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Review Article

Update on biologics in psoriasis

生物製劑治療銀屑病的更新

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Biologic therapy has emerged for more than a decade, providing a new alternative in treating moderate to severe psoriasis. There has been much research done and published for this relatively recent therapeutic option. An update on the use of biologics may help clarify some practical challenges in deciding the appropriate treatment for individual patients. This article aims to review the treatment decisions that need to be considered in prescribing biologics and their use in different patient groups with the latest evidence in this area.

生物製劑療法已經出現超過了十年的時間，這種治療對中度至嚴重程度的銀屑病患者提供了新的選擇。現時已經有許多關於這種較新治療方法的文獻研究刊登，這些更新可能會有助於澄清決定個別病人使用生物製劑治療的一些實際問題。本文的目的是以最新的醫學證據審視如何決定使用適合的生物製劑來治療各種銀屑病患者。

Keywords: Biologics, psoriasis

關鍵詞：生物製劑，銀屑病

Introduction

It has been ten years since our last review of the use of biologics in psoriasis. Since then, there have been substantial changes in this area with a lot more clinical evidence available. Therefore we decided to provide an update on the latest information. Over the past decade, much research on biologics has been published with some agents withdrawn from the market while other new agents developed. In this review, we discuss the issues that need to be considered when choosing biological agents and their use in specific groups of patients with psoriasis.

The latest estimated prevalence of psoriasis in China is 0.47%,[1] while the latest data in the United States showed that the prevalence differs in different races with the prevalence in Caucasians being 3.6%.[2] Psoriasis is now considered as a systemic disease with predominant cutaneous involvement. Treatment includes various topical agents for mild disease and systemic non-biologic therapies for moderate to severe disease.

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Biologics, which have been developed for more than a decade, target specific molecules involved in the pathogenesis of the condition. The current licensed biological agents can be divided into two groups: tumour necrosis factor (TNF) inhibitors (adalimumab, etanercept and infliximab) and interleukin antibodies (ustekinumab). Due to the risk of progressive multifocal leucoencephalopathy by efalizumab and alefacept, these have been withdrawn from the market. Biological treatment is highly effective and provides a new hope for patients, especially for those who could not tolerate or have contraindications to other systemic non-biologic therapies. However, they are not without side effects. Careful patient selection and workup are essential to minimise adverse events.

Currently there are four licensed biologics for moderate to severe psoriasis. Adalimumab (Humira®), registered in Hong Kong (HK) since 2004, is an anti-TNF α antibody fully derived from human. Etanercept (Enbrel®), registered in HK since 2001, is a recombinant human TNF α receptor IgG1 fusion protein. It can only neutralise soluble TNF transiently while the other two TNF inhibitors bind to soluble and membrane-bound TNF.[3] Infliximab (Remicade®), registered in HK since 2006, is a chimeric antibody constructed from mouse and human DNA sequences; the presence of mouse component may explain the high secondary treatment failure rate. Ustekinumab (Stelara®), registered in HK since 2010, is the only currently licensed interleukin antibody for treating psoriasis. Individual biologic characteristics are shown in Table 1. All of them should be administered by subcutaneous route except infliximab. The dosage for adults are fixed for adalimumab and etanercept but weight dependent for infliximab and ustekinumab.

Indications

The use of biologics in psoriasis should be reserved for patients with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index (PASI) or Dermatology Life Quality Index (DLQI) more than 10),[4] and those who cannot tolerate or have failed to respond to other systemic non-biological treatments or have contraindication(s) to other systemic therapies.[5-7] Early use of biologics is advocated in patients with psoriatic arthritis to suppress joint destruction.[5] Contraindications are tabulated in Table 2.

Which biologic agent is suitable for my patient?

Up till now, there is still no international consensus as to which agent is superior in the treatment of psoriasis. Besides considering the efficacy of the individual drug, physicians should also consider the age of the patient, the clinical subtype, co-morbidities and patients' preference in order to choose the right drug for the patient. This will be further elaborated in the latter part of this article.

Efficacy

Each licensed biologic agent demonstrated high efficacy in treating moderate to severe chronic plaque psoriasis. The efficacy data of individual agents from a meta-analysis is shown in Table 1. Infliximab has the highest short-term efficacy but the efficacy drops more readily than the other agents, probably due to the presence of the mouse component of the drug leading to higher anti-drug antibody (ADA) production.

Treatment failure

There are two types of treatment failure viz primary and secondary. Primary failure refers to failure to achieve PASI 50 in the initial phase.[7] The duration of initial phase varies between individual agents (Table 1).[4] Secondary failure refers to a loss of PASI 50 with time during the maintenance phase, which is the period after the initial phase.[7] As psoriasis is not a homogenous disease with different clinical subtypes, patients with different clinical subtypes may not share the same

Table 1. Characteristics of individual licensed biologic agents

	Adalimab	**Etanercept**	**Infliximab**	**Ustekinumab**
Trade name	Humira®	Enbrel®	Remicade®	Stelara®
Type	Fully human anti-TNF α antibody	Recombinant human TNF α receptor-IgG1 fusion protein	Chimeric antibody constructed from murine and human DNA	Human monoclonal antibody against interleukin 12/23
Route	Subcutaneous	Subcutaneous	Intravenous	Subcutaneous
Dosing	80 mg at 1st week, then 40 mg 2nd week	50 mg (0.8 m/kg, max 50 mg)	5 mg/kg	45 mg for <100kg 90 mg for >100kg
Frequency	Every 2 weeks	First 12 weeks: twice a week, then once a week	0, 2, 6 week, then every 8 weeks	0, 4 week, then every 12 weeks
Plasma half-life	2 weeks	70 hours	8-9.5 days	15-32 days
Decision to continue (Initial phase duration)	16 weeks	12 weeks	14 weeks	28 weeks
Efficacy (Puig et al)[35]		(50 mg every week)		(45 mg)
PASI 50 (%, 95%CI)	66.4 (62.4-70.5)	52.2 (47.1-57.3)	80.5 (74.4-86.5)	76.4 (72.5-80.2)
PASI 75 (%, 95% CI)	63.0 (59.3-66.7)	31.0 (26.6-35.4)	75.7 (72.1-79.3)	70.1 (65.8-74.3)
PASI 90 (%, 95%CI)	36.5 (25.7-47.4)	10.7 (7.8-13.6)	49.5 (45.6-53.4)	47.2 (42.6-51.8)
Adverse events (per 100 patient-years)	3 years (Gordon et al)[36]	4 years (Papp et al)[37]	78 weeks (Torii & Nakagawa)[38]	5 years (Papp et al)[39] (45 mg/90 mg)
Total patient-years	2043.8	1305.4	50 patients	8998
All AE	245.1	243.5	100%	242.6/225.3
Serious AE	7.3	7.8	12%	7.0/7.2
Serious infections	1.5	0.9	2%	0.98/1.19
NMSCs	0.8	0.5	Not a/v	0.64/0.44
Other malignancies	0.7	0.0	Not a/v	0.59/0.61
Serious CV events	0.3	1.7	Not a/v	0.56/0.36

Data in shaded box are presented with percentage of event occurrence
PASI: Psoriasis Area and Severity Index; CI: confidence interval; AE: Adverse events; NMSCs: Non-melanoma skin cancer; CV: Cardiovascular

Table 2. Contraindications for biologic treatment

Absolute Contraindications
- Pregnancy/breastfeeding
- Active infections (including active tuberculosis and active chronic hepatitis B)
- Cardiac failure (New York Heart Association (NYHA) grade III or IV) for TNF inhibitors

Relative Contraindications
- History of recurrent infections
- HIV or AIDS
- Live vaccines
- Haematological malignancies or lymphoproliferative disorders
- Solid malignancy treated less than 5 years
- Photochemotherapy (PUVA) >200 treatments (especially if followed by use of cyclosporine)
- Cardiac failure (NYHA grade I or II) for TNF inhibitors
- Concomitant systemic lupus erythematosus, demyelinating disease for TNF inhibitors

pathogenesis, therefore, not all patients respond to the medication in the same way. It was postulated that primary treatment failure was due to the targeted molecule being not the key component in the phenotype of that patient. Therefore, another group of biologics should be used, e.g. switching from TNF α antibody to TNF receptor protein or to interleukin antibody. Secondary treatment failure is due to ADA formation which is drug-specific, so switching to another biologic even in the same group should alleviate the problem.[3] A local study with 58 patients on TNF α inhibitors for rheumatological conditions showed that percentage of positive ADA against adalimumab, etanercept and infliximab was 31% (5/16), 0%(0/18), 50%(12/24) respectively. Patients with positive ADA had lower drug levels in the serum, higher drug withdrawal and poorer clinical response.[8] Another Asian study done in Japan showed that the positive rate of ADA against adalimumab and infliximab was 50% and 41% respectively.[9] A systematic review reported by Hsu et al showed that ADA prevalence against adalimumab, etanercept, infliximab and ustekinumab was 6.6%-44.8%, 0.0%-18.3%, 5.4%-43.6% and 3.8%-5.5% respectively. Anti-etanercept antibody was found to be non-neutralising while the other ADA were shown to result in some degree of drop in drug level.[10]

Combination therapy

As monotherapy may not be able to achieve a satisfactory response in all patients, combination with other non-biologic systemic therapies may be considered in selected patients if the risk and benefit of the combination is thoroughly evaluated. There have been more studies on combination therapy for etanercept than for adalimumab, infliximab and ustekinumab. Experience from Crohn's disease suggested that combination with methotrexate may reduce the immunogenicity of biologics and thus help sustain the efficacy of biologics.[11] A randomised controlled trial (RCT) which recruited 239 patients showed that combination of etanercept with methotrexate provided better efficacy than etanercept alone (PASI 75: 77.3% with combination therapy vs. 60.3% etanercept only).[12] Combination of infliximab with methotrexate was also found to be well tolerated.[13]

Etanercept was also studied in combination with acitretin. Gisondi et al reported a study with 60 patients, etanercept weekly with acitretin was equally effective as etanercept twice weekly (PASI 75 at week 24: 45% etanercept twice weekly vs 30% acitretin only vs 44% etanercept once weekly plus acitretin).[14] Combination of biologics with cyclosporine was not recommended because there is risk of leucoencephalopathy and further suppression of the patient's immunity.[5] However, a few weeks of overlap may be considered for smooth drug-switching to biologics.

Biologics are not recommended for combination treatment with phototherapy because they may increase the risk of developing skin cancer.[15] There are no long-term follow-up studies in this aspect yet. Studies have suggested an improved efficacy in combination over biologics alone.[16-18]

Stop and switching biologics

According to the National Institute for Health and Clinical Excellence guidelines, biological treatment should be continued for patients with PASI 75 or PASI 50 and a DLQI score decreased by five.[19] Indications for stopping biologics included failure to reach or to maintain an adequate response, serious adverse events, pregnancy, elective surgery and live vaccinations. Relapse of psoriasis is defined as loss of PASI 50 in those who achieved PASI 75. Upon stopping, patients on etanercept relapsed in an average of 12 weeks.[20] The mean time to relapse in patients withdrawn from ustekinumab was around 16 weeks after cessation, over 80% cases (45 mg: 83.7%; 90 mg: 85.4%) regained PASI 75 in 12 weeks upon retreatment.[21] Rebound is defined as an

increase in PASI of at least 25% compared with baseline, or an erythrodermic, pustular, or severe inflammatory flare within 12 weeks of treatment cessation. Patients on etanercept rarely experienced rebound and the drug can be restarted to achieve similar PASI after stopping.[20,22]

Switching to another biological therapy should be considered if the patient is not responding adequately to the first biological drug (primary or secondary failure), the first drug cannot be tolerated or becomes contraindicated.[19] Overlap treatment should be avoided to minimise excessive immunosuppression; the recommended interval is four drug half-lives of the first biologic.[4] A four-week interval should be allowed for switching from non-biologic therapy to biologics except for methotrexate which may be continued at the minimal required dose. Overlapping biologics with systemic non-biologic therapy, e.g. cyclosporine, can be considered in unstable disease for smooth drug transition.[4,5]

Special patient groups

Most of the clinical efficacy studies were on adult patients with chronic plaque subtype psoriasis. Studies on other clinical subtypes were limited. Localised pustular psoriasis does not respond to anti-TNF. There is still no international consensus or RCT on the use of biologics in generalised pustular psoriasis. Infliximab was approved for generalised pustular psoriasis in Japan,[5] while infliximab, etanercept and adalimumab had been reported with treatment success in this subtype.[4]

The efficacy and safety of biologics in the treatment of erythrodermic psoriasis was studied in a multicentre retrospective study in France. A total number of 28 patients treated with infliximab (n=24), adalimumab (n=7), etanercept (n=6) and ustekinumab (n=3) were recruited. The PASI 75 at 12 to 14 weeks was 48% for infliximab, 50% for adalimumab and 40% with etanercept. However, the rate of adverse events and relapse was high with 19% of patients discontinuing the treatment due to safety concerns and 34% experienced a flare up to 48 weeks.[23] Another study with 10 erythrodermic psoriasis patients on etanercept showed that the mean PASI score decreased from 39.1 to 5.1 at 24 weeks.

There is more evidence for the efficacy and safety of etanercept in paediatric age group than the other biologics. It is the only biologic approved by the European Medicines Agency for use in children over six years old.[24] In a double-blinded RCT with 211 patients aged from 4 to 17 years, 57% of patients in the treatment group and 11% of the control group achieved PASI 75 respectively at week 12.

Previously only the three anti-TNF inhibitors (adalimumab, etanercept and infliximab) were approved by the Food and Drug Administration (FDA) in the United States of America (US) for the treatment of psoriatic arthropathy. Ustekinumab was also approved by US FDA in September 2013 for this indication. Therefore all the current licenced biologics can be considered in patients with significant psoriatic arthritis.

In order to identify patients with contraindications, a list of recommended pre-treatment workup is shown in Table 3.

Tuberculosis

Latent tuberculosis can be reactivated upon the use of biologics, the risk being higher for patients receiveing infliximab or adalimumab than those receiving etanercept.[25] Therefore, screening for latent tuberculosis (TB) must be done before starting biologics. It is especially true in Hong Kong where the prevalence of TB is high. Chest X-ray and Mantoux tests should be done as as initial workup. However, Mantoux test is not valid in immunosuppressed patients and has poor specificity in patients who have received Bacillus

Table 3. Recommended workup for biologic treatment

Pre-treatment workup
Check for skin cancer and lymphadenopathy
Chest X-ray
Mantoux test and / or interferon-gamma release assays
Blood tests: Complete blood picture with differential count, liver and renal function tests, ESR, CRP, HBsAg, HBsAb, HBcAb, HCV Ab, HIV Ab
Pregnancy test, contraceptive advice
Follow-up tests
Periodic complete blood picture with differential count, liver and renal function tests
Consider TB screening as necessary
Anti-nuclear Ab, Anti-ds DNA Ab (a marker of incipient loss of response to anti-TNF treatment)[40]

Calmette-Guérin before.[26] Interferon release assay should be done in patients with a positive Mantoux test or who are on methotrexate or cyclosporine or other immunosuppressants. In a study done in Spain, isoniazid preventive therapy for 9 months reduced the incidence rate of TB by 80%.[27] The US National Psoriasis Foundation suggested delaying biologic treatment until latent TB prophylaxis is completed, but biologic therapy can be started one to two months after commencing prophylactic anti-TB treatment with good drug compliance.[28] The British Association of Dermatologists suggested biologics can be started two months after starting prophylaxis or four weeks as suggested by TBNET consensus in Europe and consensus of Hong Kong Society of Rheumatology.[4,29,30] Patients with active TB should be completely treated before initiating biologics.[29]

Hepatitis B

As TNF may help in clearing and controlling hepatitis B virus, using TNF α inhibitors in patients with hepatitis B may result in fatal reactivation.[4] Reactivation of hepatitis B was reported even in those occult hepatitis B (hepatitis B surface antigen (HBsAg) negative, anti-HBc positive) patients put on biologics. Therefore, pre-biologic treatment workup should not only include HBsAg, but also hepatitis B core antibody (HBcAb) and hepatitis B surface antibody (HBsAb) in order to identify cases of occult hepatitis B infection. Recent case series with limited patient numbers also showed hepatitis B reactivation in patients using ustekinumab.[31]

Patients with hepatitis B or C should be co-managed with hepatologist. For HBsAg positive patients, anti-HBV prophylaxis is mandatory before and during biologic treatment. Careful monitoring for occult hepatitis patients including close monitoring of liver enzymes and HBV viral load should be done.[5] In contrast, TNF plays a role in hepatitis C-induced hepatocyte injury and treatment resistance to interferon α. Etanercept was reported to improve HCV viral clearance. TNF α inhibition by specific drugs is safe and could be even beneficial for patients with hepatitis C.[32]

Malignancy

Anti-TNF might be associated with lymphoma or skin cancers and should be avoided in patients with history of lymphoproliferative disorder.[6] They should also be avoided in patients with a current or recent past history of solid malignancy, unless the malignancy has been diagnosed and treated more than five years. This group of medications is relatively contraindicated in patients who have had prior therapy with over 200 PUVA and / or

over 350 UVB treatments as their skin cancer risk is higher.[4] From post-marketing reports, patients received ustekinumab was found to have a rapid appearance of multiple cutaneous squamous cell carcinomas who had pre-existing risk factors for non-melanoma skin cancer.[33] The safety of ustekinumab in patients with a history of malignancy had not been evaluated.[33]

Pregnancy

TNF α inhibitors and ustekinumab are Pregnancy category B. As suggested by international guidelines, pregnancy should be avoided in patients on biologics. Physicians should avoid using biologics in patients who are planning to get pregnant.[4] If patients become pregnant during biologics treatment, physicians should consider stopping biologics and avoid breast feeding (infliximab is not excreted in breast milk). For males, Montagna et al showed that infliximab may reduce the sperm mobility.[34]

Conclusion

Biologic therapy is an exciting development for both patients and dermatologists. Research is continuing and the next group agents (tofacitinib, Ixekizumab) are under development. To ensure that the right agents are used in the right patients at the right time, physicians should keep updated on this ever-changing scope of medicine. In the future, the use of biologics may be more personalised. Markers like HLA CW0602, TNFAIP3 gene polymorphism may help predict the response in individual patients.

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