

Long-term safety of biologics in the treatment of psoriasis

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Abstract: Biologics are novel and important agents in the treatment of severe psoriasis. These agents block specific molecular steps in the inflammatory cascade, thereby reducing activation and proliferation of keratinocytes. Prescreening for biologic agents and careful monitoring of patients is important. There are four biologics currently licensed and used in the treatment of psoriasis in the European Union. This is an evidence-based review examining clinical trials and focusing on the long-term safety data for four biologic agents. Current British Association of Dermatology guidance for the use of biologics in psoriasis and guidelines on the management of psoriasis from the National Institute for Health and Clinical Excellence have been used. Advances on safety information since 2009 in clinical trials are reviewed. The results show that overall there is no statistical significance in the incidence of adverse effects of biologics versus placebo. However, there are serious adverse effects that are reported for biologics that need to be assessed for and addressed promptly. Results of studies discussing major adverse cardiovascular events are also reviewed.

Keywords: psoriasis, biologic agents, safety profile, major cardiovascular events

Introduction

Psoriasis is a chronic inflammatory skin condition that may be associated with joint disease and can have a significant impact on a person's quality of life. There are several forms of psoriasis, with the most common type being chronic plaque psoriasis. This is characterized clinically by well defined red-colored plaques with a silvery scale, corresponding histopathologically to angiogenesis, hyperproliferation, and loss of cell differentiation. Other subtypes include guttate, palmoplantar, flexural, and erythrodermic psoriasis.

Genetic, immunologic, and environmental factors are implicated in the pathogenesis of psoriasis. PSORS-1, a region on the major histocompatibility complex, accounts for up to 50% of genetic susceptibility to psoriasis.¹ The presence of an increased number of dendritic cells and T cells in psoriatic plaques demonstrates the functional role of a deregulated immune system in the development of psoriasis.

Biologic therapies used in psoriasis block specific molecular steps of the immunologic pathway that are important in the pathogenesis of psoriasis. Four biologic agents are recommended by the National Institute for Health and Clinical Excellence (NICE) for use in chronic plaque psoriasis, ie, adalimumab, etanercept, and infliximab, which target the cytokine tumor necrosis factor-alpha (TNF α), and ustekinumab that targets interleukin (IL)-12 and IL-23 (see Figure 1).

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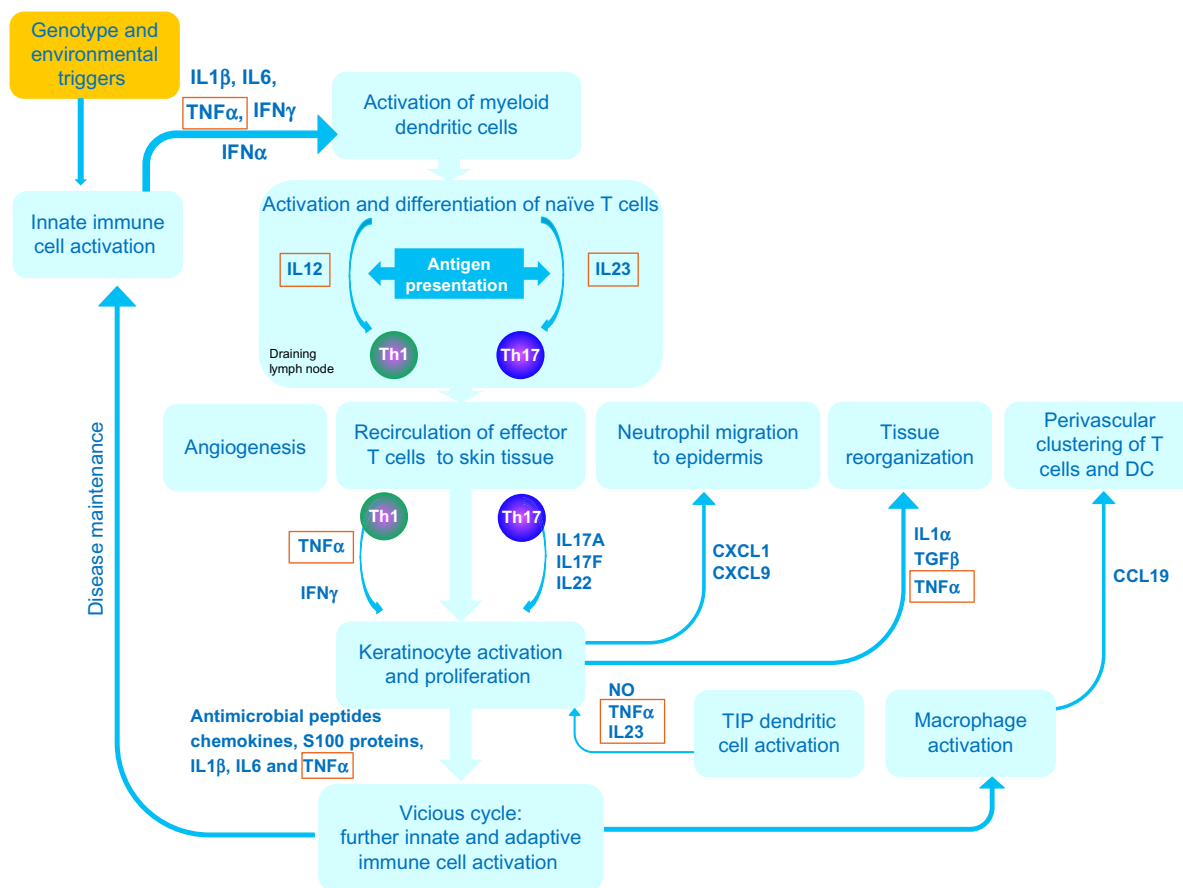


Figure 1 Mechanism of action of biologic agents.

Notes: Red box indicates cytokine targets of currently marketed biological therapies for the management of psoriasis: ustekinumab targeting the common p40 subunit of IL12 and IL23 and etanercept, adalimumab and infliximab targeting TNF α .

Abbreviations: TIP, TNF α and inducible nitric oxide synthase producing; DC, dendritic cell; NO, nitric oxide; TNF α , tumor necrosis factor-alpha; IFN, interferon; CCL, chemokine (C-C motif) ligand 19; CXCL, chemokine (C-X-C motif) ligand; IL, interleukin; Th, T helper.

Under their respective licenses, adalimumab, etanercept, infliximab, and ustekinumab are all indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, who have a contraindication to, or are intolerant of other systemic therapies, including ciclosporin, methotrexate, and psoralen + ultraviolet a (Figure 2).² The British Association of Dermatologists first published guidance on the use of biologics in psoriasis in 2005, and these were updated in 2009. NICE has recently published guidance on the management of psoriasis in 2012. The British Association of Dermatologists Biologic Intervention Register commenced in 2007 and currently has over 140 hospital sites across the UK and Eire recruiting participants for the register. This review assesses the long-term safety of the biologics. A wealth of information about long-term safety will be available on maturity of the data being collected. The longer running British Society for Rheumatology Biologics Registers has been collecting data on the safety of biologics in rheumatoid arthritis since 2001 and in ankylosing spondylitis since 2012.

However, there are potentially important differences between patients treated with biologics for psoriasis and those treated for other conditions. Patients with psoriasis are known to have an increased risk of cardiovascular disease.^{3,4} They are also likely to have had previous exposure to significant ultraviolet light treatments, which might increase the risk of cutaneous malignancies.⁵ Long-term safety data from the British Society for Rheumatology Biologics Registers may not necessarily apply to those patients treated for psoriasis. This clinical review focuses on the safety profile of biologic agents used for the treatment of psoriasis in the UK. Clinical trials on biologics in the treatment of psoriasis were searched for and analyzed.

Sources and selection criteria

This is an evidence-based review of the long-term safety of biologic agents in the treatment of psoriasis. We searched the Medline and Embase databases from 2009 to 2012 for clinical trials involving etanercept, adalimumab, ustekinumab, and infliximab. This time frame was selected because the British

Prescreening for biologics

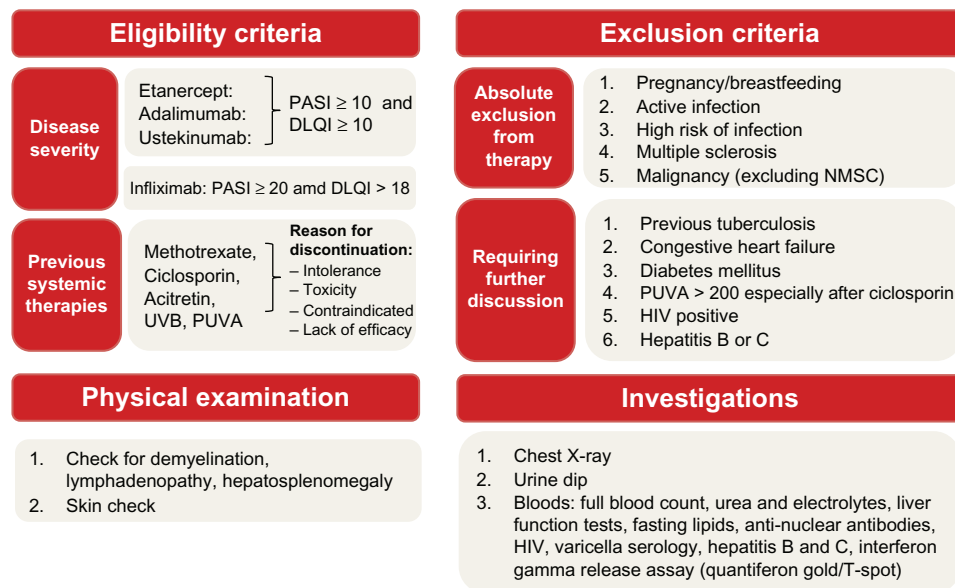


Figure 2 Prescreening for biologic agents.

Note: Screening tool used by the Department of Dermatology at Sherwood Forest Hospitals, Kingsmill Hospital, Nottinghamshire, UK.

Abbreviations: NMSC, nonmelanoma skin cancer; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; UV, ultraviolet; PUVA, psoralen + UVA; HIV, Human immunodeficiency virus.

Association of Dermatologists guidelines have reviewed clinical trials prior to 2009. Randomized controlled trials for psoriasis were searched for, because there is an abundance of published data on the disease. We also used NICE guidance published in 2012 and British Association of Dermatologists guidance on the use of biologics in psoriasis as a background for this review.^{2,6}

How do biologic agents work?

Pathogenic mechanisms in psoriasis are complex and involve close interaction between the innate and adaptive immune systems. Although the exact pathology of psoriasis remains poorly understood, it is believed that environmental danger signals activate the innate immune system in genetically predisposed individuals. Such activation of the innate immune system results in production of a number of key cytokines, including IL-1, IL-6, interferon-alpha, and TNF α which, in turn, activate myeloid dendritic cells. The latter activates, differentiates, and propagates antigen-specific T helper 1 (Th1) and T helper 17 (Th17) T lymphocyte subsets, so effectively serves as a link between the innate and adaptive immune systems. IL-12 in particular is believed to be crucially important in the production of Th1 cells, while IL-23 plays a similar role in production of Th17 cells (Figure 1). Th1 and Th17 cells both activate and stimulate proliferation of keratinocytes, as well as trigger activation of other elements of the immune response, including neutrophils and macrophages.

Numerous proinflammatory cytokines and chemokines are involved, and the resulting inflammatory response may have a lot in common with other inflammatory responses, such as those observed in lupus and atherosclerosis.⁴ Nevertheless, the intimate details of these pathways remain poorly understood. For example, it is now believed that there is a substantial heterogeneity and plasticity of T helper subsets.⁷

The biologics, which are currently licensed and used to treat psoriasis in the European Union, act on either TNF α or IL-12/23 pathways.¹ TNF α inhibitors include infliximab, adalimumab, and etanercept. Infliximab (Remicade[®], Janssen Biotech Inc, Horsham, PA, USA) is a chimeric mouse-human monoclonal antibody to TNF α . Adalimumab (Humira[®], Abbott Laboratories, North Chicago, IL, USA) is a human monoclonal antibody to TNF α . Etanercept (Enbrel[®], Amgen Inc, Thousand Oaks, CA, USA) is a neutralizing recombinant soluble TNF α receptor (human p75 TNF-receptor Fc fusion protein). Ustekinumab (Stelara[®], Janssen Biotech Inc), a IL-12/23 inhibitor, is a human monoclonal antibody to the p40 subunit, which is shared by both IL-12 and IL-23 cytokines (IL-12 is made of p19 and p40 subunits while IL-23 is made of p35 and p40 subunits).

Etanercept Guidance so far

The licensed dose of etanercept for psoriasis is 25 mg twice weekly or 50 mg once weekly. The license further allows use

of 50 mg twice weekly during the first 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. However, NICE do not recommend the use of etanercept doses above 25 mg twice weekly or 50 mg once weekly. NICE recommends that treatment should be discontinued in nonresponders at 12 weeks. Nonresponders are classed as patients who fail to achieve a 75% reduction in their Psoriasis Area and Severity Index (PASI) score from initiation or a failure of 50% reduction in PASI and a five-point reduction in Dermatology Life Quality Index (Figure 3).⁸

Advances in information regarding safety

A randomized, double-blind, multicenter Phase III trial with an open-label extension including 618 patients with moderate to severe plaque psoriasis studied the safety and efficacy of etanercept 50 mg twice weekly against placebo and demonstrated that exposure-related rates of adverse events, serious adverse events, infections, and serious infections were similar for placebo and etanercept.⁹

PRESTA was a randomized, double-blind, multicenter trial comparing two etanercept regimens for the treatment of psoriasis and psoriatic arthritis and evaluating an additional 12 weeks of open-label etanercept. This demonstrated no new safety concerns in either treatment group (etanercept 50 mg once or twice weekly) and no significant difference in safety profiles.¹⁰

The results of a randomized trial comparing ustekinumab and etanercept for moderate to severe plaque psoriasis are discussed in the ustekinumab section of this review.¹¹

CRYSTEL evaluated the efficacy and safety of continuous versus paused etanercept in patients over 54 weeks. Patients were randomized to receive continuous etanercept 25 mg twice weekly or paused etanercept 50 mg twice weekly for no more than 12 weeks until reaching a Physicians Global Assessment ≤ 2 . On relapse, etanercept was resumed at 25 mg twice weekly until a Physicians Global Assessment ≤ 2 was regained. The safety results of this study showed that 7.5% of patients had a serious adverse event (6.4% and 8.5% for the continuous and paused groups, respectively). Four patients, two in each group, had serious infections. There were no cases of tuberculosis or demyelinating diseases observed in this study.¹²

Infliximab Guidance so far

The licensed dose for infliximab is 5 mg/kg, given as an intravenous infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion, and every 8 weeks thereafter. If a patient shows no response after 14 weeks (ie, after four doses), no additional treatment with infliximab should be given.

However, under NICE guidance, the use of infliximab is restricted to its licensed indication in patients whose disease is very severe (total PASI ≥ 20 and Dermatology Life Quality Index ≥ 18) and who have failed to respond to standard systemic therapies, such as ciclosporin, methotrexate, or psoralen + ultraviolet A, or the patient is intolerant to or has a contraindication to these treatments.¹³ In addition, under

Impact of NICE guidance on use of biologics

Evidence based evaluation of efficacy and cost effectiveness

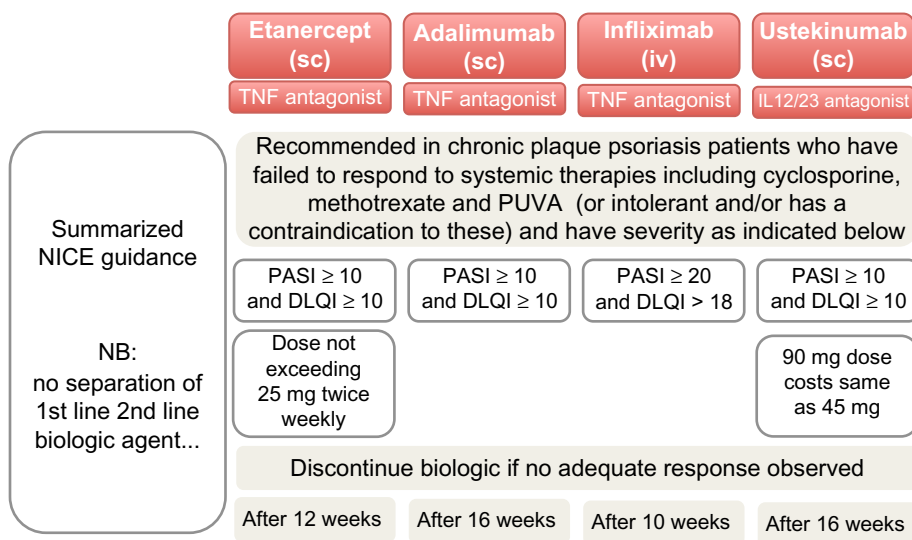


Figure 3 Summary of National Institute for Health and Clinical Excellence evidence on biologic treatments.

Abbreviations: iv, intravenous; sc, subcutaneous; TNF, tumor necrosis factor; IL, interleukin; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; NICE, National Institute for Health and Clinical Excellence PUVA, psoralen + UVA; UV, ultraviolet.

NICE, the efficacy assessment for continuation of treatment is recommended after 10 weeks of therapy (as opposed to 14 weeks in the license, Figure 3).¹³

Advances since 2009

RESTORE 1 was an open-label, randomized, active-controlled Phase III trial comparing the efficacy and safety of infliximab versus methotrexate. This study demonstrated a similar incidence of overall adverse events in both groups, but the incidence of serious adverse events was slightly higher in the infliximab group. More patients discontinued from the infliximab arm than from the methotrexate arm. Up to week 26, 12% of patients on infliximab and 4% of patients on methotrexate discontinued due to adverse events. Overall, the study concluded that infliximab was more efficacious than methotrexate and was well tolerated.¹⁴

Adalimumab

Guidance so far

Under its license, adalimumab is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to, who have a contraindication to, or are intolerant of other systemic therapy, including ciclosporin, methotrexate, and psoralen + ultraviolet A.

The recommended dose of adalimumab for adult patients is initially 80 mg administered subcutaneously, followed by 40 mg subcutaneously given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period (as per the manufacturers instructions).

Under NICE guidance, use of adalimumab is restricted to its licensed indication for patients whose disease is severe (total PASI ≥ 10 and a Dermatology Life Quality Index ≥ 10) and has failed to respond to standard systemic therapies, such as ciclosporin, methotrexate, or psoralen + ultraviolet A, or the person is intolerant of or has a contraindication to these treatments. The efficacy assessment for continuation of adalimumab is recommended after 16 weeks of treatment (Figure 3).¹⁵

Advances since 2009

In 2010, BELIEVE, a randomized, multicenter, double-blind, vehicle-controlled Phase IIIb study of the efficacy and safety of adalimumab with and without calcipotriol/betamethasone as topical treatment in patients with moderate to severe psoriasis, demonstrated safety findings similar to those in previous trials conducted with adalimumab.¹⁶ A total

of 730 patients were randomized to the study. Thirty-four developed an adverse event leading to discontinuation of the study drug (12/364 [3.3%] adalimumab + vehicle) and 22/366 [6.0%] adalimumab + calcipotriol/betamethasone). The most frequently reported serious adverse event was infection:

- four of 364 (1.1%) on adalimumab + vehicle suffered elective abortion following cytomegalovirus infection, bronchopneumonia, erysipelas, or staphylococcal infection
- six of 366 (1.6%) on adalimumab + calcipotriol/betamethasone developed pneumonia ($n = 2$), erysipelas, herpes zoster, localized infection, or osteomyelitis.

Two cases of malignancy and one case of lymphoma were not thought to be related to the study medication.¹⁶

A benefit-risk analysis performed on the CHAMPION trial comparing adverse event-free response days in terms of rate of achieving a clinical response without adverse events demonstrated that treatment with adalimumab was associated with significantly more days of adverse event-free response compared with methotrexate or placebo ($P < 0.001$ for adalimumab versus methotrexate or placebo).¹⁷

Safety analysis of adalimumab across subgroups of patients in REVEAL, a randomized, double-blind, placebo-controlled Phase III evaluation of adalimumab every other week in moderate to severe psoriasis, demonstrated no significant differences in risk of serious adverse events in adalimumab-treated versus placebo-treated patients regardless of weight category or baseline comorbidity.¹⁸

Ustekinumab

Guidance so far

Ustekinumab is recommended as a possible treatment for severe plaque psoriasis affecting quality of life, if the patient's psoriasis has not improved with other treatments, including systemic agents and phototherapy, or if the patient has previously experienced side effects or has specific contraindications as a result of other treatments that would limit their use.¹⁹

Dosing is weight-dependent and administered via the subcutaneous route. In patients weighing > 100 kg, the licensed dose is 90 mg at weeks 0, and 4, and 12, and every 12 weeks thereafter, whereas in patients weighing < 100 kg, the dose is 45 mg at weeks 0, 4, and 12, and every 12 weeks thereafter.²⁰ NICE recommends that treatment be discontinued if monitoring standards show that psoriasis has not clearly improved 16 weeks after initiation; however, the license extends for 28 weeks (Figure 3).¹⁹

Rates, types, serious adverse events, adverse events leading to treatment discontinuation, and laboratory anomalies were generally comparable between patients receiving ustekinumab 45 mg and 90 mg during both the placebo-controlled and randomized withdrawal parts of the PHOENIX 1 trial, (ie, 76-week results from this randomized, double-blind, placebo-controlled trial).²¹

Advances since 2009

A randomized, multicenter, crossover, controlled trial (n=903) comparing ustekinumab (one group receiving 45 mg and another group receiving 90 mg at weeks 0 and 4) and high-dose etanercept (50 mg twice weekly) for moderate to severe psoriasis demonstrated superior efficacy of ustekinumab over etanercept for treatment of psoriasis.¹¹ The safety analysis is as follows:

- similar proportions of patients in each treatment group had at least one adverse event in the first 12 weeks; similar proportions of patients discontinued treatment because of adverse events in both treatment groups
- the greatest disparity was observed in injection site reactions (24.8% of patients on etanercept versus 4.3% on ustekinumab 45 mg versus 3.7% on ustekinumab 90 mg); the reason for this disparity may be the frequency of injections required for etanercept
- through 64 weeks, serious infections were higher in patients receiving 90 mg of ustekinumab than in those who received 45 mg of ustekinumab
- one patient developed breast cancer and another developed an oral neoplasm on 45 mg of ustekinumab; one patient developed chronic lymphocytic leukemia and another developed mycosis fungoides on 90 mg of ustekinumab; one patient developed prostate cancer after taking etanercept and crossing over to 90 mg of ustekinumab
- the majority of skin cancers were basal cell carcinomas.

Pooled data from the randomized Phase II and III trials do not suggest an increased risk of infection or malignancy in patients treated with ustekinumab in comparison with the general population.²²

A meta-analysis of 22 randomized controlled trials including 10,183 patients, performed to evaluate previous reports of an association between major adverse cardiovascular events and IL-12/23, found that there was no significant difference in major adverse cardiovascular events in the IL-12/23 group compared with placebo. However, the follow-up was short in the meta-analysis and the study may have been underpowered.²³

Surveillance for cardiovascular events

Placebo-controlled trials are critical for evaluation of the safety and efficacy of new therapies, but may not have sufficient patient numbers or be of sufficient duration to identify rare safety signals unequivocally. In addition, specific patient inclusion and exclusion criteria may mean patient cohorts in trials are different from “real world” patients. Ethical considerations around the size and duration of placebo-controlled periods can also limit the amount of comparator adverse event data that can be generated. For this reason meta-analyses, postmarketing surveillance, and registry data are of value in identification of rare adverse events.

The evidence that patients with psoriasis have an increased risk of other serious comorbid conditions such as cardiovascular disease has been a topic of intense research for many years, and several authoritative studies have reported an increased cardiovascular risk in patients with psoriasis.^{24–26} It has been proposed that this phenomenon relates to systemic inflammation associated with psoriatic disease.

More recently, two meta-analyses of the placebo-controlled periods of all the randomized controlled trials of adalimumab, etanercept, infliximab, and ustekinumab in psoriasis have examined whether there is an increased risk of major adverse cardiovascular events (MACE) in patients with psoriasis being treated with biologic therapies.^{23,27}

MACE events include myocardial infarction, cerebrovascular accident, and cardiovascular death. Both studies compared the incidence of MACE on active drug with that in the placebo comparator groups. Ryan et al analyzed TNF antagonists and IL-12/23 antagonists, whereas Tzellos et al limited their analysis to IL-12/23 antagonists.^{23,27} Both reports included the IL-12/23 antagonist, briakinumab, in addition to ustekinumab, but briakinumab is no longer being actively developed for psoriasis.²⁸

The overall incidence of MACE was low in this meta-analysis. During the placebo-controlled phases of the anti-IL-12/23 studies, 10 of 3179 patients receiving anti-IL-12/23 therapies experienced MACE compared with zero events in 1474 patients receiving placebo. In the anti-TNF trials, only one of 3858 patients receiving these agents experienced MACE compared with one of 1812 patients receiving placebo. Ryan et al reported that there was no statistically significant increase in the incidence of MACE in patients treated with TNF antagonists or IL-12/23 antagonists. However, using an alternative statistical methodology, Tzellos et al reported a small but statistically significant increase in MACE in patients taking IL-12/23 inhibitors compared with placebo.

Both analyses reported several potential confounding factors which could have influenced their findings, and were clear that their analyses may not have been powered to detect small but significant differences in MACE rates, so it is clear that larger studies will be needed in the future to advance our understanding of this topic. Table 1 summarizes adverse events observed with the four biologic agents discussed in this review.

Discussion

Clinical trials on the approved biologic agents demonstrate good efficacy and safety data for their use in patients with moderate to severe psoriasis. The Biologics Intervention Register will highlight important safety issues for biologic agents over a long time period and will determine their future use.

Infections, opportunistic infections, malignancies, and cardiovascular and neurologic disease are some of the more frequent adverse effects observed when using biologic agents. Pretreatment screening is essential for the safety of the patient commencing on biologic therapy, and monitoring during and after treatment is necessary. Many of the trials mentioned

above have compared biologic agents with placebo to evaluate both efficacy and safety. Placebos are not used as treatment in clinical practice, and hence there is an emerging need for head-to-head trials comparing biologic agents with longer follow-up periods.

Postmarketing surveillance allows collection of larger datasets but depends on voluntary reporting, so may under-report. In addition, lack of placebo groups in postmarketing surveillance can create “unknown denominator effects”. Lastly, safety registries allow prospective systematic collection of large quantities of “real world” data over prolonged periods, so can provide valuable data on long-term safety and detection of rare adverse events. It is important to note that treatments may not be standardized and may introduce confounding variables, eg, coadministration or dose escalation.

Thoughts for the future

The use of biologic agents for severe psoriasis has been shown to improve disease outcome and quality of life. The risk of experiencing adverse events exists with any agent that suppresses the immune system, so careful monitoring of patients

Table 1 Summary of adverse events observed with the four biologic agents

	Etanercept	Adalimumab	Ustekinumab	Infliximab
Infections	Upper Respiratory Tract Infection (URTI), skin and soft tissue infection, pneumonia, opportunistic infections – tuberculosis, fungal, protozoan	URTI, skin and soft tissue infections, fungal infections, meningitis opportunistic infections – coccidioidomycosis, histoplasmosis and mycobacterium avium complex infection, tuberculosis	URTI, Nasopharyngitis, Cellulitis, Diverticulitis, Osteomyelitis, Gastroenteritis, Viral infection, Urinary tract infection	Viral, Bacterial, Opportunistic infections – pneumocytosis, candidiasis, listeriosis, aspergillosis and tuberculosis
Tuberculosis (TB)	Evaluate (history and examination) and screen for TB. Not for treatment if active TB or untreated latent TB			
Hepatitis B virus	Can reactivate therefore test prior to initiation and get specialist advise if positive			
Allergic reactions	Angioedema, urticaria	Anaphylaxis	Hypersensitivity, Severe angioedema	Anaphylaxis, Delayed hypersensitivity reaction
Malignancy	Lymphoma, Leukemia, Melanoma and NMSC	Non melanoma skin cancer (NMSC), Lymphoma	NMSC, Prostate, Colorectal, Breast, Melanoma in-situ	Lymphoma, Leukemia, Melanoma
Neurological	Central and peripheral demyelination	Central and peripheral demyelination	Dizziness, Headache, Facial palsy	Headache, vertigo dizziness, demyelinating disorders
Cardiac	Worsen cardiac failure	Worsen cardiac failure	–	Tachycardia, Cardiac Failure, Myocardial infarction
Gastrointestinal	Autoimmune hepatitis	Abdominal pain, nausea, vomiting	Diarrhea	Diarrhea, uncommon – intestinal stenosis and perforation, pancreatitis, Liver failure
Vaccinations	Live viral or bacterial vaccines not to be given – ensure vaccinations up-to-date before commencing treatment			
Other	Injection site reactions	Lupus like syndrome	Injection site reactions	Antinuclear antibodies, Mood changes, Interstitial lung disease

before, during, and after use of such agents is important to ensure patient safety. Using biologics to target specific pathways in the immune system for disease control has been very useful in understanding the pathophysiology of psoriasis.

Achieving better disease control in patients with psoriasis in the future is dependent on both improving patients understanding of the condition and developing newer agents that are more specific. There are three anti-IL-17 drugs now that are proving to be remarkably effective in Phase III trials. These include brodalumab, ixekizumab, and secukinumab. Patients treated in Phase II studies with anti-IL-17 agents showed significant improvement in their psoriasis.²⁹⁻³¹

In addition to new biologic agents, there are also a number of “small molecule” oral agents in Phase III trials for psoriasis, eg, tofacitinib, which acts intracellularly to inhibit Janus-activated kinase enzymes which act downstream of a number of key cytokines. Apremilast also acts intracellularly to inhibit the phosphodiesterase 4 enzyme, activity of which is required for synthesis of a number of cytokines. Both of these agents have efficacy and safety data supportive of further clinical development, and could offer valuable alternative oral therapies for psoriasis.

In a Phase II trial, Papp et al identified that 67% of patients achieved a PASI of 75% using tofacitinib. This agent does not have the same safety issues as the other biologic agents.³² There are promising developments in therapies for psoriasis, but it is vital to have long-term safety information because severe side effects can take years to come to the surface.

Conclusion

Biologic agents are an important treatment option for patients with moderate to severe psoriasis. Achieving good control of psoriasis in an individual has been shown to improve their overall quality of life. It is of prime importance whilst selecting any treatment to keep the patient at the center of care. Identifying patient preferences, such as mode of administration and access, can help increase concordance with therapy.

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Disclosure

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Group of the UK Dermatology Clinical Trial Network; he has received fellowships, plus educational grants, consultancy fees, and acted as an investigator or a member of an advisory board or a director for Abbott Laboratories, Novartis, Pfizer, Procter and Gamble, Merck Serono, Leo Pharma, Basilea Pharmaceutica, Apodi, Genus Pharmaceuticals, GlaxoSmithKline, Medefield, EMS Research, CSD Health Research, XBioCell, Bryter Research, Genactis, Medicus, The Research House, All Global, Keyquest, Teva, Almirall, and Galderma. JM is the Deputy Lead of the Comprehensive Local Research Networks Dermatology Specialty Group, and has received educational grants, consultancy fees, or acted as an investigator for Novartis, Galderma, Abbott, Leo Pharma, Genus Pharmaceuticals, and Almirall. HC is an employee of Novartis.

The authors report no other conflicts of interest in this work.

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