

Therapeutic drug monitoring of biologics in psoriasis

MeiQi May Liau¹
Hazel H Oon²

¹Division of Dermatology, University Medicine Cluster, National University Hospital, Singapore; ²National Skin Centre, Singapore

Abstract: Biologics are an important component of the armamentarium of drugs in the treatment of moderate to severe psoriasis. There is increasing evidence that therapeutic drug monitoring (TDM) encompassing the measurement of trough concentrations and anti-drug antibodies (ADA), together with clinical response is emerging as a valuable tool for clinical decision making. It aids in targeted dose adjustments in patients with low drug concentrations, monitoring of adherence and assessment of patients who lose response to biologics or do not respond at all. The high prevalence of psoriasis, its impact on patients' lives and costs spent on therapy motivate an evidence-based and cost-effective utility of biologics. We performed a literature review on the TDM of TNF alpha antagonists (adalimumab, infliximab, etanercept), IL12/23 antagonists (ustekinumab, guselkumab, tildrakizumab), IL17A inhibitors (secukinumab, ixekizumab) and biosimilars used in the treatment of psoriasis. Although establishing target therapeutic ranges for biologics is ideal, this has only been explored in adalimumab. We also propose a treatment algorithm for the practical application of TDM depending on drug trough concentrations, presence/absence of anti-drug antibodies and clinical response of patients. The practice of TDM is recommended in routine clinical practice where possible.

Keywords: psoriasis, biologics, therapeutic drug monitoring

Introduction

Psoriasis is a complex, chronic, immune-mediated disorder affecting the skin and joints.¹ Previous studies have shown there is a complex interplay between the innate and adaptive immune system during disease progression in response to an unidentified trigger which can be either genetic, environmental or immunologic.^{2,48} The precise mechanism of its pathogenesis remains poorly understood.

Recent studies looking at systems biomarkers in psoriasis pathogenesis have identified several novel proteins, pushing the boundaries of our current knowledge. Sevimoglu et al³ discovered PI3 as a candidate biomarker with high expression in psoriasis patients, as well as gender differences in which PC4 and WIF1 proteins were higher in healthy states than disease states in males and females, respectively. Manczinger et al⁴ reaffirmed several already published psoriasis-associated protein-coding genes including CCNA2, FYN and PIK3R1 identified as genes play a central role in psoriasis pathogenesis. Another study analysed the expression patterns from 12 microarray studies (534 patients) from the Gene Expression Omnibus.⁵ The authors identified 11 core differentially expressed genes (DEGs) for being commonly identified in at least 10 of the 12 datasets. These were IFIT1, OAS2, PI3, STAT1, NMI, TRIM22,

Correspondence: Hazel H Oon
National Skin Centre, 1 Mandalay Rd,
Singapore 308205
Tel +65 6253 4455
Email hazeloon@nsc.com.sg

RSAD2, WIF1, SUB1, MAD2L1 and IFI44. These studies present valuable information for future work on drug target identification and discovery.

Although the precise pathophysiology is yet to be clearly elucidated, various cytokines and growth factors including; tumour necrosis factor (TNF- α), interleukin (IL)-23, IL-22 and IL-17 are involved.⁶⁻⁸ Accordingly, the treatment of psoriasis has also evolved to include biologic therapies which target these agents. Although biologics have been shown to be highly effective, not all patients respond to these modalities (primary failure). Some initial responders also lose effect over time (secondary failure) which has been attributed to the development of drug antibodies and low serum concentrations.

Therapeutic drug monitoring (TDM) is the clinical practice of measuring serum drug and/or anti-drug antibody (ADA) concentrations to guide clinical decision making. Studies evaluating optimal cutoff trough values of the various biologics in terms of clinical efficacy are also invaluable. In patients with inflammatory bowel disease and rheumatoid arthritis, adequate serum concentrations of biologics have been associated with sustainable clinical responses. Similarly, there is growing evidence to suggest that TDM is beneficial in patients with psoriasis. We aim to review the available evidence on TDM of biologic agents used in the treatment of patients with psoriasis and its impact on treatment efficacy.

TDM of adalimumab in psoriasis

The incidence rates of anti-adalimumab antibodies (AAA) in psoriatic patients ranged from 6.5% to 45% in the literature.⁹⁻¹⁴ Lecluse et al⁹ were the first to examine the relationship between development of AAA and adalimumab trough concentrations in psoriasis patients. They reported the development of AAA in 45% (13/29) of patients. They found that the development of AAA was associated with lower adalimumab trough concentrations and consequently impaired treatment outcome. These findings were supported by subsequent studies.¹⁰⁻¹³

In addition, there have been attempts to determine the therapeutic range of adalimumab in the treatment of psoriasis. In 2010, Lecluse et al⁹ reported that the minimal trough level of adalimumab in good responders (PASI >75) at the 24-week mark of treatment was 9.7 $\mu\text{g/mL}$. Takahashi et al¹² determined this to be 7.84 $\mu\text{g/mL}$ (PASI >75) via a receiver-operator characteristics (ROC) analysis. Recently, in 2015, Menting et al¹⁴ established a therapeutic range for adalimumab trough levels of 3.51–7.00 mg/L that corresponds

with good clinical response (PASI 75) in psoriatic patients. The lower and upper margin of the therapeutic range was identified using ROC analysis and concentration effect curve respectively. Interestingly, it was observed that the trough concentrations exceeded the therapeutic window (>7 mg/L) in one-third of patients.

TDM of infliximab

Several studies have demonstrated that the presence of anti-infliximab antibody (AIA) is associated with lower serum infliximab concentrations and consequently poorer clinical outcomes.^{12,16} AIAs have been reported in 5.4%–43.6% of patients in the literature.¹⁷⁻²⁰ In 2013, Takahashi reported the minimum plasma infliximab trough level for good responders (PASI >75) to be 0.92 $\mu\text{g/mL}$ via a ROC analysis.¹² In addition, Reich et al²¹ studied the efficacy and safety of continuous vs intermittent Infliximab maintenance therapy in 222 patients. At week 52, a greater proportion of patients on continuous therapy achieved PASI 75 compared to those on intermittent therapy (80% vs 47%). Fewer serious infusion-related reactions were also reported in the continuous therapy group compared to those on intermittent therapy (<1% vs 4%)

TDM of etanercept

Etanercept appears to exhibit immunogenicity less often than the other monoclonal antibodies. Anti-etanercept antibodies (AEA) have been reported in 0%–18.3% of patients in the literature.^{10,22-25} None of these studies demonstrated a significant difference in clinical response associated with AEA.

TDM of ustekinumab

Anti-ustekinumab antibodies (AUA) have been reported in 3.8%–6.0% of patients.²⁶⁻³¹ Two studies have demonstrated the relationship between detection of AUAs and a reduced PASI response. Papp et al²⁸ reported detection of AUA in 12.7% (20/158) of patients with PASI 50, compared to 2.0% (12/590) of PASI 75 patients. In addition, serum ustekinumab concentrations are affected by weight, with lower serum concentrations observed in heavier patients at various doses. In the PHOENIX phase I and II studies,^{32,33} median ustekinumab serum concentrations at week 28 were similar in lighter patients (≤ 100 kg) who received 45 mg every 12 weeks, compared to those in heavier patients (>100 kg) receiving 90 mg every 12 weeks. This observation was paralleled by clinical efficacy, as evidenced by similar PASI 75 response rates between both groups.

TDM of secukinumab and ixekizumab

Secukinumab and ixekizumab are newer biologic agents recently approved in the treatment of plaque psoriasis. Both are recombinant humanized monoclonal antibodies that selectively bind and neutralize interleukin-17A, the primary effector of Th17 cells. Little is known about their immunogenicity potential. In two phase III clinical trials (up to 52 weeks) in patients treated with secukinumab,³⁴ low levels of immunogenicity have been reported. In the FIXTURE and ERASURE studies, prevalence of anti-secukinumab antibodies (ASA) have been reported in 0.4% (4/980) and 0.3% (2/702) patients, respectively. Blauvelt et al³⁵ reported higher levels of immunogenicity in patients with psoriasis treated with ixekizumab at 12 weeks. AIAs were detected in 9% of patients receiving two weekly ixekizumab and 13.4% of those receiving four weekly ixekizumab. The development of AIA was associated with poorer clinical outcomes. Twelve-week PASI 75 response rates was 36.8% in patients with high AIA titres, compared to 90.7% in those with undetectable AIA.

This lowered immunogenicity potential of secukinumab was borne out by a side-by-side ELISpot assay where healthy donors showed less frequent T cell responses and elaborated lower counts of pre-existing T cells to secukinumab than to ixekizumab and also adalimumab.

TDM of newer biologics

Guselkumab and tildrakizumab are novel monoclonal antibodies targeting interleukin-23, a key regulator in the pathophysiology of psoriasis. It bridges the innate and adaptive immune responses and plays a key role in inducing Th17 cell differentiation. Together with brodalumab (anti-interleukin 17 receptor antibody), these are the three biologics approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe psoriasis between 2017 and 2018. There is currently a paucity of data in the literature with regards to measurement of their trough levels and anti-drug antibody formation.

TDM of biosimilars

According to the US FDA, a biosimilar is “highly similar to an FDA-approved biological product” and “has no clinically meaningful differences in terms of safety and effectiveness”.³⁶ To date, the following biosimilars have been approved for the treatment of chronic plaque psoriasis - Remsima[®] and Inflectra[®] (infliximab biosimilars), Erelzi[®] (etanercept biosimilar) and Amjevita[®] (an adalimumab biosimilar).

Overall, there is a paucity of data in terms of therapeutic drug monitoring in patients with chronic plaque psoriasis treated with biosimilars. The TDM data available in the literature is centered on the use of infliximab biosimilars in inflammatory bowel disease and rheumatoid arthritis. These studies suggest that switching to biosimilars is feasible with few adverse events, including limited anti-drug antibody formation and loss of response. For example, Ben-Horin et al³⁷ tested the sera of patients with inflammatory bowel disease with or without measurable infliximab (Remicade[®]) antibodies, for their cross-reactivity to Remsima (infliximab biosimilar). All 56 patients who tested negative for anti-Remicade antibodies tested negative for antibodies to Remsima; all 69 patients who tested positive for anti-Remicade antibodies also tested positive for antibodies to Remsima. The antibody titres against Remicade and Remsima were strongly correlated ($P < 0.001$). Similarly, Schmitz et al³⁸ reported that 27 patients with diverse rheumatological conditions switched from infliximab to a biosimilar had no significant difference in infliximab serum levels and disease activity up to 12 months after the switch.

Discussion

Biologic agents currently represent the end of the therapeutic spectrum for moderate to severe plaque psoriasis. Hence, it is crucial to identify and optimize factors impairing clinical response as far as possible.

Recent attempts at determining the therapeutic ranges of some of the biologics provide a stepping stone to developing an algorithm for TDM-based treatment in our psoriatic patients (Table 1). For adalimumab, the minimal serum trough level to achieve PASI 75 has been determined by Lecluse and Takahashi to be 9.7 mg/L and 7.84 µg/mL, respectively.^{9,12} These are higher than the therapeutic range of 3.51–7.00 mg/L reported by Menting et al.¹⁴ In addition, Menting et al¹⁴ described a substantial proportion of patients whose adalimumab levels exceeded the upper therapeutic level of 7 mg/L with no further beneficial effect on treatment response. This suggests that this subset of patients is being overtreated, and could be subject to unnecessary immunosuppression. It has been proposed that lengthening the dosing interval can lead to trough concentrations within the therapeutic range without losing clinical efficacy, as well as cost savings.

In 2015, Menting et al³⁹ reported there was no correlation between the clinical efficacy and trough levels of ustekinumab, with a correlation coefficient of -0.36 at week 16. He offered several possible explanations for these

findings. Firstly, the study had a small sample size of 41 patients. Secondly, patients may have been overtreated resulting in complete blockade of interleukins 12/23 during the intervals of successive doses. Thirdly, a different indicator besides trough levels may be required due to the infrequent administration of ustekinumab (12 weekly) compared to other biologics.

Furthermore, optimal trough levels of biologics appear to vary amongst diseases. For example, the minimum trough level of infliximab in good responders (PASI >75) was reported to be 0.92 µg/mL by Takahashi et al.¹² This was compatible with that in rheumatoid arthritis (>1.0 µg/mL). In contrast, a considerably lower infliximab trough level of 0.33 µg/mL has been reported for the control of Crohn's disease. This suggests disease-specific differences in trough levels required to achieve adequate control. Multiple factors, genetic and non-genetic, may influence response to treatment.¹⁵ Differences in baseline patient characteristics, including mean body mass index, race and ethnicity may account in part for these differences. Lastly, as patents for the biologic agents reach their expiration dates, a wave of biosimilars is

expected to enter the market and further research on their efficacy and immunogenicity is vital.

We recommend the measurement of biologic serum trough concentrations and anti-drug antibody levels in routine clinical practice where possible. A proposed algorithm for practical application of therapeutic drug monitoring is outlined in Table 2. If routine TDM is not feasible, it should at least be performed in patients who lose response to biologics or do not respond at all. The rationale for this is that improvement is unlikely in the presence of high antibody titres and to prevent prolonged use of costly, inadequate or unsuitable biologic therapy. Although one of the benefits of TDM is to monitor for poor patient adherence, a practical challenge posed is when patients take the medication at the time of visits but skip doses in between. Closer intervals of TDM in clinical practice may circumvent this problem, although there is a need to balance this with available resources. While biologics should be administered as continuous therapy with regular fixed time intervals where possible, actual use may vary. Given the issues of patient adherence, lifestyle, financial constraints and funding, studies examining TDM of biologics

Table 1 Therapeutic drug monitoring of biologics for chronic plaque psoriasis.

Drug class	Drug	Incidence of anti-drug antibodies	Minimum trough level to achieve PASI >75 (mg/L)	Target therapeutic trough range (mg/L)
TNF-alpha antagonist	Adalimumab	6.5%–45.0%	3.51, ¹⁴ 7.84, ¹² 9.7 ⁹	3.51–7.00
	Infliximab	5.4%–43.6%	0.92	Unk
	Etanercept	0.0%–18.3%	Unk	Unk
IL 12/23 antagonist	Ustekinumab	3.8%–6.0%	Unk	Unk
	Guselkumab	Unk	Unk	Unk
	Tildrakizumab	Unk	Unk	Unk
IL 17a antagonist	Secukinumab	0.3%–0.4%	Unk	Unk
	Ixekizumab	9%–13.4%	Unk	Unk

Abbreviations: IL, interleukin; TNF, tissue necrosis factor; Unk, unknown – no established levels or ranges yet; PASI, Psoriasis Area and Severity Index.

Table 2 Therapeutic drug monitoring (drug trough concentrations, anti-drug antibodies) algorithm in chronic plaque psoriasis

Drug trough concentrations	Anti-drug antibodies	Quiescent psoriasis (responders)	Active psoriasis (non-responders)
Above therapeutic range	Absent	Consider tapering regimen, particularly if drug toxicity experienced (ie, reduce dose or increase dosing interval)	Switch drug class
Within therapeutic range, or above minimum trough level	Absent	Maintain regimen	Switch drug class
Below therapeutic range or minimum trough level	Undetectable	Maintain regimen vs intensification vs stop	Intensify regimen
	Detectable	Close monitoring, consider stopping	Switch to another drug class or intensify regimen
Undetectable	Undetectable	Check for drug compliance, intensify regimen, consider stopping	Check for drug compliance. If present then intensify regimen
	Detectable	Close monitoring, consider stopping	Switch drug class

in a real world setting where these drugs are used in a start/stop manner, lengthened intervals and off-label dosing, are important in throwing more light on drug survival.

The continued development of effective therapies in psoriasis is urgently needed. The concept of drug repositioning, the application of approved drugs for new therapies, has been gaining popularity in recent years. With the availability of established clinical drug libraries and rapid advances in disease biology, genomics and bioinformatics, drug repositioning provides an efficient route for drug discovery.

For example, expression levels of the protein STAT3 are higher in the skin lesions of psoriasis patients than in normal skin. Drugs that target STAT3 are under investigation. One example is benzo[b]thiophen-2-yl-3-bromo-5-hydroxy-5H-furan-2-one (BTH) which can reduce the proliferation of keratinocytes by inhibiting the anti-inflammatory activity of the NK-kB signalling pathway and impair STAT3 phosphorylation, preventing it from translocating to the nucleus and resulting in a decrease in keratinocyte proliferation.⁴⁴ Other drug repositioning strategies to the following have been proposed: interleukin-1 β (eg, diacerein,⁴¹ glucosamine⁴²), EGFR (eg, zalutumumab,⁴³ panitumumab^{44,45}), and VEGF (eg, bevacizumab,⁴⁶ minocycline⁴⁷).

Conclusion

There is increasing evidence to suggest that TDM will allow for more tailored and rational use of biologic therapy. Further research efforts are required to evaluate target therapeutic ranges for the various agents, particularly the newer biologics, in prospective patient cohort studies, as well as identifying and minimizing factors contributing to ADA development.

Disclosure

MML has no conflicts of interest. HHO has served as a speaker, advisory board member and researcher for Janssen, Novartis, and Galderma. HHO is also a clinical investigator for Pfizer and an advisory board member and speaker for AbbVie, Eli Lilly, and LEO Pharma. The authors report no other conflicts of interest in this work.

References

- Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. *J Am Acad Dermatol*. 2009;60(2):218–224.
- Perera GK, di Meglio P, Nestle FO. Psoriasis. *Annu Rev Pathol Mech Dis*. 2012;7(1):385–422.
- Sevimoglu T, Turanlı B, Bereketoglu C, Arga KY, Karadag AS. Systems biomarkers in psoriasis: integrative evaluation of computational and experimental data at transcript and protein levels. *Gene*. 2018;647:157–163.
- Manczinger M, Kemény L. Novel factors in the pathogenesis of psoriasis and potential drug candidates are found with systems biology approach. *PLoS One*. 2013;8(11):e80751.
- Sevimoglu T, Arga KY. Computational systems biology of psoriasis: are we ready for the age of omics and systems biomarkers? *OMICS*. 2015;19(11):669–687.
- Ce G, Barker JN. Pathogenesis and clinical features of psoriasis. *The Lancet*. 2007;370(9583):263–271.
- Ettehadhi P, Greaves MW, Wallach D, Aderka D, Camp RD. Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions. *Clin Exp Immunol*. 1994;96(1):146–151.
- Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med*. 2004;199(1):125–130.
- Lecluse LLA, Driessen RJB, Spuls PI, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. *Arch Dermatol*. 2010;146(2):127–132.
- Mahil SK, Arkir Z, Richards G, et al. Predicting treatment response in psoriasis using serum levels of adalimumab and etanercept: a single-centre, cohort study. *Br J Dermatol*. 2013;169(2):306–313.
- Asahina A, Nakagawa H, Etoh T, Ohtsuki M, Adalimumab M04-688 Study Group. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. *J Dermatol*. 2010;37(4):299–310.
- Takahashi H, Tsuji H, Ishida-Yamamoto A, Iizuka H. Plasma trough levels of adalimumab and infliximab in terms of clinical efficacy during the treatment of psoriasis. *J Dermatol*. 2013;40(1):39–42.
- Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58(1):106–115.
- Menting SP, Coussens E, Pouw MF, et al. Developing a therapeutic range of adalimumab serum concentrations in management of psoriasis: a step toward personalized treatment. *JAMA Dermatol*. 2015;151(6):616–622.
- Karczewski J, Poniedziałek B, Rzymiski P, Adamski Z. Factors affecting response to biologic treatment in psoriasis. *Dermatol Ther*. 2014;27(6):323–330.
- Bito T, Nishikawa R, Hatakeyama M, et al. Influence of neutralizing antibodies to adalimumab and infliximab on the treatment of psoriasis. *Br J Dermatol*. 2014;170(4):922–929.
- Gottlieb AB, Evans R, Li S, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2004;51(4):534–542.
- Krathen RA, Berthelot CN, Hsu S. Sustained efficacy and safety of infliximab in psoriasis: a retrospective study of 73 patients. *J Drugs Dermatol*. 2006;5(3):251–254.
- Gottlieb AB, Kalb RE, Blauvelt A, et al. 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*. 2012;67(4):642–650.
- Menter A, Feldman SR, Weinstein GD et al. 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*. 2007;56:e1–e15.
- Reich K, Wozel G, Zheng H, et al. Efficacy and safety of infliximab as continuous or intermittent therapy in patients with moderate-to-severe plaque psoriasis: results of a randomized, long-term extension trial (RESTORE2). *Br J Dermatol*. 2013;168(6):1325–1334.
- Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152(6):1304–1312.
- Gordon KB, Gottlieb AB, Leonardi CL, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. *J Dermatolog Treat*. 2006;17(1):9–17.
- Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice Weekly in patients with psoriasis. *Arch Dermatol*. 2007;143(6):719–726.

25. Leonardi C, Strober B, Gottlieb AB, et al. Long-term safety and efficacy of etanercept in patients with psoriasis: an open-label study. *J Drugs Dermatol*. 2010;9(8):928–937.
26. 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. *J Invest Dermatol*. 2004;123(6):1037–1044.
27. Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med*. 2007;356(6):580–592.
28. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (Phoenix 2). *Lancet*. 2008;371(9625):1675–1684.
29. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med*. 2010;362:118–128.
30. Tsai TF, Ho JC, Song M, et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). *J Dermatol Sci*. 2011;63(3):154–163.
31. Kimball AB, Papp KA, Wasfi Y, et al. Long-term efficacy of ustekinumab in patients with moderate-to-severe psoriasis treated for up to 5 years in the Phoenix 1 study. *J Eur Acad Dermatol Venereol*. 2013;27(12):1535–1545.
32. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (Phoenix 1). *Lancet*. 2008;371(9625):1665–1674.
33. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2).
34. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. *N Engl J Med*. 2014;371(4):326–338.
35. Blauvelt a, Langley R, Leonardi C, et al. Ixekizumab, a novel anti-IL-17A antibody, exhibits low immunogenicity during long-term treatment in patients with psoriasis. *J Am Acad Dermatol*. 2016;74(5):AB258.
36. US Food & Drug [homepage on the Internet]. Information on biosimilars. Available from: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm>. Accessed April 09, 2019.
37. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut*. 2016;65(7):1132–1138.
38. Schmitz EMH, Meier AJL, Meier AJL, et al. Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients: results of a 12-month observational prospective cohort study. *Clin Rheumatol*. 2017;36(9):2129–2134.
39. Menting SP, van den Reek JMPA, Baerveldt EM, et al. The correlation of clinical efficacy, serum Trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. *Br J Dermatol*. 2015;173(3):855–857.
40. Andrés RM, Montesinos MC, Navalón P, Payá M, Terencio MC. NF- κ B and STAT3 inhibition as a therapeutic strategy in psoriasis: in vitro and in vivo effects of BTH. *J Invest Dermatol*. 2013;133(10):2362–2371.
41. Moghddam SRM, Ahad A, Aqil M, Imam SS, Sultana Y. Formulation and optimization of niosomes for topical diacerein delivery using 3-factor, 3-level Box-Behnken design for the management of psoriasis. *Mater Sci Eng C Mater Biol Appl*. 2016;69:789–797.
42. Kim CH, Kim JY, Lee AY. Therapeutic and immunomodulatory effects of glucosamine in combination with low-dose cyclosporine A in a murine model of imiquimod-induced psoriasis. *Eur J Pharmacol*. 2015;756:43–51.
43. Ruuls SR, Lammerts van Bueren JJ, van de Winkel JGJ, Parren PWHI. Novel human antibody therapeutics: the age of the Umabs. *Biotechnol J*. 2008;3(9-10):1157–1171.
44. Okamoto K, Maeda H, Shiga T, et al. Cetuximab and panitumumab in a patient with colon cancer and concomitant chronic skin disease: a potential beneficial effect on psoriasis vulgaris. *World J Gastroenterol*. 2015;21(12):3746–3749.
45. Nishizawa A, Satoh T, Yokozeki H. Erythrodermic psoriasis improved by panitumumab, but not bevacizumab. *Acta Derm Venerol*. 2012;92(4):360–361.
46. Datta-Mitra A, Riar NK, Raychaudhuri SP. Remission of psoriasis and psoriatic arthritis during bevacizumab therapy for renal cell cancer. *Indian J Dermatol*. 2014;59(6):632.
47. Udkoff J, Cohen PR. Severe infliximab-induced alopecia and scalp psoriasis in a woman with Crohn's disease: dramatic improvement after drug discontinuation and treatment with adjuvant systemic and topical therapies. *Dermatol Ther*. 2016;6(4):689–695.
48. Ayala-Fontánez N, Soler DC, McCormick TS. Current knowledge on psoriasis and autoimmune diseases. *Psoriasis (Auckl)*. 2016;6:7–32.

Biologics: Targets and Therapy

Publish your work in this journal

Biologics: Targets and Therapy is an international, peer-reviewed journal focusing on the patho-physiological rationale for and clinical application of Biologic agents in the management of autoimmune diseases, cancers or other pathologies where a molecular target can be identified. This journal is indexed on PubMed Central, EMBase, and Scopus.

Submit your manuscript here: <https://www.dovepress.com/biologics-targets-and-therapy-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.