Chapter

Biologics: Beyond the Basics

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Abstract

Biologics are novel targeted therapies aimed at blocking specific cells or proteins created by the immune system that mediate the inflammatory process. Currently, the American Food and Drug Administration (FDA) has approved 12 different biologics that are administered either through intravenous infusion or intramuscularly for the treatment and prevention of psoriasis and arthritic psoriasis. These biologics categorically inhibit different cytokines, mainly IL-23, IL-17A, and IL-17F, that are activated and mediate the psoriasiform process with better long-term effectiveness and reduced side effects as compared to traditional systemic and topical steroids. The benefit of biologics also extends to a larger time interval between medication dosing as patients may achieve therapeutic levels for weeks to months before needing another dose. Transition to biologics from standard therapy should be considered for the right patients who have failed to improve, however with caution towards inherently immunocompromised patients as biologics may increase the risk of developing infections through compounded immune system suppression. This risk can be stratified with prophylactic blood tests, TB testing, and other examinations while on the biologics to ensure proper patient safety and therapeutic benefit.

Keywords: psoriasis, biologics, immunology, pharmacology, dermatopathology

1. Introduction

Biologics are a different class of medications than traditional systemic drugs that target the entire immune system. These agents are able to specifically target parts of the immune system that may mediate a certain pathology without affecting other normal functioning aspects of the immune system and thus yield less risk of side effects involving the liver, kidneys and other organs typically affected by immunosuppressive medications [1]. The biologics used to treat psoriasis distinctively block a set of cytokines which are proteins that facilitate the immune system response. Cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin 17-A, interleukin 12, and interleukin 23 serve a major role in manifesting the disease process of psoriasis and psoriatic arthritis which include joint damage, osteopenia, and chronic inflammation involving the skin and other organs [2, 3]. Currently there are 11 biologics that have been approved by the American FDA to treat psoriasis and arthritic psoriasis for both adults and children over 4 years of age [1, 3]. These approved biologics have a relatively good safety profile, however judicious discretion is warranted in selecting appropriate therapy for the right patient in order to achieve the best therapeutic outcome [1, 3].

2. TNF-a inhibitors

The adoption of biologic therapy has significantly enhanced the treatment of moderate to severe psoriasis. Earlier first line therapy was limited to oral agents such as methotrexate, cyclosporine and retinoids with extensive black box warnings and potential risk of death [3]. This advancement in therapy is linked to better understanding of the underlying pathophysiology of psoriasis as more extensive than hyperproliferation of the epidermis as previously postulated [3]. Recent literature has been able to produce a clear pathophysiological mechanism with direct association of specific cytokines in the disease process. In the first part of the pathophysiological cascade interleukin 12 and interleukin 23 are secreted from macrophages, keratinocytes, and natural killer T cells. These interleukins illicit the differentiation of native T cells to Th1, Th17, and Th22 cells which go on to produce tumor necrosis factor alpha (TNF-a), interleukin 17, and interleukin 22 which represent the ending inflammatory cascade [3–5]. The interleukin 23 mediated Th17 activation pathway has been identified as the major patho-immunological contributor in the inflammatory response involving psoriasis [3]. Current evidence shows that biologic treatment aimed at inhibiting TNF-a, interleukin 23, and Interleukin 17 has been more effective in treating psoriasis which further reinforces their greater roles in the disease process [5].

As the therapeutic apparatus enlarges and more treatment options become available the choice of which agent is more appropriate for which patient becomes harder to make. As a result, the use of biologics in the treatment of psoriasis can become both an art and a science. The earliest approved biologic option, Adalimumab (Humira), is a human monoclonal antibody targeting TNF-a and has been widely effective in reducing joint destruction in psoriatic arthritis patients and has been prescribed for plaque psoriasis in children [6]. An ongoing 10-year international prospective observational registry evaluating the long-term safety and effectiveness of adalimumab has shown low numbers of events adverse events including serious infections, cardiovascular pathology, or malignancy [7]. Data from the pregnancy inflammatory bowel disease and neonatal outcomes (PIANO) has also shown no increased risk of poor outcomes during pregnancy [8]. However, over prolonged use adalimumab has shown reduced efficacy as opposed to newer agents, in addition there is well documented and established association between TNF-a inhibitors and reactivation of the tuberculosis virus which mandates careful monitoring preinitiation of treatment [5].

Etanercept (Enbrel) is another a TNF-a inhibitor that is used for treatment of moderate to severe adult and pediatric plaque psoriasis as well as psoriatic arthritis, however, the use of this biologic has significantly decreased over the last 10 years due to its association with progressive multifocal leukoencephalopathy triggered by the human polyomavirus 2 [9]. Despite this association, Etanercept has been effectively utilized in the geriatric population as one of the best safety profile biologics in treatment of severe psoriasis and was the first biologic approved for pediatric use down to 4 years of age [5].

Infliximab (Remicade) is a TNF-a inhibitor approved for use in treatment of psoriasis, psoriatic arthritis and other inflammatory syndromes in both adults and children, however since it is administered intravenously it is not commonly utilized by dermatologists [5].

Certolizumab (Cimzia) is a TNF-a blocker that functions in a dose dependent manner. This biologic is utilized in the treatment of psoriatic arthritis and moderate

to severe plaque psoriasis [5]. Certolizumab has maintained its efficacy in treatment of psoriatic arthritis in patients with and without prior use of other TNF-a inhibitors [10]. Certolizumab has shown superior efficacy in phase 3 clinical trials as compared with other TNF-a inhibitors, achieving a 75% improvement in the psoriasis area and severity index (PASI) in 81.6% of patients by week 16 since onset of first dose [11]. In addition, certolizumab has been demonstrated to be safe during pregnancy with minimal transfer across the placenta as well as into breast milk [12, 13]. Safety wise, certolizumab has recorded data only up to 3 years of use and it requires more frequent dosing than other biologics [5].

3. Interleukin-17 inhibitors

The subsequent class of biologic agents to be approved by the FDA focused their action on inhibiting interleukin-17A and the first biologic approved for plaque psoriasis and psoriatic arthritis in that class was secukinumab (Cosentyx). This agent has shown excellent efficacy in treating traditionally resistant disease domains including the scalp, nails, and palmoplantar psoriasis [14–16]. Furthermore, in a trial comparing secukinumab to etanercept and ustekinumab (interleukin-12/23 inhibitor), secukinumab showed superior results in clearing the skin of patients with moderate to severe plaque psoriasis [17]. Moreover, the American FDA has recognized secukinumab's efficacy in inhibiting joint destruction in patients with psoriatic arthritis and as a result it is currently the preferred agent for psoriatic arthritis as opposed to interleukin-12/23 or interleukin-23 inhibiting agents [18]. Secukinumab has also displayed significant recapturing properties, exhibiting a 75% improvement in PASI by week 12 in 95% of patients who discontinued and restarted the medication after experiencing a disease exacerbation [5]. There is an increased risk of new onset or exacerbation of existing inflammatory bowel disease with interleukin-17 inhibitors as well as minor risk of fungal and yeast infections [5]. Yet, secukinumab has no black box warnings issued by the American FDA and has been monitored the longest for safety out of all the interleukin-17 inhibitors [5, 19]. According to phase 3 clinical trials, while on secukinumab, fungal and yeast infection rates were higher than placebo but less than 1% and 1.3% respectively [5]. The incidence of new onset inflammatory bowel disease in patients taking secukinumab has been documented to be 0.001% of patients [5].

Brodalumab (Siliq) was the subsequent interleukin-17 inhibitor to be approved by the American FDA for the treatment of moderate to severe plaque psoriasis in adult patients [5]. Brodalumab's mechanism of action is unique among its class because it is the only biologic to completely inhibit all parts of the interleukin-17 receptor including 17A, 17F, 17A/F, and 17E [5]. As a result, brodalumab has shown excellent efficacy and rapid onset of action in phase 3 clinical trials accomplishing 100% improvement in the psoriasis area and severity index in 44% of patients by week 12 and since onset of first dose [5]. In comparison to ustekinumab, brodalumab's rapid onset of action achieved a statistically significant 90% improvement in the psoriasis area and severity index by 2 and 100% improvement by week 4 [5]. Additionally, brodalumab has shown effectiveness in rescuing patients from other failed and non-responsive interleukin-17A inhibitor treatment [20]. This effectiveness is compounded in literature displaying that by 52 weeks of treatment, less than 3% of patients developed resistance to treatment [5]. The American FDA has issued a warning for suicide regarding brodalumab, however no scientific evidence has emerged to show any increased risk of completed suicides,

suicide attempts, major cardiac events, tuberculosis, or other inflammatory bowel diseases based on a recently published one-year pharmacovigilance study in 2020 [21]. In addition, analysis of the phase III clinical trials done around the world has shown 4 completed suicides in 4464 patients with all patients having an underlying or associated psychiatric disorders or stressors. Moreover, no other country except the United States has issued an increased risk of suicides with use of brodalumab [5, 22]. The incidence of new onset inflammatory bowel disease in patients taking brodalumab has been reported as 1 out of 4464 patients with the risk of yeast infection being 0.9% as opposed to 0.2% while on placebo [5]. Based upon the reassuring PASI data, cost effectiveness, as well as relatively safe profile, brodalumab serves as a first line treatment for moderate to severe psoriasis.

Ixekizumab (Talz) is another agent that inhibits the interleukin-17 receptor through blocking its interaction with the interleukin-17A receptor component [5]. This biologic is indicated for plaque psoriasis in adults and kids as early as 6 years of age, and it is the only American FDA approved actor for treatment of genital plaque psoriasis [5]. Ixekizumab has displayed superior effectiveness in treating moderate to severe pediatric plaque psoriasis during clinical trials as compared to placebo with similar safety profile results seen in adults [23]. Ixekizumab has shown a 75% improvement on the PASI scale in 90% patients by week 12 and has demonstrated superior results in onset of action and nail clearing when compared to other biologics such as adalimumab and guselkumab (interleukin-23 inhibitor) [24, 25]. Currently ixekizumab has no black box warning issued by the American FDA and has displayed a relatively safe profile of use with the incidence of inflammatory bowel disease development being less than 1 out of 1000 patients [5]. Like other interleukin-17 inhibitors, ixekizumab carries an increased risk of fungal and yeast infections however in phase 3 clinical trials the incidence of yeast infection was 0.6% as compared to 0.5% while on placebo [26].

Bimekizumab (Bimzelx) is a dual interleukin-17A and interleukin-17F inhibitor which has shown improved therapeutic benefit as compared to sole blockage of interleukin-17A and has been indicated for treatment of moderate to severe plaque psoriasis and psoriatic arthritis in adults [27]. In a head-to-head comparison, Bimekizumab has demonstrated better clinical results than ustekinumab (interleukin-12/23 inhibitor) that translated into achieving a 90% improvement in the PASI scale for 85% of patients by week 16 vs. 49.7% of patients on ustekinumab [28]. Furthermore, following one dose, bimekizumab has demonstrated quicker onset of response when compared with ustekinumab where, a 75% improvement on the PASI was observed in 76.9% of patients taking bimekizumab vs. 15.3% of the patients on ustekinumab [28]. Unfortunately, bimekizumab is still undergoing the approval process by the American FDA for use in plaque psoriasis and it is currently available throughout the European Union, Australia, and Asia.

4. Interleukin-23 inhibitors

The interleukin-23 inhibitors are a relatively newer class of biologic agents developed to treat plaque psoriasis and the first biologic in this class to be approved by the American FDA was guselkumab (Tremfya) [5]. This agent halts the immune cascade mediated through the interleukin-23 receptor by inhibiting the p19 subunit of the interleukin-23 receptor and is currently the only interleukin-23 inhibitor to

also be approved for treatment of psoriatic arthritis [5]. Guselkumab has displayed excellent clinical results with achieving a 75% improvement on the PASI scale in 90% of patients by week 16 [29]. In a head-to-head comparison, guselkumab has shown superior clinical results against secukinumab in achieving a 90% improvement on the PASI scale at week 48, in addition to performing better than adalimumab in the treatment of scalp plaque psoriasis and palmoplantar psoriasis [30, 31]. Guselkumab reports a slower onset time when compared to ixekizumab, however, was able to achieve a similar end point by week 24 [5]. Safety wise, the drug has garnered safety data for over 3 years with no significant evidence for increased risk of tuberculosis, fungal infections, yeast infections, or inflammatory bowel disease [5].

Tildrakizumab (Ilumya) was the next interleukin-23 inhibitor to be approved by the American FDA and it functions through the same mechanism as its predecessor guselkumab by binding the p19 subunit of the interleukin-23 receptor and preventing its downstream participation in the immune cascade [5]. This drug is currently only approved for treatment of moderate to severe plaque psoriasis and has shown high recapture rates where approximately 85–96% of patients showed a 75% improvement on the PASI scale after stopping and restarting the medication [32]. Moreover, tildrakizumab has also demonstrated a sustained therapeutic effect without redosing, where patients were able to maintain a 75% improvement on the PASI scale for 7.4 months before losing their response [33]. Safety wise, tildrakizumab had least number of adverse effects occurring at least in 1% of patients among all the biologics available for treatment of psoriasis [5]. The downside to this biologic is that both the onset of action and peak efficacy are slower in comparison to other interleukin-23 inhibitors [5].

Risankizumab (Skyrizi) is the latest interleukin-23 inhibitor approved by American FDA and it exerts its antagonism of interleukin-23 by selectively targeting the p19 subunit of the interleukin-23 receptor [5]. The drug is currently indicated for moderate to severe plaque psoriasis in adults. Currently the drug requires four sets of dosing per year and one set of dosing per year is currently being reviewed by the American FDA [5]. Risankizumab has shown good efficacy in clinical trials with a 90% improvement on the PASI scale in 74.8%–75.3% of the patients by week 1 [5]. Risankizumab has also performed well in head-to-head trials, displaying superior efficacy in comparison to adalimumab, ustekinumab, and secukinumab with a similar fast onset as secukinumab [34–36]. Furthermore, risankizumab has shown high durability as patients experienced recurrence of moderate to severe pathology an average of 295 days post discontinuation [5]. Unfortunately, there is no long-term safety data available like older medications, however risankizumab has shown excellent safety profile data both for short term use (16 weeks) and for long term use including up to 69 months [37]. Like other interleukin-23 class agents, risankizumab has no concern for increased risk of inflammatory bowel disease or tuberculosis reactivation, and the most common adverse effects are upper respiratory infections, headache, and injection site infections [5].

Mirikizumab is the latest investigational interleukin-23 inhibitor which also targets the p19 subunit of the cytokine receptor however it is not yet approved by the American FDA for treatment of plaque psoriasis [5]. Clinical trial data has shown mirikizumab increases PASI by 90% by week 16 in 67% of the patients with the most common adverse effects being viral and upper respiratory tract infections [38]. Trials have also demonstrated that continued use for patients who do

not achieve the primary end point of 90% improve in PASI scale by 16 weeks may achieve it with continued use up to 104 weeks [39].

5. Interleukin-12/23 inhibitors

The interleukin-12/23 inhibitors treat psoriasis by exhibiting a combination of blockade on the interleukin-12 and interleukin-23 receptors. Currently, ustekinumab (Stelara) is the only medication in this class that is FDA approved to treat moderate to severe plaque psoriasis and psoriatic arthritis in adults and pediatric population down to 6 years of age [5]. Ustekinumab's mechanism of action entails binding with high affinity and specificity to the p40 subunit of both the interleukin-12 and interleukin-23 receptors and suppressing the inflammation facilitated by these cytokines [40]. This agent is less efficacious than other biologics and some patients may experience worsening of psoriatic symptoms during the 3rd month of medication use and may benefit from an increased dose or an increased frequency of dosing [5]. Ustekinumab has long track record of good safety profile data for over 20 years and uniquely it is the only biologic approved for dose changes based on a patient's weight without increase risk of adverse events [5].

6. Conclusion

The arsenal of biologic options for the treatment of psoriasis is continually expanding with each agent containing its own merits and demerits with respect to other available biologics. After reviewing the facts of each biologic an informed clinician may cater the most appropriate therapy for the right patient so as to produce the best possible patient care and patient satisfaction (**Figure 1** and **Table 1**).

Figure 1.
Biologics are large molecule proteins that must be administered subcutaneously or intravenously. Subcutaneous injections can be delivered in multiple anatomical locations such as the outer surface of the upper arm, top of the thigh, the buttocks, or in the abdomen. In the photograph here, a patient self-administers a biologic treatment in the outer abdomen. Importantly, the abdominal injections must occur above the waistline and not include the navel.

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Medication name (Brand Name)	Biologics class	Efficacy	Potential side effects	Average cost per month (US Dollars)
Infliximab (Remicade)	TNF-a Inhibitor	A 75% improvement from baseline PASI score in chronic recalcitrant plaque psoriasis by week 10. FDA indications for moderate to severe plaque psoriasis. Off label uses for pyoderma gangrenosum, hidradenitis suppurative, and Uveitis in Behcet's syndrome	Injection site reaction, headache, and rash. Also risk of serious infection, in particular, reactivation of latent tuberculosis. Evidence of infliximab-induced severe depression and suicide ideation	$987
Certolizumab (Cimzia)	TNF-a Inhibitor	Superior efficacy in phase 3 clinical trials as compared with other TNF-a inhibitors, achieving a 75% improvement in 81.6% of patients by week 16	Injection site reaction, headache, and rash. Also risk of serious infection, in particular, reactivation of latent tuberculosis. Evidence of optic neuritis, in ~3 patients out of 1000	$1, 040
Adalimumab (Humira)	TNF-a Inhibitor	78% of treated patients achieved 75% improvement at week 16	Injection site reaction, headache, and rash. Also risk of serious infection, in particular, reactivation of latent tuberculosis	$7, 000
Etanercept (Enbrel)	TNF-a Inhibitor	A 56% of patients achieving PASI 75 and 77% of patients achieving PASI 50 by week 24	Injection site reaction, headache, and rash. Also risk of serious infection, in particular, reactivation of latent tuberculosis	$10, 500
Bimekizumab (Bimzelx)	Interleukin-17 Inhibitor	A 90% improvement for 85% of patients by week 16 vs. 49.7% of patients on ustekinumab	Injection site reaction, headache, pimples (acne), nausea, and generalized fatigue	$2, 552
Brodalumab (Siliq)	Interleukin-17 Inhibitor	A 100% improvement in the psoriasis area and severity index in 44% of patients by week 12 and since onset of first dose	Injection site reaction, black tarry stools, headache, joint pain, nausea, and pale skin. American FDA warning for suicide ideation	$3, 500
Ixekizumab (Taltz)	Interleukin-17 Inhibitor	A 75% improvement in 90% of patients by week 12	Injection site reaction, arthralgias, headache, neutropenia, thrombocytopenia, and risk of candidiasis or tinea infections. Evidence of inflammatory bowel disease exacerbation, in less than 1 patient out of 1000	$6, 586
Secukinumab (Cosentyx)	Interleukin-17 Inhibitor	A 75% improvement in PASI by week 12 in 95% of patients who discontinued and restarted the medication after experiencing a disease exacerbation	Injection site reaction, inflammatory bowel disease flareups, arthralgias, back pain, cough, headache, pruritus, and rhinorrhea. Evidence of fungal and yeast infections, in ~12 patients out of 1000	$6, 924

Medication name (Brand Name)	Biologics class	Efficacy	Potential side effects	Average cost per month (US Dollars)
Guselkumab (Tremfya)	Interleukin-23 Inhibitor	A 75% improvement for 90% of patients by week 16. Shown superior clinical results against secukinumab in achieving a 90% improvement on the PASI scale at week 48, in addition to performing better than adalimumab in the treatment of scalp plaque psoriasis and palmoplantar psoriasis	Injection site reaction, arthralgias, diarrhea, headaches	$1, 651
Mirikizumab (Omvoh)	Interleukin-23 Inhibitor	A 90% improvement by week 16 in 67% of patients	Arthralgias, headaches, viral and upper respiratory tract infections	$9, 976
Tildrakizumab (Ilumya)	Interleukin-23 Inhibitor	Recapture rate where approximately 85–96% of patients showed a 75% improvement after stopping and starting medication in 85–96% of patients	Injection site reaction, diarrhea, and upper respiratory infections.	$17, 296
Risankizumab (Skyrizi)	Interleukin-23 Inhibitor	A 90% improvement in 74.8%–75.3% of patients by week 1. Displaying superior efficacy in comparison to adalimumab, ustekinumab, and secukinumab with a similar fast onset as secukinumab	Headaches, swelling of face, eyelids, lips, mouth, tongue, or throat, hives or pruritus. May induce low blood pressure leading to dizziness, lightheadedness, and fainting. May cause burning with urination or increase urinary frequency	$19, 734
Ustekinumab (Stelara)	Interleukin-12/23 Inhibitor	A 90% improvement by week 16 in 49.7% of patients	Injection site reaction, abdominal pain, diarrhea, headache, and generalized fatigue	$2, 051

**Injection site reactions can include erythema, itching, pain, and swelling and usually last 1–3 days [41].*

Table 1.
Detailed synopsis of the biologics with appropriate indications, contraindications and comparisons amongst different classes.

Additional information

The views expressed herein are those of the authors and do not reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Army, the Department of the Air Force and Department of Defense or the U.S. Government.

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References

[1] Psoriasis treatment: Biologics. American Academy of Dermatology. 2022. Available from: https://www.aad.org/public/diseases/psoriasis/treatment/medications/biologics

[2] Tsai YC, Tsai TF. Anti-interleukin and interleukin therapies for psoriasis: Current evidence and clinical usefulness. Theraputic Advances in Musculoskeletal Disease. 2017;**9**(11):277-294. DOI: 10.1177/1759720X17735756

[3] Brownstone ND, Hong J, Mosca M, et al. Biologic treatments of psoriasis: An update for the clinician. Biologics. 2021;**15**:39-51. DOI: 10.2147/BTT.S252578

[4] Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: A review. Journal of the American Medical Association. 2020;**323**(19):1945-1960. DOI: 10.1001/jama.2020.4006

[5] Alwan W, Nestle FO. Pathogenesis and treatment of psoriasis: Exploiting pathophysiological pathways for precision medicine. Clinical and Experimental Rheumatology. 2015;**33**(5 Suppl 93):S2-S6

[6] Elewski BE, Baker CS, Crowley JJ, et al. Adalimumab for nail psoriasis: Efficacy and safety over 52 weeks from a phase-3, randomized, placebo-controlled trial. Journal of the European Academy of Dermatology and Venereology. 2019;**33**(11):2168-2178. DOI: 10.1111/jdv.15793

[7] Wu JJ, Abramovits W, Valdecantos WC, et al. 10-year interim results from the ESPRIT registry: Real-world safety, effectiveness, and patient-reported outcomes of adalimumab for moderate-to-severe psoriasis. Journal of the American Academy of Dermatology. 2020;**83**(6):AB17. DOI: 10.1016/j.jaad.2020.06.155

[8] Mahadevan U, Martin CF, Dubinsky M, Kane SV, Sands BE, Sandborn W. 960 exposure to anti-TNFα therapy in the third trimester of pregnancy is not associated with increased adverse outcomes: Results from the PIANO registry. Gastroenterology. 2014;**146**(5):S170. DOI: 10.1016/S0016-5085(14)60602-8

[9] Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: Clinical features and pathogenesis. The Lancet Neurology. 2010;**9**(4):425-437. DOI: 10.1016/S1474-4422(10)70040-5

[10] Van Der Heijde D, Deodhar A, FitzGerald O, et al. 4-year results from the RAPID-PsA phase 3 randomised placebo-controlled trial of certolizumab pegol in psoriatic arthritis. RMD Open. 2018;**4**(1). DOI: 10.1136/rmdopen-2017-000582

[11] Gottlieb AB, Blauvelt A, Thaçi D, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). Journal of the American Academy of Dermatology. 2018;**79**(2):302-314. DOI: 10.1016/j.jaad.2018.04.012

[12] Clowse ME, Förger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: Results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. Annals of the Rheumatic Diseases. 2017;**76**(11):1890-1896. DOI: 10.1136/annrheumdis-2017-211384

[13] Mariette X, Förger F, Abraham B, et al. Lack of placental transfer of certolizumab pegol during pregnancy: Results from CRIB, a prospective, postmarketing, pharmacokinetic study. Annals of the Rheumatic Diseases. 2018;**77**(2):228-233. DOI: 10.1136/annrheumdis-2017-212196

[14] Bagel J, Duffin KC, Moore A, et al. The effect of secukinumab on moderate-to-severe scalp psoriasis: Results of a 24-week, randomized, double-blind, placebo-controlled phase 3b study. Journal of the American Academy of Dermatology. 2017;**77**(4):667-674. DOI: 10.1016/j.jaad.2017.05.033

[15] Reich K, Sullivan J, Arenberger P, et al. Secukinumab shows high and sustained efficacy in nail psoriasis: 2.5-year results from the randomized placebo-controlled transfigure study. British Journal of Dermatology. 2020;**184**(3):425-436. DOI: 10.1111/bjd.19262

[16] Gottlieb AB, Kubanov A, Doorn MV, et al. Sustained efficacy of secukinumab in patients with moderate-to-severe palmoplantar psoriasis: 2·5-year results from GESTURE, a randomized, double-blind, placebo-controlled trial. British Journal of Dermatology. 2020;**182**(4):889-899. DOI: 10.1111/bjd.18331

[17] Bagel J, Nia J, Hashim PW, et al. Secukinumab is superior to ustekinumab in clearing skin in patients with moderate to severe plaque psoriasis (16-week CLARITY results). Dermatology and Therapy. 2018;**8**(4):571-579. DOI: 10.1007/s13555-018-0265-y

[18] Mease P, van der Heijde D, Landewé R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: Primary results from the randomised, double-blind, phase III FUTURE 5 study. Annals of the Rheumatic Diseases. 2018;**77**(6):890-897. DOI: 10.1136/annrheumdis-2017-212687

[19] Deodhar A, Mease PJ, McInnes IB, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: Integrated pooled clinical trial and post-marketing surveillance data. Arthritis Research & Therapy. 2019;**21**(1):111. DOI: 10.1186/s13075-019-1882-2

[20] Kimmel G, Chima M, Kim HJ, et al. Brodalumab in the treatment of moderate to severe psoriasis in patients when previous anti-interleukin 17A therapies have failed. Journal of the American Academy of Dermatology. 2019;**81**(3):857-859. DOI: 10.1016/j.jaad.2019.05.007

[21] Lebwohl M, Leonardi C, Wu JJ, et al. One-year pharmacovigilance update of brodalumab. Journal of Drugs in Dermatology. 2020;**19**(8):807-808. DOI: 10.36849/JDD.2020.5138

[22] Lebwohl MG, Papp KA, Marangell LB, et al. Psychiatric adverse events during treatment with brodalumab: Analysis of psoriasis clinical trials. Journal of the American Academy of Dermatology. 2018 Jan;**78**(1):81-89.e5. DOI: 10.1016/j.jaad.2017.08.024

[23] Paller AS, Seyger MMB, Magariños GA, et al. Efficacy and safety of ixekizumab in a phase III, randomized, double-blind, placebo-controlled study in paediatric patients with moderate-to-severe plaque psoriasis (IXORA-PEDS). British Journal of Dermatology. 2020;**183**(2):231-241. DOI: 10.1111/bjd.19147

[24] Blauvelt A, Leonardi C, Elewski B, et al. A head-to-head comparison of ixekizumab vs. guselkumab in patients with moderate-to-severe

plaque psoriasis: 24-week efficacy and safety results from a randomized, double-blinded trial. British Journal of Dermatology. 2021;**184**(6):1047-1058. DOI: 10.1111/bjd.19509

[25] Smolen JS, Sebba A, Ruderman E, et al. Op0228 efficacy and safety of ixekizumab versus adalimumab (spirit-H2h) with and without concomitant conventional synthetic disease-modifying antirheumatic drugs (dmard) in biologic dmard-naïve patients with psoriatic arthritis: 52-week results. Annals of the Rheumatic Diseases. 2020;**79**(Suppl 10):143-144. DOI: 10.1136/annrheumdis-2020-eular.4615

[26] Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. The New England Journal of Medicine. 2016;**375**(4):345-356. DOI: 10.1056/NEJMoa1512711

[27] Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus Secukinumab in Plaque Psoriasis. The New England Journal of Medicine. 2021;**385**(2):142-152. DOI: 10.1056/NEJMoa2102383

[28] Reich K, Papp KA, Blauvelt A, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): Efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. The Lancet. 2021;**397**(10273):487-498. DOI: 10.1016/S0140-6736(21)00125-2

[29] Blauvelt A, Papp KA, Griffiths CEM, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. Journal of the American Academy of Dermatology. 2017;**76**(3):405-417. DOI: 10.1016/j.jaad.2016.11.041

[30] Reich K, Armstrong AW, Langley RG, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): Results from a phase 3, randomised controlled trial. The Lancet. 2019;**394**(10201):831-839. DOI: 10.1016/S0140-6736(19)31773-8

[31] Reich K, Armstrong AW, Foley P, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. Journal of the American Academy of Dermatology. 2017;**76**(3):418-431. DOI: 10.1016/j.jaad.2016.11.042

[32] Papp K, Kimball A, Tyring S, et al. Maintenance of treatment response in chronic plaque psoriasis patients continuing treatment or discontinuing treatment with tildrakizumab in a 64-week, randomized controlled, phase 3 trial. Journal of the American Academy of Dermatology. 2017;**76**(6):AB164. DOI: 10.1016/j.jaad.2017.04.637

[33] Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: Pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. British Journal of Dermatology. 2020;**182**(3):605-617. DOI: 10.1111/bjd.18232

[34] Reich K, Gooderham M, Thaçi D, et al. Risankizumab compared with adalimumab in patients with

moderate-to-severe plaque psoriasis (IMMvent): A randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019;**394**(10198):576-586. DOI: 10.1016/S0140-6736(19)30952-3

[35] Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): Results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;**392**(10148):650-661. DOI: 10.1016/S0140-6736(18)31713-6

[36] Warren RB, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): Results from a phase III, randomized, open-label, efficacy–assessor-blinded clinical trial. British Journal of Dermatology. 2020;**184**(1):50-59. DOI: 10.1111/bjd.19341

[37] Gordon KB, Lebwohl M, Papp KA, et al. Long-term safety of risankizumab from 17 clinical trials in patients with moderate-to-severe plaque psoriasis. British Journal of Dermatology. 2022;**186**(3):466-475. DOI: 10.1111/bjd.20818

[38] Reich K, Rich P, Maari C, et al. Efficacy and safety of mirikizumab (LY3074828) in the treatment of moderate-to-severe plaque psoriasis: Results from a randomized phase II study. British Journal of Dermatology. 2019;**181**(1):88-95. DOI: 10.1111/bjd.17628

[39] Bissonnette R, Maari C, Menter M, et al. 15328 efficacy and safety of mirikizumab in patients with moderate to severe plaque psoriasis: 104-week results from a randomized phase 2 study. Journal of the American Academy of Dermatology. 2020;**83**(6):AB147. DOI: 10.1016/j.jaad.2020.06.677

[40] Kauffman CL, Aria N, Toichi E, et al. A phase I study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis. The Journal of Investigative Dermatology. 2004;**123**(6):1037-1044. DOI: 10.1111/j.0022-202X.2004.23448.x

[41] Goel N, Stephens S. Certolizumab pegol. mAbs. 2010;**2**(2):137-147. DOI: 10.4161/mabs.2.2.11271