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Review Article

Biologic therapies in psoriasis: a personalised approach

以個性化方法使用生物治療來處理銀屑病

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This article aims to equip the reader with the knowledge and skills to individualising their selection and dosing strategies of biologic therapies for patients with moderate to severe psoriasis.

本文的宗旨是教導讀者如何選擇或更換生物藥劑來處理銀屑病，以及生物藥劑適當的調整方法（劑量與頻率）。

Keywords: Biologic therapies, dosing, individualising, psoriasis, selection

關鍵詞：生物藥劑、劑量、更換、銀屑病、選擇

Introduction

Psoriasis is a persistent skin disorder characterised by the hyperproliferation of keratinocytes, with development of scaly erythematous plaques. Progressive basic scientific research has led to a better understanding of the pathophysiology, and now dysregulation of the immune system has been identified to be a crucial event in the disease (Figure 1). Attention focusing on more specific targets for psoriasis treatment in recent years has been transformative in its clinical management. A summary of various national guidelines for consideration of biologic agents for moderate-to-severe psoriasis is shown in Table 1. Drug molecule characteristics including mechanism of action, selectivity and limitation, dosing regimen, and key measures of efficacy such as onset time, response rates and the safety data from pivotal clinical trials are summarised in Table 2.[1-6]

In general, we see the onset of clinical effect ranging from one to four weeks and at least 50% of the patients achieve PASI 75 response from biologics usage. If we take a closer look at the level of psoriasis control with newer agents such as adalimumab and ustekinumab, the PASI 75 response is relatively consistent at around 70%, but with PASI 90 the response drops to around 45% and PASI 100 response is not studied in these

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agents. However, secukinumab, the latest and first in class biologic that specifically targets IL-17A promises superior levels of PASI 75, PASI 90, and PASI 100 responses. Indeed, a recently published clinical trial which directly compared secukinumab with ustekinumab demonstrated clear superiority of secukinumab in terms of "clearing skin" of patients with moderate-to-severe psoriasis (PASI 90 responders of 79% vs 57.6% at week 16, and 74.9% vs 60.6% at week 52). The proportion of patients with DLQI 0/1 response was also consistently and statistically higher in the secukinumab group at every monthly timepoint.[7]

Given the achievement of new levels of psoriasis control, current treatment guidelines and algorithms may not have caught up with the availability of some of the newest drugs, and more importantly there is a need to re-think on how applicable current treatment goals are as we enter into a new era in use of biological agents. With increasing clinical experience, this review attempts to look at the practical use of biologic therapies in moderate-to-severe psoriasis with a personalised and holistic approach, addressing the question of the choice of the right biologic for the right patient at the right time.

Environmental and genomic factors contribute to a dysregulation of keratinocytes producing pro-inflammatory cytokines which in turn activate dendritic cells. Activated dendritic cells release IL-12 and IL-23 which polarise naïve T cells into type 1 T helper (Th1) and type 17 T helper (Th17) cells, respectively. IL-17A is the signature cytokine product of Th17 cells while IL-23 is necessary to

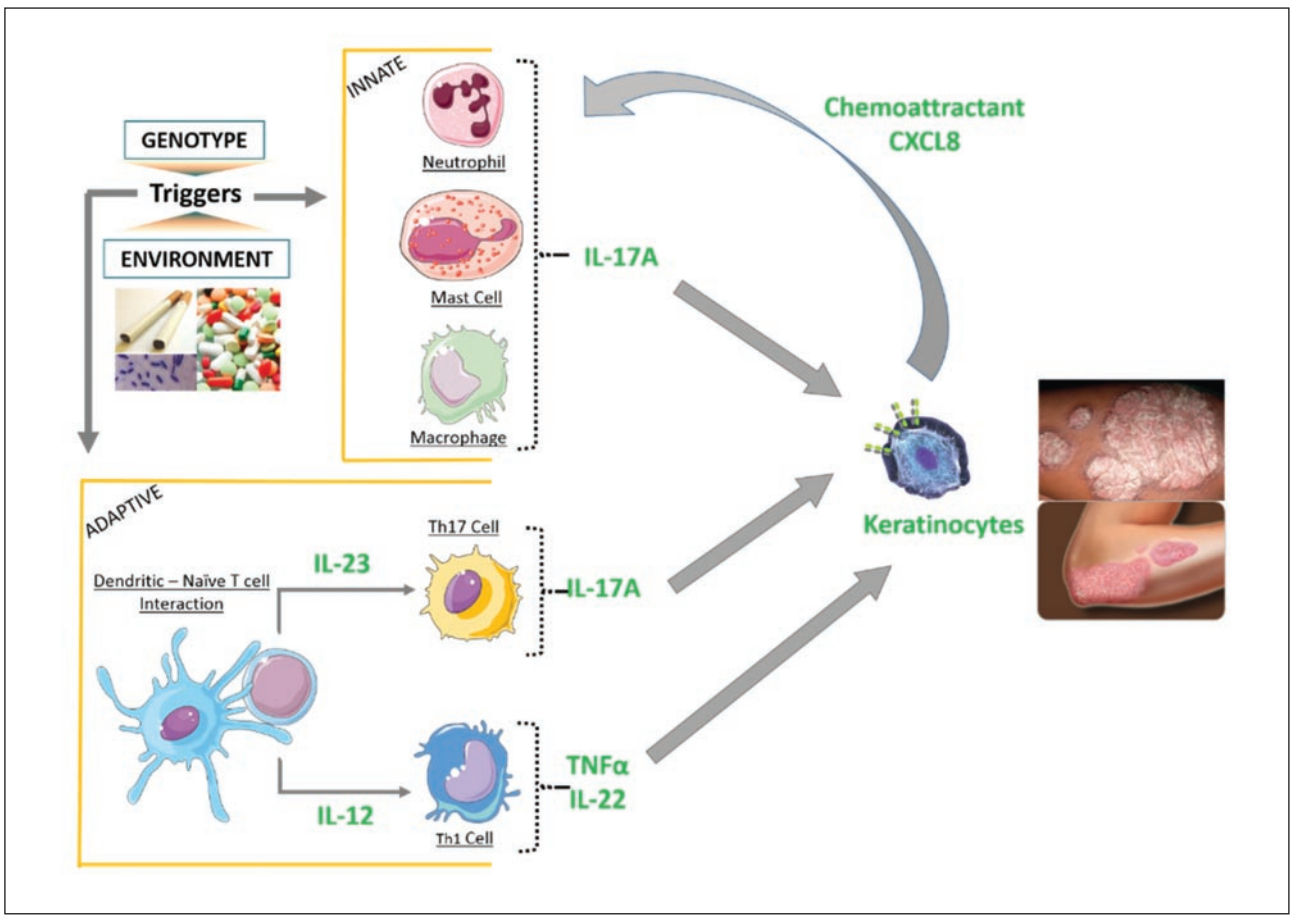

Figure 1. IL-17A both directly induces and synergises with other cytokines to promote autoimmune tissue inflammation.

stabilise Th17 cell activation. Both cytokines are considered to play crucial and integral roles in the development of psoriatic plaques. IL-17A is not only a major activator of keratinocytes causing epidermal changes but it also induces in keratinocytes the release of chemokines that attract neutrophils, mast cells, and macrophages to the skin. Infiltration and crosstalk between these different immune cells lead to the release of even more IL-17A as well as additional cytokines such as TNF-α and IL-22 that further drive keratinocyte activation and the commencement of a positive feedback inflammatory loop. This current model for psoriasis pathogenesis focuses on the roles of innate immune cells in local tissue, adaptive T cell response, and in particular, the key inflammatory cytokines IL-23/IL-17A axis. A plethora of cytokines including TNF-α, IFN-γ, IL-6, IL-12, IL-17, IL-22, and IL-23 leads to increased keratinocyte activation and the commencement of a positive feedback inflammatory loop.[8]

How to use biologic treatment in special situations

A. Physiological categories

For a long time, etanercept (0.8 mg/kg weekly, up to maximum dose of 50 mg) was the only biologic approved in the EU for ≥6 years old and UK for ≥8 years old.[24] Adalimumab (weight-based dosing, 10-40 mg) was recently approved in the EU for ≥4 years old.[25] Ustekinumab was recently shown in a phase 3 study (CADMUS) to be safe

Table 1. Summary of various national guidelines for consideration of biologic agents for moderate-to-severe psoriasis

American Academy of Dermatology[2]	BSA ≥5%
British Association of Dermatologists[9]	BSA >10% or PASI >10 + DLQI >10 + Unable to use or failed standard systemic Rx
European Academy of Dermatology & Venereology[10]	DLQI >10 + Unable to use or failed standard systemic Rx
Malaysian Clinical Practice Guidelines[11]	Criteria A (Severe Disease): 1. PASI ≥20 OR 2. BSA ≥30% OR 3. DLQI ≥18 + Criteria B (Clinical Categories): 1. Contraindications to standard systemic treatment AND/OR 2. Intolerance to standard systemic treatment AND/OR 3. Failed standard systemic treatment
Singapore Clinical Practice Guidelines[12]	Moderate-to-severe psoriasis and intolerance/contraindication/ failure of phototherapy or standard systemic therapy, or severe unstable life-threatening disease. ("standard systemic therapy" is defined as cyclosporine 2-5 mg/ kg/day for 12 weeks, methotrexate 15 mg-25 mg weekly for 12 weeks, acitretin 25-50 mg daily for 12-24 weeks)

Table 2. Summary of characteristics of biological agents approved for moderate-to-severe psoriasis

	Etanercept (Enbrel®)	**Infliximab (Remicade®)**	**Adalimumab (Humira®)**	**Ustekinumab (Stelara®)**	**Secukinumab (Cosentyx®)**	**Ixekizumab (Taltz®)**	**Brodalumab (Siliq®)**
Mechanism of action	TNFα inhibition *Soluble decoy TNF receptor fused to FcMAB*	TNFα inhibition *Chimeric MAB to TNF*	TNFα inhibition *Fully human MAB to TNF*	IL-12/23 inhibition *Fully human MAB to p40 subunit shared by IL-12 and IL-23*	IL-17A inhibition *Fully human MAB to IL-17A*	IL-17A inhibition *Humanised MAB to IL-17A*	IL-17 inhibition *Fully human MAB to IL-17RA*
Half-life	102±30 hours	7.7 to 9.5 days	2 wks, ranging from 10 to 20 days	14.9±4.6 to 45.6±80.2 days	22 to 31 days	13 days	–
Dosing	S, 50 mg following Start: twice weekly for 3 mths Then: every wk	IV 5 mg/kg Start: 0, 2, 6 wk Then: every 8 wks	SC following Start: 80 mg at wk 0 Then: 40 mg every other wk	SC 45 mg or 90 mg if weight >100 kg following Start: 0, 4 wk Then: every 12 wks	SC 300 mg following Start: 0, 1, 2, 3, 4 wk Then: every 4 wks	SC following Start: 160 mg at wk 0 Then: 80 mg every 2 wks	SC 140 mg or 210 mg every 2 wks
Short-term (3-4 mths) efficacy							
PASI75	47%[13]	80%[1]	71%[14]	68-74%[15]	77-82%[4]	87-90%[17]	67-86%[18]
PASI90	21%	57%	45%	36-45%	54.2-59.2%-wk 12	68-71%	–
PASI100	–	–	–	–	72.4-79%[16]-wk 16	–	26-44%
Long-term (>1 year) efficacy							
PASI75	51.6%[19]	56.8%[20]	84%[21]	71.4-78.9%[22]	74.3-78.6%[5]	83%[6]	–
PASI90	22.8%	39.4%	58%	45.9-55.1%	60-65%	73%	–
PASI100	–	–	33%	–	36.2-39.2%	55%	–
Screening labs	Screen for infections e.g. HIV, HepB/C, active or LTBI	Screen for infections e.g. HIV, HepB/C, active or LTBI	Screen for infections e.g. HIV, HepB/C, active or LTBI	Screen for infections e.g. HIV, HepB/C, active or LTBI	Screen for infections e.g. HIV, HepB/C, active or LTBI	Screen for infections e.g. HIV, HepB/C, active or LTBI	Screen for infections e.g. HIV, HepB/C, active or LTBI
Monitoring labs	- Signs/ Symptoms for infections esp. TB - No live vaccinations	- Signs/ Symptoms for infections esp. TB - No live vaccinations	- Signs/ Symptoms for infections esp. TB - No live vaccinations	- Signs/ Symptoms for infections esp. TB - No live vaccinations	- Signs/ Symptoms for infections esp. TB - No live vaccinations	- Signs/ Symptoms for infections esp. TB - No live vaccinations	- Signs/ Symptoms for infections esp. TB - No live vaccinations
Adverse events of special interest	- Reactivation of LTBI - Hepatosplenic T-cell lymphoma and other malignancies	- Reactivation of LTBI - Hepatosplenic T-cell lymphoma and other malignancies	- Reactivation of LTBI - Hepatosplenic T-cell lymphoma and other malignancies	- Reactivation of LTBI - Reversible Posterior Leukoencephalopathy syndrome	- Higher incidence of Candida infections - Risk of neutropenia - IBD	- Higher incidence of Candida infections - Oral herpes - Risk of neutropenia - IBD	- Higher incidence of Candida infections - Risk of neutropenia - Risk of suicidal ideation[23]

Abbreviations: wk=week, mth=month, SC=subcutaneous, IV=intravenous

and efficacious for adolescents (12-17 years old) over one year.[26] All other biologics, if used in **children**, are off-label and reported as case series or reports.

The use of biologics in **women planning for pregnancy or who are pregnant** relates to the safety profile and all biologics (in Table 2) are listed as pregnancy category B. Several publications have looked at the outcomes of pregnancy following exposure to TNF-α inhibition but in diseases other than psoriasis. The latest European League Against Rheumatism (EULAR) recommendations are that TNF-α inhibitors can be continued during the first part of pregnancy but that only etanercept be considered for use throughout pregnancy due to low rate of transplacental passage. Where **breastfeeding** is concerned, TNF-α inhibitors can be continued since low transfer to breast milk has been shown.[27] The newer biologics should be avoided in pregnancy and lactation until more safety data becomes forthcoming.

Elderly people of >65 years old have clinical features that differ from younger patients and the introduction of biologic therapy in the elderly has been slow. A retrospective review of patient visits for psoriasis and psoriatic arthritis collected over a seven-year period showed similar efficacy between conventional systemic therapy and biologic therapy in patients 65 years of age and older, but a higher rate of adverse events in the elderly on conventional systemic therapy; suggesting that biologic therapy may be a safer option for an elderly patient.[28] In the latest secukinumab phase 3 clinical trials, of the 3,430 patients, a total of 230 were 65 years of age or older and 32 patients were 75 years of age or older – based on population pharmacokinetic analysis, clearance in elderly patients was similar to that in patients less than 65 years of age.[29]

B. Comorbidities

Obesity is a prevalent comorbidity in patients with psoriasis and may reduce the response to therapy of some biologics. In fact, obesity was found to be one independent factor contributing to shortened drug survival in an American observational study of 427 patients receiving biologics over an 8-10 year period.[30] Of all the biologics discussed, note that only ustekinumab has a weight-based dosing protocol.

A comprehensive review of 46 studies, most of which were retrospective studies in rheumatoid arthritis and inflammatory bowel patients, essentially concluded that TNF-α inhibitors can be safely continued through low-risk **procedures** (such as endoscopy, ophthalmolgical and any ambulatory procedures). A case-by-case approach should be adopted based on the patient's risk factors and comorbidities for intermediate-risk (such as orthopaedic, urological and prostate surgery) and high-risk procedures (such as cardiothoracic and vascular surgery and surgery lasting longer than 4 hours).[31] For patients undergoing major surgery, it is widely recommended that biologics be stopped for at least 4 to 5 half-lives prior due to possible increased risk of infections. Biologics can be restarted post-operatively if there is no evidence of infection and that wound healing is satisfactory. It was deemed insufficient evidence to make firm recommendations with regards to the newer biologics.

Hepatitis B viral (HBV) reactivation in patients on certain biologic therapy may occur. Patients with chronic HBV infection (HBsAg+, HBcAb+, persistently or intermittently elevated LFT results) should be evaluated by a hepatologist and undergo further testing (HBeAg, HBeAb, HBV DNA quantification) to determine if they are active or inactive carriers. For chronic active carriers (HBeAg+, HBV DNA >105 copies/mL), antiviral prophylaxis is recommended. Chronic inactive HBV carriers (HBeAg-, HBV DNA <104 copies/mL) may be treated, but this decision should be made in consultation with a hepatologist.[32] As such, antiviral therapy for 2-4 weeks preceding the treatment is recommended if biologics are

required for a HBV positive individual with inactive disease.[12] Small studies showed that TNF-α inhibition (when combined together with interferon and ribavirin) is safe in **Hepatitis C viral** positive patients.[33] There are several reports of successful TNF-α inhibition in rheumatological conditions in **HIV**-positive patients.[34]

For patients with **latent TB infection** (LTBI), it is generally recommended to start prophylactic isoniazid for 6 to 9 months (it would be prudent to adhere to local country guidelines) but biologics can be started after at least one month of prophylaxis.[35]

C. Psoriasis subtypes

Psoriatic arthritis is a heterogeneous disease that involves inflammation in the joints and spine, soft tissue inflammation, dactylitis and enthesitis and occurs in about 30% of patients with psoriasis. TNF-α inhibition with good ACR 20 response is perceived as the gold standard for such patients. Recent phase 3 clinical trials in patients with psoriatic arthritis demonstrated for the first time that anti-17A targeted therapy can have ACR responses in the range of TNF-α inhibition.[36]

It is well known that **nail and scalp psoriasis** are often correlated with more severe skin disease and resistance to available therapies. Encouragingly, all biologics so far have shown slow but excellent results in nail psoriasis.[37] For scalp psoriasis, infliximab and ustekinumab exhibited the greatest efficacy compared to adalimumab and etanercept in a retrospective comparative study in a tertiary psoriasis centre.[38] It is unsurprising that secukinumab is showing very promising results too but published literature is eagerly anticipated.

Most, if not all, biologics have shown promising results in treatment of **erythrodermic and pustular psoriasis** in case-reports, case-series and uncontrolled trials.[39] It would appear that pustular psoriasis generally is more responsive to biologic therapy than erythroderma.

Finally, **palmoplantar psoriasis** is another variant that is notoriously resistant to treatment. There is some evidence of effectiveness with TNF-α inhibition (infliximab & adalimumab >etanercept), but these drugs sometimes initiate a paradoxical psoriasis and pustular flare.[40] Ustekinumab dosed at 90 mg has been tried in an investigator-initiated open-label trial and appears be effective in controlling the signs and symptoms of palmoplantar psoriasis where 35% of ustekinumab-treated subjects had an improvement of 50% in PGA at week 16.[41] Results from an ongoing study with secukinumab are anticipated.

How to get the best out of a particular biologic

A. Monitoring while on biologics

How patients on biologics should be monitored is not fully characterised yet and more importantly clinical practices and guidelines vary. A 5-year prospective study of 162 patients on anti-TNF showed that routine testing is largely unsupported because laboratory abnormalities detected were not clinically meaningful.[42] We would like to advocate that clinicians adopt a country-specific and rational approach on a case-by-case basis. For example, the author (DCWA) performs annual assessments of interferon-gamma release assays for his biologic-treated patients who stay in TB-endemic areas.

B. Dose escalation

Some biologics may exhibit gradual loss of efficacy over time likely due to the development of treatment-emergent anti-drug antibodies.[43] Off-label biologic regimens may be necessary and commonly employed strategies to improve efficacy for non-responders are dose increase (as seen most commonly with infliximab and etanercept) or dose frequency increase (as seen most commonly with adalimumab and ustekinumab).

C. Dose reduction

With newer biologics like secukinumab and ustekinumab that deliver high efficacy, many physicians and patients find dose reduction or tapering a tempting thought. All of the biologics discussed do not exhibit rebound phenomenon on cessation and may be stopped abruptly. However, patients must be aware that psoriasis is a chronic disease and will invariably relapse on cessation of therapy. Continuous therapy is definitely more efficacious and is associated with less development of anti-drug antibodies (with associated loss of efficacy and side effects). Indeed, previous dose reduction studies conferred that decreased dosing of biologic therapy resulted in poorer outcomes than standard biologic treatment.

D. Switching between biologics

In our experience, switching to another biologic is not infrequent for various reasons. This appears to provide response even if the second biologic is from the same class of action e.g. TNF-α inhibition. If switching is performed for reason of lack of efficacy, the standard induction dose may be administered at the time of the next scheduled dose without the need for a washout period.[44] However, real-world data has demonstrated a shortening of drug survival in patients who switch from one biologic to another.[45] Plausible explanations are that some patients have higher rate of antibody catabolism which is independent of its specificity, or that long-term suppression of a cytokine causes an induction of other pro-inflammatory cytokines with the redundant function. As far as possible, physicians should thus try to optimise the current biologic before considering a switch in biologic.

Conclusion

There is increasing recognition of the value of biologics therapy in psoriasis and hence an increasing importance of a holistic clinical approach when treating patients. This review gives an up-to-date overview of the emerging treatment paradigms for the optimal management of patients with psoriasis and attempts to provide a best practice viewpoint with key discussion on the role of emerging new biological agents, individualised approach of using biologics, and developing strategies to ensure the optimal and successful outcomes of therapy.

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