Title: A Review: Immunogenicity of biologics used in the treatment of moderate to severe psoriasis

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Abstract: The number of biologic drugs available for the treatment of psoriasis continue to expand. However, being biological proteins and thus potentially immunogenic, there is evidence that anti-drug-antibodies develop against the various therapeutic proteins currently being utilised. Although chimeric antibodies that contain elements of the parental monoclonal antibodies are immunogenic, anti-drug antibodies occur even if the biologic is a fully human protein and these can impact on clinical efficacy and safety. However, there is a wide variation in the reported level of anti-drug-antibodies for the same and different treatments that is highlighting issues with various assays used in anti-drug antibody detection. Here we review the available data on the occurrence of anti-drug antibodies in people with psoriasis treated with biologic agents.

**Keywords:** Psoriasis, immunotherapy, biologic disease modifying therapies, anti-drug antibodies.

Introduction: Psoriasis is a chronic inflammatory skin condition affecting 125 million people globally [1]. However, its impacts are not limited to the skin, since it is associated with many comorbidities, such as cardiovascular and inflammatory bowel diseases, mental disorders and psoriatic arthritis [2]. While the pathogenesis is complex, the immune system is thought to play a crucial role in disease development [3]. Greater understanding of pathogenesis has facilitated the development of monoclonal antibodies specifically targeting and inhibiting key molecules implicated in the pro-inflammatory pathways, broadening treatment options for those with moderate to severe psoriasis. Although this class of drugs has significantly improved treatment outcomes for patients, their immunogenic potential is of concern, with anti-drug antibodies (ADAs) being produced against them, which impacts on efficacy and patient benefits [3].

There are several types of psoriasis, the most common being plaque psoriasis, which accounts for 80-90% of all cases [3]. This subtype presents as well-defined, raised, red plaques on the skin, which are covered in silvery-white scale, which typically appear on the lower back, knees, scalp and elbows. Thus, those suffering may have a significantly lowered quality of life (QoL) [3]. Despite the involvement of genetic and environmental factors, it is primarily the immune system that dominates in the pathogenesis of psoriasis, with the IL-23/Th17 pathway at the centre of disease progression [4], which can be modulated by a number of therapeutic antibodies as illustrated in Figure 1.

Fig. 1. The pathogenesis of psoriasis and therapeutic cytokine targeting by biological disease modifying agents. Created using Biorender.com.
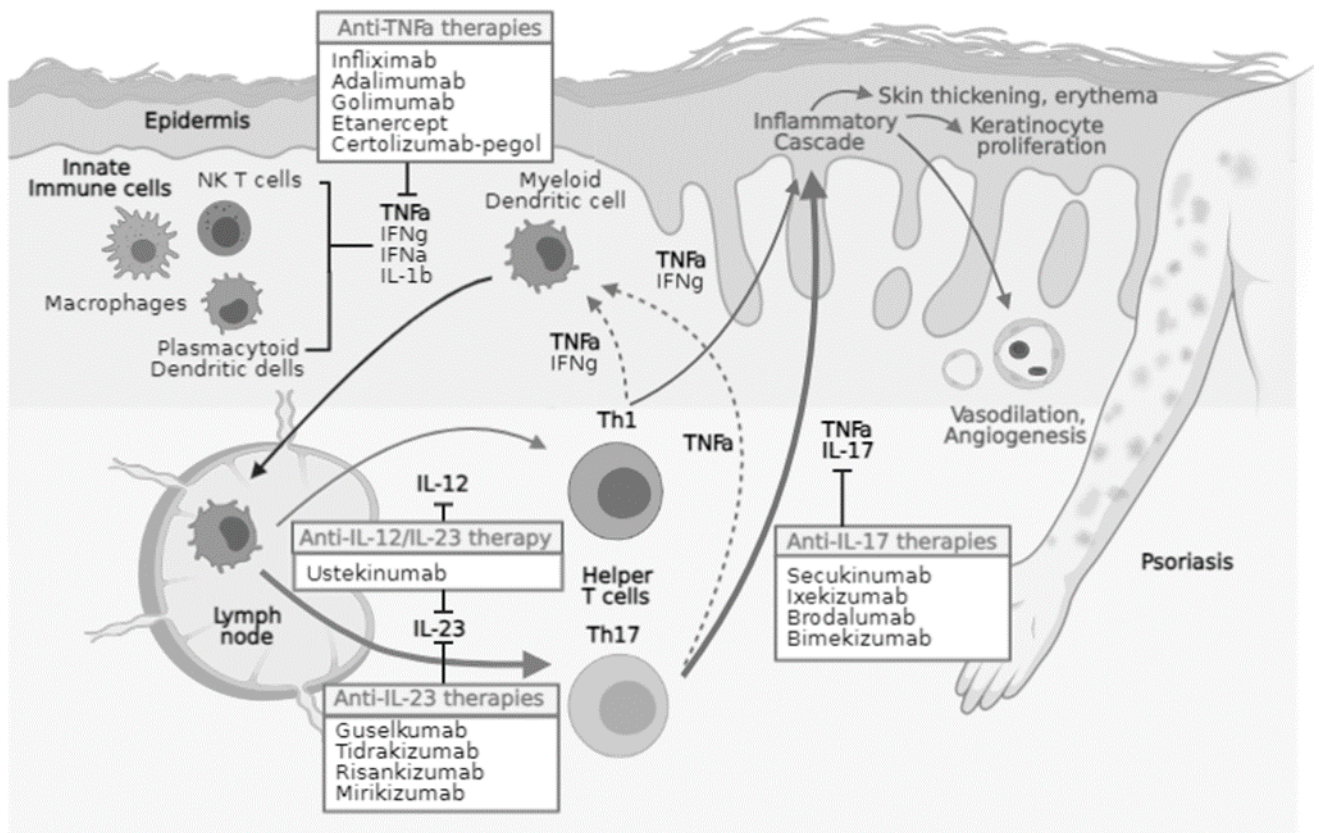
Innate immune cells including: natural killer (NK) T cells, macrophages, plasmacytoid dendritic cells and keratinocytes, activate myeloid dendritic cells. The latter act as antigen presenting cells and secrete IL-12 and IL-23, which facilitates T cell differentiation into Th1 and Th17 cells respectively. On activation, Th17 cells produce tumour necrosis factor α (TNFa), interleukin-17 (IL-17) and others such as IL-22. These cytokines, alongside those secreted by Th1 cells, activate a feed-forward inflammatory response in keratinocytes, which, in turn, release pro-inflammatory cytokines and chemokines (Figur1). This non-resolving inflammatory cascade cause keratinocyte proliferation, epidermal thickening and angiogenesis that result in psoriatic plaque formation [4].

Current treatments for psoriasis: Given the chronic nature of psoriasis, the main goal of treatment is to achieve and maintain remission, through controlling the inflammatory process and reducing plaque formation. The choice of treatment depends on the severity of psoriasis and its impact on the quality of life (QoL) [5]. Topical therapies, the primary treatment for mild psoriasis, are

available in a variety of formulations, including creams, lotions and ointments. The type used depends on patient preference and area needing coverage. Phototherapy, conventional (non-biologic) systemic therapies and apremilast are reserved for more moderate to severe cases [6]. There are a plethora of drugs used in psoriasis treatment (Table 1).

Table 1. Current psoriasis treatments: Treatments, their indicated disease severity, mechanism of action and side-effect profile

Psoriasis Severity	Description
Mild	**Topical Therapy:** **Topical corticosteroids**. Reduce inflammation and proliferation through down-regulating cytokine gene expression. Recommended to be used with vitamin D analogues to improve efficacy and reduce adverse effects. **Topical vitamin D analogues.** Bind to vitamin D-selective receptors, preventing abnormal proliferation and differentiation of keratinocytes. Examples include calcipotriol. **Topical tar and dithranol.** Declined usage due to agents with greater efficacy being available. Adverse effects common to both include staining of clothes and unpleasant odour.
Moderate to severe	**Phototherapy:** Moderate to severe Includes narrow-band UVB or PUVA (oral methoxsalen + UVA), the former preferred due to its lower skin cancer risk. Treatment is delivered in hospital/special clinics. Adverse effects include phototoxicity and burning. **Traditional (non-biologic) systemic therapy:** **Oral retinoids:** A form of vitamin A aimed to control skin cell growth. Examples include acitretin. **Methotrexate** A folate antagonist which reduces proliferation of keratinocytes and inflammation. Despite its effectiveness, adverse effects include hepatotoxicity. **Ciclosporin.** Inhibits T cells and cytokines e.g. IL-2. Though effective, adverse effects include nephrotoxicity, hepatotoxicity and hypertension, so used in patients with extensive disease. **Apremilast**. An oral inhibitor of phosphodiesterase-4. Modulates cyclic adenosine monophosphate levels intracellularly, causing reduced expression of TNF-α, IL-17 and IL-23.

Biologics used in psoriasis: Research advances in understanding psoriasis pathophysiology has allowed for the introduction of biologics, a class of drugs highly effective in treating moderate to severe psoriasis. Biologics are monoclonal antibodies (mAbs), fusion proteins or antibody fragments, which specifically target the pro-inflammatory cytokines involved in psoriasis (Figure 1), aiming to reduce the side effects typically seen from using the aforementioned drug (Table 1) therapies [7].

Anti-TNF-α therapies were developed more than two decades ago and demonstrated good efficacy. However, in more recent years, newer biologics have been developed, including IL-12/23 inhibitors (which target the p40 subunit present in both IL-12 and IL-23), IL-17 inhibitors and IL-23 inhibitors [4]. There are four major classes of biologics (**Table 2**).

Table 2. Anti-psoriatic biological therapeutic agents

Target	Research name	Trade name
Anti-TNF-α	Infliximab	Remicade
	Adalimumab	Humira
	Etanercept	Enbrel
	Certolizumab-pegol	Cimzia
	Golimumab	Simponi
Anti-IL-12/23	Ustekinumab	Stelara
Anti-IL-23	Tildrakizumab	Ilumetri
	Risankizumab	Skyrizi
	Guselkumab	Tremfya
	Mirikizumab	(Withdrawn)
Anti-IL-17	Secukinumab	Cosentyx
	Brodalumab	Siliq
	Ixekizumab	Taltz
	Bimekizumab	(Awaiting approval)

Despite Mirikizumab meeting the primary and all key secondary endpoints versus placebo at Week 16 and all key secondary endpoints versus Cosentyx® (secukinumab) at Week 16 and Week 52,

including superiority in skin clearance at Week 52 [8] the drug sponsors withdrew this drug for the psoriasis indication, but will pursue its use to treat Inflammatory bowel disease (IBD) [9]. Maybe off-label use in psoriasis will follow?

Antidrug Antibodies: Since biologics are proteins, they may give rise to ADAs and thus are considered to be potentially immunogenic. These ADAs can be classified as either binding antibodies (BAbs) or neutralising antibodies (NAbs). The latter reduces drug functionality through binding to the active site of the drug, consequently inactivating it. BAbs attach to non-active site regions, forming an immune-complex with the biologic which promotes its clearance [10]. Hence, the presence of these ADAs can reduce drug efficacy, diminishing the therapeutic effects seen in people with psoriasis. There is growing evidence that a variety of factors are involved in ADA formation. These can be generally classified into drug-related, patient-related and treatment-related factors. Within drug-related factors, the molecular structure of biologics is thought to be a key determinant of immunogenicity [11]. Murine antibodies were the first therapeutics used in oncology treatment but demonstrated high immunogenicity since they were rodent-derived [12, 13]. This led to the development of mAbs composed of human constant regions and murine variable regions, termed chimeric antibodies, such as infliximab. Although this reduced immunogenicity, ADAs were still predicted to occur [14]. Hence, humanisation [15] was implemented, where the variable regions were humanised to contain only the complementarity determining regions of the original rodent antibody in humanized antibodies such as Campath-1H. However, even humanised antibodies are in some individuals immunogenic and give rise to ADA formation [16] and reduce the efficacy of treatment [17]. Despite theoretically possessing a reduced immunogenic potential, even fully human mAbs produce ADAs, which are of anti-idiotypic nature [18]. Patient characteristics may further influence the production of ADAs. Genetic factors may influence how the immune system responds to biologics, creating variability amongst patients. Similarly, patients may respond differently to biologics depending on their age. Those

suffering from chronic infections may have an enhanced immune response, increasing their likelihood of developing ADAs in comparison to those with impaired immune function. Additionally, prior exposure to similar proteins may pre-sensitise and induce immune responses in patients, producing immunological memory which may hinder the therapeutic benefits of subsequent biologics [19].

The treatment protocol can also contribute to ADA formation. It has been suggested that biologics are less immunogenic if a higher dose is given continuously over an extended period of time, in comparison to a lower dose delivered intermittently for a shorter period. Administration routes can also affect ADA formation, with intravenous administration deemed less immunogenic than subcutaneous and intramuscular routes [19]. Furthermore, it has been noted that concomitant use of immunosuppressants can aid in reducing ADA development, with studies showing a lower incidence of ADAs in psoriasis patients receiving concomitant methotrexate [11]. Therefore, it can be appreciated that numerous factors are involved in ADA formation.

Measuring ADA: There are numerous assays available to detect ADAs, though their varying sensitivity and specificity adds to the complexity of measuring ADA levels. Standard assays include conventional radio-immunoassays and enzyme-linked immunosorbent assays (ELISA). However, a major challenge with these formats is drug interference. This occurs when ADAs become bound to the drug, which is present in excess, in an immune-complex, so remain undetected by the assay. Thus, standard assays can only measure free ADA, leading to an underestimation of immunogenicity and false negative results. This raises questions about their sensitivity [11, 20]. However, there are 'drug tolerant' assays, examples of which are affinity capture elution assays [21], acid-dissociation radio immunoassay [22], and pH-shift anti-idiotype antigen-binding tests [23], which can help to overcome these challenges. These assays include an acidification step which causes the dissociation of immune complexes, freeing bound ADAs and allowing for their detection [23]. Hence, these assays are more sensitive, which can result in fewer false negative

results when used. More recently a sensitive assay has been developed as a generic platform for ADA testing using recombinant reporter which incorporates a dual tandem nanoluciferase between the drug VH and VL domains (GloBody™). The ADA-GloBody complexes are captured on immobilised Protein G and the retained nanoluciferase activity determined [24]. The amount of light generated being proportional to the amount of ADA in the sample. This assay can be performed with and without an acidification step to provide total and free ADA measures.

Biologics and ADA responses in psoriasis: The issue of immunogenicity is recognised across all disease/conditions where biologic therapies are used [25]. There is increasing evidence regarding the immunogenicity of biologics used in the treatment of psoriasis as shown in Table 3.

Table 3. Anti-drug antibody incidence against biologics currently available to treat psoriasis.

Target	Drug	ADA incidence	Reference
Anti-TNF-α	Infliximab	35.8-51.5%	[26]
		5.4%	[27]
	Adalimumab	45.1% (85% NAbs)	[28]
		8.8%	[29]
	Etanercept	1.9% (BAbs)	[1]
		1.5% (BAbs)	[30]
	Certolizumab-pegol	4-25%	[31]
Anti-IL-12/23	Ustekinumab	5.2%	[32]
		3.8-10.6% (≥ 85% NAbs)	[33]
		14.7%	[34]
Anti-IL-23	Tildrakizumab	6.5-8.2% (2.5-3.2% NAbs)	[35]
		18%	[36]
	Risankizumab	24% (14% NAbs)	[37]
	Guselkumab	8.5% (0.5% NAbs)	[38]
		9%	[34]
Anti-IL-17	Secukinumab	0.4% (33% NAbs)	[39]

	<1% (28% NAbs)	[40]
Brodalumab	1.8-2.3% (0% NAbs)	[41]
	2.7% (0% NAbs)	[42]
Ixekizumab	17.4% (3.5% NAbs)	[43]

Anti-TNF-α drugs: Differing levels of ADAs have been seen amongst the biologics within this subclass. A randomised controlled trial, involving 835 patients suffering from psoriasis, found anti-infliximab antibodies in 35.8-41.5% of patients on 5mg/kg of infliximab, with higher levels (46.2-51.5%) seen in those on 3mg/kg. It was also found that those with ADAs were less likely to maintain treatment response. With regards to safety, those deemed ADA positive were more likely to experience infusion reactions, though these were generally mild reactions. This could suggest that the presence of ADAs reduces the clinical efficacy of infliximab [26]. Conversely, a prospective study detected a significantly lower ADA incidence against infliximab, at 5.4%. However, there are limitations to this study. The short follow up period of 22 weeks may have not been long enough for ADA development to be observed [27].

An earlier randomised controlled trial found anti-adalimumab antibodies in 8.8% of 825 patients treated with the biologic over a 52-week period. This study also concluded that some patients who were ADA positive experienced reduce efficacy, though the effect was minimal. Nonetheless, ADAs were not linked to adverse effects seen in patients [29]. A significantly higher ADA incidence was found in a recent 51-week randomised, double-blinded phase III trial. At 17 weeks, ADAs were seen in 34.1% of patients, increasing to 45.1% at week 51. Of the latter, 85% were NAbs [28]. However, this difference in prevalence could be due to the use of more sensitive assays in the recent study, since there was no reporting on the testing modality used in the earlier study. Although the newest of the group, certolizumab-pegol displays moderate immunogenicity. A study found the ADA prevalence at week 12 to be 5% and 4% in patients taking 200mg and 400mg of the drug respectively, increasing to 18% and 25% at week 24 [31]. The lowest incidence of ADAs

within this group was seen in a study involving etanercept. This randomised controlled trial, comparing etanercept to its biosimilar, found just 1.9% of psoriasis patients developed anti-etanercept antibodies, all of which were BAbs, at week 12 of treatment. By week 52, there were no reported ADAs in patients [1]. This result is in line with a previous study, where 1.5% of 606 patients tested positive for BAbs, following serum analysis after 12 weeks. The presence of anti-etanercept antibodies had no adverse impact on clinical efficacy [30].

Anti-IL-12/23 drugs: Ustekinumab is the only biologic which falls under this category of targeting IL-12 and IL-23 through the shared p40 subunit and generally shows a lower immunogenicity compared to most anti-TNF-α inhibitors. A phase III trial conducted over 5 years, identified anti-ustekinumab antibodies in 5.2% of patients with moderate to severe psoriasis, with 64% being neutralising ADAs. Additionally, there were no safety concerns related to their presence [32]. In contrast, a more recent observational cross-sectional study assessed the immunogenicity of ustekinumab in 340 patients using both a radioimmunoassay and a newer drug tolerant assay. The results showed an ADA incidence of 3.8% and 10.6% when each assay was used, respectively. This difference in prevalence may be due to the differing sensitivities of the assays, since the newer drug tolerant assay was able to detect ADAs when present at low levels. Of the ADAs detected, at least 85% were reported to be neutralising. Furthermore, it was reported that ADAs were linked to increased disease activity and lower levels of circulating ustekinumab in ADA positive patients, which in turn impaired clinical response [33]. A 2017 randomised controlled trial, involving 871 patients with more severe forms of psoriasis, identified an ADA incidence of 14.7% when a highly sensitive, drug tolerant assay was used. This aligns with the findings from the aforementioned study, highlighting how the use of such assays allows for greater ADA detection [34].

Anti-IL-23 drugs: Despite the biologics within this group being humanised or fully human, they still display immunogenicity. In multiple phase III trials, involving a total of 1079 patients being treated with 150mg of risankizumab over 52 weeks, the ADA incidence was 24%, with 14% of these being

NAbs. Likewise, the presence of these ADAs did not impact the safety and clinical efficacy of risankizumab. However, there was no specification on the type of assay used to detect ADAs, providing weakness to this study [37].

Moreover, a recent study, investigating the development of ADAs against tildrakizumab, found patients treated with 100mg had an incidence of 6.5%, increasing to 8.2% in those taking 200mg.The incidence of NAbs was 2.5% and 3.2% for each dose, respectively. Additionally, the presence of NAbs, in those who were ADA positive, was associated with increased clearance of tildrakizumab and a reduction in clinical response by 10-15% [35]. Conversely, an earlier study showed 18% of patients produced ADAs against tildrakizumab following treatment. Despite this, the clinical response in ADA-positive patients was no different those who were negative for ADAs, contradicting the findings of the aforementioned study. However, the small sample size was a drawback to this study and may have influenced the outcomes [36].

In recent randomised controlled trials, assessing the incidence of ADAs against guselkumab and their impact, it was reported that 8.5% of patients were ADA positive following 100 weeks of drug exposure. Of those positive, 0.5% had NAbs. As with risankizumab, the presence of ADAs had no influence on the clinical efficacy of guselkumab. Furthermore, the use of a sensitive drug assay, alongside the large population (1829 patients) involved in this study, provides strength to the reported outcomes [38]. The results from these trials are consistent with a prior randomised controlled trial, which analysed patient serum samples, using a highly sensitive drug tolerant assay, to find an ADA incidence of 9% [34].

Anti-IL-17 drugs: Generally, IL-17 inhibitors demonstrate low immunogenicity when used in the management of moderate to severe psoriasis. A study, assessing the ADA prevalence against ixekizumab over a 60-week period, found that 17.4% of patients produced ADAs, of which 3.5% were neutralising. Furthermore, only patients with high-titre ADAs (2.4%) experienced a decrease in ixekizumab serum concentrations and a reduced clinical response. This finding suggests the

impact of ADAs against ixekizumab may be related to ADA titre. Nonetheless, other factors which may influence ADA development, such as disease status and patient characteristics, were not explicitly investigated in this study, posing as a limitation [43].

In phase III trials for brodalumab, anti-brodalumab antibodies were detected in 1.8-2.3% of patients following a 52-week period of being treated with the drug. Additionally, no NAbs were detected in patients and there was no association with loss of efficacy as a result of ADAs [41]. A similar result was seen in clinical trials which assessed immunogenicity in a total of 4461 patients. Here, 2.5% of patients who were pre-treatment negative developed ADAs, and as with the previous study, all were BAbs. The presence of these ADAs had a small effect on clinical efficacy, with a majority of patients maintaining response through the 52 weeks of treatment. Analysis of the impact of ADAs on safety revealed no hypersensitivity reactions occurred from ADAs, with only a small percentage (1.8%) experiencing injection site reactions [42].

Furthermore, a study, investigating the development of ADAs against secukinumab across six phase III studies, reported that only 0.4% of patients developed ADAs, of which 33% were NAbs. There was a small impact on clinical efficacy, with a few patients experiencing loss of efficacy due to the presence of ADAs. Similarly, there were no apparent adverse effects related to ADAs, suggesting their presence has minimal impact on safety. It was suggested the low ADA incidence may be due to fully human antibodies, such as secukinumab, having a lower immunogenic potential [39].

A more recent study reported similar results to the aforementioned study. It was found that the incidence of ADAs, which was evaluated over 5 years, was <1% for patients with moderate to severe psoriasis. Of those who tested positive, 28% had NAbs. It was also concluded that ADAs had no effect on the efficacy and safety of secukinumab, in line with the previous study. Although a highly sensitive assay was used to detect ADAs, a minority of patients had secukinumab levels

exceeding the drug tolerance level of the assay, which may have led to false negatives arising, weakening this study [40].

Conclusion: The development of biologics has been a significant advance in the management of psoriasis, with patients seeing improvements following their usage. However, it is evident there are still concerns with their use, a major one of which is their immunogenic potential. There appear to be discrepancies in the measuring of free ADAs and those bound in immune complexes (Table 3). This had led to different values relating to immunogenicity being published in the literature. Ideally, it would be useful to determine the total amount of ADAs and free ADAs in psoriasis patients being treated with these biologics. Thus, assays which can determine these two extreme values should be developed, to improve the accuracy and consistency of ADA reporting.

References

[1] C.E.M. Griffiths, J.M. van der Walt, D.M. Ashcroft, C. Flohr, L. Naldi, T. Nijsten, M. Augustin, The global state of psoriasis disease epidemiology: a workshop report, Br J Dermatol 177(1) (2017) e4-e7.
[2] E. Christophers, Comorbidities in psoriasis, Clin Dermatol 25(6) (2007) 529-34.
[3] A.W. Armstrong, C. Read, Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review, JAMA 323(19) (2020) 1945-1960.
[4] W. Alwan, F.O. Nestle, Pathogenesis and treatment of psoriasis: exploiting pathophysiological pathways for precision medicine, Clin Exp Rheumatol 33(5 Suppl 93) (2015) S2-6.
[5] J. Gorelick, D. Shrom, K. Sikand, L. Renda, R. Burge, C. Dworkin, C. Krebsbach, R.P. Patel, C. Karki, D. Rosmarin, Understanding Treatment Preferences in Patients with Moderate to Severe Plaque Psoriasis in the USA: Results from a Cross-Sectional Patient Survey, Dermatol Ther (Heidelb) 9(4) (2019) 785-797.
[6] A. Chiricozzi, Psoriasis, BMJ Best Practice, BMJ, BMJ Best Practice, 2020.
[7] S. Dutta, S. Chawla, S. Kumar, Psoriasis: A Review of Existing Therapies and Recent Advances in Treatment, Journal of Rational Pharmacotherapeutics and Research 4 (2018) 16-18.
[8] Eli-Lilly, Lilly's Mirikizumab Superior to Cosentyx® (secukinumab) in a Phase 3 Study for Patients withModerate to Severe Plaque Psoriasis, 2020. https://investor.lilly.com/node/43511/pdf.
[9] P. Taylor, Crowded psoriasis market cuts Lilly's mirikizumab ambitions, 2021. https://pharmaphorum.com/news/crowded-psoriasis-market-cuts-lillys-mirikizumab-ambitions/. (Accessed April 28, 2021.
[10] S. Sethu, K. Govindappa, M. Alhaidari, M. Pirmohamed, K. Park, J. Sathish, Immunogenicity to biologics: mechanisms, prediction and reduction, Arch Immunol Ther Exp (Warsz) 60(5) (2012) 331-44.
[11] D. Jullien, J.C. Prinz, F.O. Nestle, Immunogenicity of biotherapy used in psoriasis: the science behind the scenes, J Invest Dermatol 135(1) (2015) 31-38.

[12] M. Steinitz, S. Tamir, J.E. Frodin, A.K. Lefvert, H. Mellstedt, Human monoclonal anti-idiotypic antibodies. I. Establishment of immortalized cell lines from a tumor patient treated with mouse monoclonal antibodies, J Immunol 141(10) (1988) 3516-22.

[13] D.M. Goldberg, Editorial: Challenges to the therapy of cancer with monoclonal antibodies J Natl Cancer Inst 16(83) (1991) 78-79.

[14] M. Bruggemann, G. Winter, H. Waldmann, M.S. Neuberger, The immunogenicity of chimeric antibodies, J Exp Med 170(6) (1989) 2153-7.

[15] L. Riechmann, M. Clark, H. Waldmann, G. Winter, Reshaping human antibodies for therapy, Nature 332(6162) (1988) 323-7.

[16] D. Baker, L. Ali, G. Saxena, G. Pryce, M. Jones, K. Schmierer, G. Giovannoni, S. Gnanapavan, K.C. Munger, L. Samkoff, A. Goodman, A.S. Kang, The Irony of Humanization: Alemtuzumab, the First, But One of the Most Immunogenic, Humanized Monoclonal Antibodies, Front Immunol 11 (2020) 124.

[17] G. Saxena, J.M. Moore, M. Jones, G. Pryce, L. Ali, G.R. Leisegang, V. Vijay, S. Loveless, N.P. Robertson, K. Schmierer, G. Giovannoni, S. Gnananpavan, D. Baker, E.C. Tallantyre, A.S. Kang, Detecting and predicting neutralization of alemtuzumab responses in MS, Neurology - Neuroimmunology Neuroinflammation 7(4) (2020) e767.

[18] G.J. Wolbink, L.A. Aarden, B.A. Dijkmans, Dealing with immunogenicity of biologicals: assessment and clinical relevance, Curr Opin Rheumatol 21(3) (2009) 211-5.

[19] EMA, Guideline on Immunogenicity assessment of therapeutic proteins, in: C.f.M.P.f.H.U. (CHMP) (Ed.) EMEA/CHMP/BMWP/14327/2006 Rev 1, 2017.

[20] C.E. Heron, R.I. Ghamrawi, E.A. Balogh, S.R. Feldman, Immunogenicity of Biologic and Biosimilar Therapies for Psoriasis and Impact of Novel Immunoassays for Immunogenicity Detection, Am J Clin Dermatol 22(2) (2021) 221-231.

[21] J.S. Bourdage, C.A. Cook, D.L. Farrington, J.S. Chain, R.J. Konrad, An Affinity Capture Elution (ACE) assay for detection of anti-drug antibody to monoclonal antibody therapeutics in the presence of high levels of drug, J Immunol Methods 327(1-2) (2007) 10-7.

[22] H.W. Smith, A. Butterfield, D. Sun, Detection ofantibodies against therapeutic proteins in the presence of residual protein using solidphase extraction with acid dissociation (SPEAD) sample treatment prior to ELISA, Regul. Toxicol. Pharmacol 49(3) (2007) 230-237.

[23] P.A. van Schouwenburg, C.L. Krieckaert, T. Rispens, L.A. Aarden, G.J. Wolbink, D. Wouters, Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation, Ann Rheum Dis 72(10) (2013) 1680-6.

[24] G.K. Saxena, I. Theocharopoulos, N.T. Aziz, M. Jones, S. Gnanapavan, G. Giovannoni, K. Schmierer, J.A. Garnett, D. Baker, A.S. Kang, GloBody Technology: Detecting Anti-Drug Antibody against VH/VL domains, Sci Rep 10(1) (2020) 1860.

[25] Z.E. Sauna, S.M. Richards, B. Maillere, E.C. Jury, A.S. Rosenberg, Editorial: Immunogenicity of Proteins Used as Therapeutics, Frontiers in Immunology 11(2834) (2020).

[26] A. Menter, S.R. Feldman, G.D. Weinstein, K. Papp, R. Evans, C. Guzzo, S. Li, L.T. Dooley, C. Arnold, A.B. Gottlieb, A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis, J Am Acad Dermatol 56(1) (2007) 31 e1-15.

[27] A.B. Gottlieb, R.E. Kalb, A. Blauvelt, M.P. Heffernan, H.L. Sofen, L.K. Ferris, F.A. Kerdel, S. Calabro, J. Wang, U. Kerkmann, M. Chevrier, The efficacy and safety of infliximab in patients with plaque psoriasis who had an inadequate response to etanercept: results of a prospective, multicenter, open-label study, J Am Acad Dermatol 67(4) (2012) 642-50.

[28] A. Blauvelt, J.P. Lacour, J.F. Fowler, Jr., J.M. Weinberg, D. Gospodinov, E. Schuck, J. Jauch-Lembach, A. Balfour, C.L. Leonardi, Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches, Br J Dermatol 179(3) (2018) 623-631.

[29] A. Menter, S.K. Tyring, K. Gordon, A.B. Kimball, C.L. Leonardi, R.G. Langley, B.E. Strober, M. Kaul, Y. Gu, M. Okun, K. Papp, Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial, J Am Acad Dermatol 58(1) (2008) 106-15.

[30] S. Tyring, A. Gottlieb, K. Papp, K. Gordon, C. Leonardi, A. Wang, D. Lalla, M. Woolley, A. Jahreis, R. Zitnik, D. Cella, R. Krishnan, Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial, Lancet 367(9504) (2006) 29-35.

[31] K. Reich, J.P. Ortonne, A.B. Gottlieb, I.J. Terpstra, G. Coteur, C. Tasset, P. Mease, Successful treatment of moderate to severe plaque psoriasis with the PEGylated Fab' certolizumab pegol: results of a phase II randomized, placebo-controlled trial with a re-treatment extension, Br J Dermatol 167(1) (2012) 180-90.

[32] A.B. Kimball, K.A. Papp, Y. Wasfi, D. Chan, R. Bissonnette, H. Sofen, N. Yeilding, S. Li, P. Szapary, K.B. Gordon, P. Investigators, Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the PHOENIX 1 study, J Eur Acad Dermatol Venereol 27(12) (2013) 1535-45.

[33] F.C. Loeff, T. Tsakok, L. Dijk, M.H. Hart, M. Duckworth, D. Baudry, A. Russell, N. Dand, A. van Leeuwen, C.E.M. Griffiths, N.J. Reynolds, J. Barker, A.D. Burden, R.B. Warren, A. de Vries, K. Bloem, G.J. Wolbink, C.H. Smith, T. Rispens, Badbir, B.S. Groups, P. consortium, Clinical Impact of Antibodies against Ustekinumab in Psoriasis: An Observational, Cross-Sectional, Multicenter Study, J Invest Dermatol 140(11) (2020) 2129-2137.

[34] R.G. Langley, T.F. Tsai, S. Flavin, M. Song, B. Randazzo, Y. Wasfi, J. Jiang, S. Li, L. Puig, Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial, Br J Dermatol 178(1) (2018) 114-123.

[35] A.B. Kimball, T. Kerbusch, F. van Aarle, P. Kulkarni, Q. Li, A. Blauvelt, K.A. Papp, K. Reich, D. Montgomery, Assessment of the effects of immunogenicity on the pharmacokinetics, efficacy and safety of tildrakizumab, Br J Dermatol 182(1) (2020) 180-189.

[36] T. Kopp, E. Riedl, C. Bangert, E.P. Bowman, E. Greisenegger, A. Horowitz, H. Kittler, W.M. Blumenschein, T.K. McClanahan, T. Marbury, C. Zachariae, D. Xu, X.S. Hou, A. Mehta, A.S. Zandvliet, D. Montgomery, F. van Aarle, S. Khalilieh, Clinical improvement in psoriasis with specific targeting of interleukin-23, Nature 521(7551) (2015) 222-6.

[37] Y. Pang, A. Khatri, A.A. Suleiman, A.A. Othman, Clinical Pharmacokinetics and Pharmacodynamics of Risankizumab in Psoriasis Patients, Clin Pharmacokinet 59(3) (2020) 311-326.

[38] Y. Zhu, J.C. Marini, M. Song, B. Randazzo, Y.K. Shen, S. Li, H. Zhou, Immunogenicity of Guselkumab Is Not Clinically Relevant in Patients with Moderate-to-Severe Plaque Psoriasis, J Invest Dermatol 139(8) (2019) 1830-1834.

[39] K. Reich, A. Blauvelt, A. Armstrong, R.G. Langley, T. Fox, J. Huang, C. Papavassilis, E. Liang, P. Lloyd, G. Bruin, Secukinumab, a fully human anti-interleukin-17A monoclonal antibody, exhibits minimal immunogenicity in patients with moderate-to-severe plaque psoriasis, Br J Dermatol 176(3) (2017) 752-758.

[40] K. Reich, A. Blauvelt, A. Armstrong, R.G. Langley, A. de Vera, F. Kolbinger, S. Spindeldreher, M. Ren, G. Bruin, Secukinumab, a fully human anti-interleukin-17A monoclonal antibody, exhibits low immunogenicity in psoriasis patients treated up to 5 years, J Eur Acad Dermatol Venereol 33(9) (2019) 1733-1741.

[41] M. Lebwohl, B. Strober, A. Menter, K. Gordon, J. Weglowska, L. Puig, K. Papp, L. Spelman, D. Toth, F. Kerdel, A.W. Armstrong, G. Stingl, A.B. Kimball, H. Bachelez, J.J. Wu, J. Crowley, R.G. Langley, T. Blicharski, C. Paul, J.P. Lacour, S. Tyring, L. Kircik, S. Chimenti, K. Callis Duffin, J. Bagel, J. Koo, G. Aras, J. Li, W. Song, C.E. Milmont, Y. Shi, N. Erondu, P. Klekotka, B. Kotzin, A. Nirula, Phase

3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis, N Engl J Med 373(14) (2015) 1318-28.

[42] J. Bagel, M. Lebwohl, R.J. Israel, A. Jacobson, Immunogenicity and skin clearance recapture in clinical studies of brodalumab, J Am Acad Dermatol 82(2) (2020) 344-351.

[43] K. Reich, K. Jackson, S. Ball, S. Garces, L. Kerr, L. Chua, T.M. Muram, A. Blauvelt, Ixekizumab Pharmacokinetics, Anti-Drug Antibodies, and Efficacy through 60 Weeks of Treatment of Moderate to Severe Plaque Psoriasis, J Invest Dermatol 138(10) (2018) 2168-2173.