases
Interleukin inhibitors		
IL-17 inhibitors	IL-17 facilitates neutrophil recruitment from the circulation to the skin by expressing neutrophil-recruiting chemokines Blockade of IL-17A reduces mucocutaneous host defenses against fungal infections, particularly candidiasis	Mucocutaneous candidiasis (infection rate of 1~5% in psoriatic patients with secukinumab; 2.6% in psoriatic arthritis patients with ixekizumab vs. 0.4% in the placebo; 3.5~4% in psoriatic patients with brodalumab vs. placebo, ustekinumab, or etanercept groups)
IL-12/23 inhibitors	IL-23 is known to be involved in the optimal anti-fungal response against certain fungi such as *C. albicans* Blockade of IL-23 pathway may increase *Candida* infections	No increased risk of mucocutaneous *Candida* infections or deep fungal infections related to IL-23 inhibitors
CD20 inhibitors	B-cell depletion exerts a deleterious impact on the induction, maintenance and activation of cell-mediated immunity Impaired cellular immunity may contribute to the potential for opportunistic infections	No increased risk of invasive candidiasis, aspergillosis, or *Pneumocystis* pneumonia infections in rituximab users
JAK inhibitors	The effects of small-molecule protein kinases inhibitors on the immune system and the associated risk for the development of fungal infections are difficult to predict The synergistic effects of other immunosuppressive medications including corticosteroids and chemotherapy may increase the risk of fungal infections	Cryptococcosis, aspergillosis, and *Candida* esophagitis have very rarely been reported in patients treated with tofacitinib, baricitinib, and ruxolitinib regardless of the underlying diseases
Immune checkpoint inhibitors	Patients who receive PD-1 inhibitors are likely to have suppressed regulatory T cell responses and polarized T helper-1 immune responses, making them more susceptible to *Aspergillus* infection	Invasive aspergillosis (n = 2), invasive candidiasis (n = 1), and *Pneumocystis* pneumonia (n = 3) were reported in 740 melanoma patients who received PD-1 inhibitors

or vaginal candidiasis at a rate of 1% to 5%. A pooled analysis of 10 clinical studies has also reported that the exposure-adjusted incidence rates per 100 subject-years were 3.55, 1.85, and 1.37 for 150 and 300 mg secukinumab and etanercept, respectively[15]. From another study, the infection rate of *Candida* infections was 2.6% in psoriatic arthritis patients treated with ixekizumab and 0.4% in the placebo group[16].

Furthermore, mucocutaneous candidiasis was more common in patients with psoriasis treated using brodalumab (3.5~4%) versus placebo, ustekinumab, or etanercept groups, as reported by another study[9]. Therefore, various studies have shown that this class of drugs increases susceptibility to fungal infections, especially *Candida*.

2.3. IL-12 and IL-23 inhibitors

IL-12 and IL-23 inhibitors have been used for treating psoriasis, psoriatic arthritis, and inflammatory bowel diseases. However, ustekinumab inhibits both the IL-12 and IL-23 pathways, whereas guselkumab and tildrakizumab block only the IL-23 pathway. By contrast, risankizumab more selectively targets IL-23A. Studies have shown that IL-23 but not IL-12

is involved in optimal antifungal responses against certain fungi, such as *Candida albicans* (*C. albicans*). Theoretically, the blockade of the IL-23 pathway should therefore increase susceptibility to *Candida* infections[17]. However, compared with secukinumab, guselkumab did not increase the susceptibility to mucocutaneous *Candida* infections[18]. Additionally, no increase in deep fungal infections related to IL-23 inhibitors has been reported through observational studies of more than 5 years[19,20].

2.4. CD20 inhibitors

CD receptors are cell surface molecules present on hematopoietic cells. CD20 inhibitors are used for treating pemphigus, leukemia, lymphoma, and multiple myeloma. Rituximab is a first-generation CD20 monoclonal inhibitor. It does not immediately block the production of immunoglobulins because CD20 antigens are not expressed on B-cell precursors or plasma cells[21].

Invasive candidiasis and aspergillosis have thus rarely been reported in rituximab users. Still, *Pneumocystis jirovecii* pneumonia was once suggested to be related to the use of rituximab. Nevertheless, *Pneumocystis jirovecii* pneumonia was reported only in two of 1085 pemphigus vulgaris patients in a systematic review of rituximab use over 16 years[21].

It is therefore difficult to attribute fungal infections directly to CD20 inhibitors, considering the effects of the concomitant use of immunosuppressive drugs, neutropenia, and underlying diseases on infection risks. A recent study supporting this fact also reported that rituximab itself did not increase *Pneumocystis jirovecii* pneumonia infections, including those in lymphoma patients[22]. However, patients on rituximab taking at least 20 mg of corticosteroids longer than 4 weeks required anti-*Pneumocystis* prophylaxis[22].

2.5. JAK inhibitors

Various small-molecule inhibitors are used for treating autoimmune diseases and cancers[23]. JAK/STAT inhibitors are among these representative small-molecule inhibitors that are used in treating rheumatoid arthritis, polycythemia vera, myelofibrosis, alopecia areata, atopic dermatitis, psoriasis, and psoriatic arthritis. The JAK inhibitor drugs include tofacitinib, baricitinib, and ruxolitinib. Newer JAK inhibitors, such as upadacitinib and abrocitinib, which inhibit various combinations of the JAK/STAT pathway, have also been developed.

Systematic reviews and retrospective multicenter database analyses have reported that cryptococcosis, aspergillosis, and *Candida* esophagitis were rarely reported in patients treated with tofacitinib, baricitinib, and ruxolitinib regardless of the underlying diseases[23]. Furthermore, no studies have evaluated fungal infections in patients with alopecia areata or atopic dermatitis treated with JAK inhibitors. Interestingly, ruxolitinib turned out to have a therapeutic effect on chronic mucocutaneous candidiasis patients related to STAT1 gain-of-function by blocking the JAK/STAT pathway[24].

2.6. Immune checkpoint inhibitors

Programmed cell death-1 (PD-1 and CD270) is an immune inhibitory receptor belonging to the CD28:B7 family of costimulatory molecules. PD-1 inhibitors and anticytotoxic T-lymphocyte-association protein 4 (CTLA-4) antibodies have been used for treating various malignancies, such as malignant melanoma, non-small cell lung cancer, and hematologic malignancies. Ipilimumab is an anti-CTLA-4 antibody, and pembrolizumab in addition to nivolumab are representative PD-1 inhibitors widely used for treating melanoma.

A study reported that PD-1 not only acts as an immune inhibitory receptor but also serves as a negative regulator of α-(1,3)-glucan-mediated regulatory T-cell polarization, which is important in *Aspergillus* infections[25]. Theoretically, another study reported that patients who received PD-1 inhibitors had their regulatory T-cell responses and polarized T helper-1 immune responses suppressed[26]. In another invasive pulmonary aspergillosis mouse model, treatment with PD-1 inhibitors significantly improved survival and decreased the fungal burden[27]. However, invasive aspergillosis (n = 2), invasive candidiasis (n = 1), and *Pneumocystis* pneumonia (n = 3) were reported in 740 melanoma patients who received PD-1 inhibitors. The main risk factors of serious infections, including invasive fungal infections, were also associated with the simultaneous use of corticosteroids or infliximab[28]. Thus, host factors and the concomitant use of the drugs should be considered in determining the risk of PD-1 inhibitors.

3. FUNGAL INFECTIONS ACCORDING TO INVASIVENESS AND FUNGAL SOURCES

3.1. The incidence of invasive fungal infections in patients using biologics for dermatological diseases is rare.

Deep fungal infections are extremely rare. However, delayed diagnosis can be life-threatening. Thus, physicians should

be aware of the clinical symptoms of deep fungal infections and strive to make an early diagnosis.

Invasive fungal infections that developed among patients on biologics and small-molecule inhibitors were all taking concomitant immunosuppressants or had an immunocompromised status, such as graft-versus-host disease after hematopoietic stem cell transplantations[1,29]. Furthermore, the development of deep fungal infections in patients with skin diseases taking biologics is much more rarely reported. For example, the overall incidence of serious infections, including deep fungal infections in patients with rheumatoid arthritis, has been reported to be approximately 1.97/100 person-years for patients taking adalimumab and 2.47/100 person-years for those taking infliximab[2]. By contrast, the incidence of deep fungal infections in patients diagnosed with psoriasis taking adalimumab or infliximab was close to zero after the analysis of long-term follow-up data of 19 randomized clinical trials[2].

Next, we reviewed the incidence of deep fungal infection depending upon the fungal sources, which was reported to be related to the use of biologics and small-molecule inhibitors for treating skin diseases. Below are some of the important infectious fungal microbes.

3.1.1. Cryptococcosis

The incidence of cryptococcosis was reported to arise in 5.08 cases/100,000 persons of the overall patients treated with infliximab[30,31]. Among the reported cases, pulmonary cryptococcosis was the predominant manifestation. Additionally, among the patients on TNF-α inhibitors for treating skin diseases, only a case of cutaneous deep fungal cryptococcosis, which occurred in a 14-year-old boy on the scalp mimicking a kerion, was reported to be related to the use of etanercept for treating psoriasis[32]. A 65-year-old male patient with psoriasis also developed pulmonary cryptococcosis during treatment with tofacitinib[33]. Furthermore, a case of disseminated cryptococcosis was reported in a patient with severe psoriasis who was treated with methotrexate, cyclosporine, and efalizumab (an anti-CD11a antibody)[34]. However, no case reports of cryptococcosis related to the use of interleukin inhibitors have been reported to date.

3.1.2. Aspergillosis

Aspergillosis developed at a rate of 6.19 to 8.63 cases/100,000 persons among the general users of TNF-α inhibitors [30,31]. One case of cutaneous aspergillosis was reported in a psoriasis patient taking TNF-α inhibitors[35]. However, no case reports of aspergillosis related to the use of interleukin inhibitors, JAK inhibitors, or rituximab have been reported in patients with skin diseases.

3.1.3. Histoplasmosis[36,37]

Life-threatening histoplasmosis has been reported in patients taking TNF-α inhibitors[37]. Subsequently, the Food and Drug Administration (FDA) requested a black box warning for histoplasmosis. However, among the patients diagnosed with psoriasis, only one case of histoplasmosis was reported in a patient who concomitantly received infliximab, methotrexate, and corticosteroid, in addition to living in an endemic histoplasmosis area. The patient was treated with amphotericin B[36]. Besides this case, no other case reports of histoplasmosis related to the use of interleukin or JAK inhibitors in patients with skin diseases have been reported.

3.1.4. *Pneumocystis* infection

Patients diagnosed with rheumatoid arthritis receiving infliximab with other immunosuppressants, such as corticosteroids, methotrexate, or cyclosporine, have been proposed to be at a higher risk of *Pneumocystis* pneumonia[38]. Prophylaxis has also been indicated for patients using high-dose corticosteroids for prolonged periods with or without biologics[38]. However, in psoriasis or psoriatic arthritis patients, treatment with TNF-α inhibitors without the use of other immunosuppressants did not increase the incidence of *Pneumocystis* pneumonia. A case of *Pneumocystis* pneumonia was reported in a 54-year-old man diagnosed with refractory pustular psoriasis who received infliximab. The patient workup revealed an IL-36RN deficiency, which was resolved by anakinra treatment[39]. In another study, a 41-year-old man on etanercept for treating psoriatic arthritis was reported to develop *Pneumocystis* pneumonia[40].

Pneumocystis pneumonia was also reported in only two patients in a systematic review and meta-analysis of polycythemia vera patients taking ruxolitinib[41]. Rituximab did not increase the susceptibility to *Pneumocystis* pneumonia in pemphigus patients. However, two melanoma patients who received immunosuppressants to control ipilimumab-induced adverse effects developed *Pneumocystis* pneumonia[42].

3.2. Noninvasive fungal infections are relatively common with the use of some biologics, especially mucocutaneous candidiasis during anti-IL-17 treatment.

3.2.1. Candidiasis

Candidiasis is the most common fungal infection in patients under treatment with biologics and is reported to account for approximately 70% of fungal infections. However, the overall incidence is low. Studies have also shown that *C. albicans* infections occurring in the oral (42.1%) or genital (41.7%) areas are not serious. However, invasive candidiasis can seldom occur in patients with immunocompromised status.

TNF-α-related candidiasis was reported to occur in 5.31~10.15 per 100,000 people between 1998 and 2002, depending on the type of drug, according to the FDA's Adverse Events Reporting System[30,31]. Candidiasis was also reported in 1.7~4.0% of the patients on IL-17 inhibitors depending on the drugs. Conversely, incidences of 0.3% and 2.3% were reported in patients taking placebo and ustekinumab, respectively[43].

3.2.2. Dermatophytosis

It has been difficult to find a causal relationship between biologics and dermatophytosis because dermatophytosis is common in healthy populations. Localized dermatophytosis involving perianal lesions was therefore reported in two female patients diagnosed with psoriasis during treatment with secukinumab[44]. Widespread tinea corporis was also reported in a 38-year-old male patient 4 weeks after starting secukinumab use to treat psoriasis[45]. In another study, a 64-year-old woman developed invasive dermatophytosis during the treatment period of infliximab and corticosteroid[46]. Dermatophyte infections in patients with psoriatic on IL-23 inhibitors have also not been reported.

3.2.3. *Malassezia* infection

Malassezia infections related to using biologics have rarely been reported. However, small numbers of patients with atopic dermatitis receiving the IL-4 inhibitor, dupilumab, developed facial redness. The cause of the redness was not well known; however, it was assumed to be caused by enhanced Th1 immune responses due to the blocked Th2 response by dupilumab. This redness also triggered severe inflammation in patients with *Malassezia* hypersensitivity. Reports on dupilumab facial redness were however improved after itraconazole treatment in two of the patients diagnosed with severe atopic dermatitis[47].

Furthermore, seven of 153 psoriasis patients on TNF inhibitors were diagnosed with pityriasis versicolor in one institute. In this study, only one patient was cured with topical antifungals, and the other six were treated with systemic antifungal agents[48].

4. CONCLUSIONS

The use of biologics in treating rheumatoid arthritis increases the risk of opportunistic fungal infections, whereas the use of biologics in treating other skin disorders, such as psoriasis or psoriatic arthritis, does not increase the risk of fungal infections. Sporadic cases of deep fungal infections are also rare in patients diagnosed with psoriasis or psoriatic arthritis. Furthermore, in most of the reported cases, the patients received concomitant immunosuppressants because of disease severity. By contrast, studies showed that noninvasive mucocutaneous candidiasis was common during anti-IL-17 treatment, especially in patients with psoriasis. Therefore, in determining the susceptibility and risk to fungal infections associated with biologics, JAK inhibitors, CD inhibitors, and immune checkpoint inhibitors, individual approaches are needed, considering host factors, such as underlying disease and the concomitant use of other immunosuppressants.

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CONFLICT OF INTEREST

In relation to this article, we declare that there is no conflict of interest.

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REFERENCES

1. Davis MR, Thompson GR 3rd, Patterson TF. Fungal infections potentiated by biologics. Infect Dis Clin North Am 2020;34:389-411

2. Jourabchi N, Adelzadeh L, Wu JJ. The risk of deep fungal infections during biologic therapy for psoriasis. J Eur Acad Dermatol Venereol 2014;28:1277-1285
3. Friedman DZP, Schwartz IS. Emerging fungal infections: new patients, new patterns, and new pathogens. J Fungi (Basel) 2019;5:67
4. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc 2008;83:181-194
5. Pérez-Sola MJ, Torre-Cisneros J, Pérez-Zafrilla B, Carmona L, Descalzo MA, Gómez-Reino JJ. Infections in patients treated with tumor necrosis factor antagonists: incidence, etiology and mortality in the BIOBADASER registry. Med Clin (Barc) 2011;137:533-540
6. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275-2285
7. Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, et al. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev 2009;8:266-273
8. Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2008;6:644-653
9. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol 2016;175:273-286
10. Hay RJ. *Candida* infections and interleukin-17 inhibitors used in dermatology. Br J Dermatol 2017;177:10-11
11. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 2011;332:65-68
12. Burstein VL, Guasconi L, Beccacece I, Theumer MG, Mena C, Prinz I, et al. IL-17-mediated immunity controls skin infection and T helper 1 response during experimental *Microsporum canis* dermatophytosis. J Invest Dermatol 2018;138:1744-1753
13. Puerta-Arias JD, Mejía SP, González Á. The role of the interleukin-17 axis and neutrophils in the pathogenesis of endemic and systemic mycoses. Front Cell Infect Microbiol 2020;10:595301
14. Sawada Y, Nakamura M, Kabashima-Kubo R, Shimauchi T, Kobayashi M, Tokura Y. Defective epidermal innate immunity and resultant superficial dermatophytosis in adult T-cell leukemia/lymphoma. Clin Cancer Res 2012;18:3772-3779
15. van de Kerkhof PC, Griffiths CE, Reich K, Leonardi CL, Blauvelt A, Tsai TF, et al. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol 2016;75:83-98.e4
16. Mease P, Roussou E, Burmester GR, Goupille P, Gottlieb A, Moriarty SR, et al. Safety of ixekizumab in patients with psoriatic arthritis: results from a pooled analysis of three clinical trials. Arthritis Care Res (Hoboken) 2019;71:367-378
17. Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against *Candida albicans*. J Immunol 2010;185:5453-5462
18. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med 2015;373:1318-1328
19. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 2013;168:844-854
20. Gordon KB, Papp KA, Langley RG, Ho V, Kimball AB, Guzzo C, et al. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (Part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. J Am Acad Dermatol 2012;66:742-751
21. Tavakolpour S, Mahmoudi H, Balighi K, Abedini R, Daneshpazhooh M. Sixteen-year history of rituximab therapy for 1085 pemphigus vulgaris patients: A systematic review. Int Immunopharmacol 2018;54:131-138
22. Mikulska M, Lanini S, Gudiol C, Drgona L, Ippolito G, Fernández-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect 2018;24 Suppl 2:S71-S82
23. Bechman K, Galloway JB, Winthrop K. Small-molecule protein kinases inhibitors and the risk of fungal infections. Current Fungal Infection Reports 2019;13:229-243

24. Zimmerman O, Rösler B, Zerbe CS, Rosen LB, Hsu AP, Uzel G, et al. Risks of ruxolitinib in STAT1 gain-of-function-associated severe fungal disease. Open Forum Infect Dis 2017;4:ofx202
25. Stephen-Victor E, Karnam A, Fontaine T, Beauvais A, Das M, Hegde P, et al. *Aspergillus fumigatus* cell wall α-(1,3)-glucan stimulates regulatory T-cell polarization by inducing PD-L1 expression on human dendritic cells. J Infect Dis 2017;216:1281-1294
26. Daver N, Kontoyiannis DP. Checkpoint inhibitors and aspergillosis in AML: the double hit hypothesis. Lancet Oncol 2017;18:1571-1573
27. Wurster S, Robinson P, Albert ND, Tarrand JJ, Goff M, Swamydas M, et al. Protective activity of programmed cell death protein 1 blockade and synergy with caspofungin in a murine invasive pulmonary aspergillosis model. J Infect Dis 2020;222:989-994
28. Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infec Dis 2016;63:1490-1493
29. Maertens JA, Girmenia C, Brüggemann RJ, Duarte RF, Kibbler CC, Ljungman P, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. J Antimicrob Chemother 2018;73:3221-3230
30. Filler SG, Yeaman MR, Sheppard DC. Tumor necrosis factor inhibition and invasive fungal infections. Clin Infect Dis 2005;41 Suppl 3:S208-212
31. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004;38:1261-1265
32. Hoang JK, Burruss J. Localized cutaneous *Cryptococcus albidus* infection in a 14-year-old boy on etanercept therapy. Pediatr Dermatol 2007;24:285-288
33. Seminario-Vidal L, Cantrell W, Elewski BE. Pulmonary cryptococcosis in the setting of tofacitinib therapy for psoriasis. J Drugs Dermatol 2015;14:901-902
34. Tuxen AJ, Yong MK, Street AC, Dolianitis C. Disseminated cryptococcal infection in a patient with severe psoriasis treated with efalizumab, methotrexate and ciclosporin. Br J Dermatol 2007;157:1067-1068
35. Osório F, Magina S, Azevedo F. Primary cutaneous aspergillosis complicating tumor necrosis factor-α blockade therapy in a patient with psoriasis. Actas Dermosifiliogr 2012;103:939-941
36. Kamili QU, Menter A. Atypical presentation of histoplasmosis in a patient with psoriasis and psoriatic arthritis on infliximab therapy. J Drugs Dermatol 2010;9:57-60
37. Lee JH, Slifman NR, Gershon SK, Edwards ET, Schwieterman WD, Siegel JN, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 2002;46:2565-2570
38. Harigai M, Koike R, Miyasaka N. *Pneumocystis* pneumonia associated with infliximab in Japan. N Engl J Med 2007;357:1874-1876
39. Podlipnik S, de la Mora L, Alsina M, Mascaró JM, Jr. *Pneumocystis jirovecii* pneumonia in a patient with pustular psoriasis with an IL-36RN deficiency treated with infliximab: Case report and review of the literature. Australas J Dermatol 2017;58:e44-e47
40. Lahiff C, Khiaron OB, Nolan N, Chadwick GA. *Pneumocystis carinii* pneumonia in a patient on etanercept for psoriatic arthritis. Ir J Med Sci 2007;176:309-311
41. Lussana F, Cattaneo M, Rambaldi A, Squizzato A. Ruxolitinib-associated infections: A systematic review and meta-analysis. Am J Hematol 2018;93:339-347
42. Arriola E, Wheater M, Krishnan R, Smart J, Foria V, Ottensmeier C. Immunosuppression for ipilimumab-related toxicity can cause *Pneumocystis* pneumonia but spare antitumor immune control. Oncoimmunology 2015;4:e1040218
43. Saunte DM, Mrowietz U, Puig L, Zachariae C. *Candida* infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol 2017;177:47-62
44. Quach OL, Hsu SH. Perianal dermatophytosis during secukinumab therapy for plaque psoriasis. JAMA Dermatol 2016;152:486-487
45. Neema S, Singh S, Pathak N, Khan MA. Widespread superficial dermatophytosis in patient on secukinumab for treatment of chronic plaque psoriasis. Indian Dermatol Online J 2019;10:76-78
46. Lowther AL, Somani AK, Camouse M, Florentino FT, Somach SC. Invasive *Trichophyton rubrum* infection occurring with infliximab and long-term prednisone treatment. J Cutan Med Surg 2007;11:84-88
47. de Beer FSA, Bakker DS, Haeck I, Ariens L, van der Schaft J, van Dijk MR, et al. Dupilumab facial redness: Positive effect of itraconazole. JAAD Case Rep 2019;5:888-891
48. Balestri R, Rech G, Piraccini BM, Antonucci A, Ismaili A, Patrizi A, et al. Pityriasis versicolor during anti-TNF-α monoclonal antibody therapy: therapeutic considerations. Mycoses 2012;55:444-446