# Biologic therapies in dermatology

***Biologic therapies, the anti-cytokines in particular, have proved to be a significant addition to the dermatologist's armamentarium for the management of severe skin disease. This article summarizes the mechanism of action, dosage, approved indications, off-label uses and the future of biologic therapies in dermatology.***

Biologic therapies or protein therapeutics are protein-based molecules produced by living organisms for treatment or prevention of human disease. Biologic therapies include those that target specific pathways such as antibodies against cytokines or cell surface receptors, fusion proteins and those that are identical to an endogenous protein, e.g. interferons and pooled immunoglobulins. The structure of biologic therapies can be inferred by their suffix as follows:

1. -ximab: chimeric monoclonal antibody which is a hybrid monoclonal antibody consisting of human and murine antibody components
2. -zumab: humanized monoclonal antibody
3. -umab: human monoclonal antibody
4. -cept: receptor blocker protein.

This article will address the licensed and unlicensed uses of biologic therapies for skin disease.

## Biologic therapies targeting tumour necrosis factor

Tumour necrosis factor (TNF)-α, a pro-inflammatory cytokine, plays a central role in the pathogenesis of immune-mediated inflammatory diseases such as psoriasis, rheumatoid arthritis and Crohn's disease. TNF-α is released from a wide variety of cell types, including keratinocytes, as a soluble cytokine (sTNF) following cleavage from its cell surface-bound precursor (tmTNF). Both sTNF and tmTNF act by binding TNF receptor1 (TNFR1, p55) and TNF receptor2 (TNFR2, p75) leading to NF-κB activation which promotes keratinocyte proliferation and/or inhibition of keratinocyte apoptosis.

**Table 1. Biologic therapies targeting tumour necrosis factor**

| TNF antagonists | | Structure |
|---|---|---|
| Monoclonal antibody TNF antagonists | Infliximab | A chimeric human-murine monoclonal IgG1 antibody (25% mouse-derived protein) |
| | Adalimumab | The first fully human monoclonal IgG1 antibody |
| | Golimumab | The second fully human monoclonal IgG1 antibody |
| TNF receptor blocking protein | Etanercept (sTNF receptor protein) | The extracellular portion of human TNFR2 (p75) linked to the Fc domain of human IgG1 |
| PEGylated TNF antagonist | Certolizumab-pegol | A humanized antigen-binding fragment (Fab') of a monoclonal antibody conjugated to polyethylene glycol (a longer serum half-life) |

IgG = immunoglobulin G; TNF = tumour necrosis factor

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Currently, there are three types of TNF antagonists used in dermatology (*Table 1*). Adalimumab, infliximab and etanercept specifically bind either sTNF or tmTNF and act by blocking TNFR-mediated mechanisms and inducing tmTNF itself, therefore acting as a ligand to promote cell activation, cytokine suppression or apoptosis of the tmTNF-bearing cell (reverse-signalling events). Etanercept also binds TNF-β but the biological significance of this is unclear. Infliximab and adalimumab seem to have a greater propensity to cause lymphocyte apoptosis than etanercept as they can lyse cells with tmTNF through complement activation and/or antibody-dependent, cell-mediated cytotoxicity. Adalimumab has greater similarity in efficacy to infliximab than to etanercept because it has a similar mechanism of action (Burns et al, 2004).

Golimumab and certolizumab-pegol are licensed for use in rheumatological conditions. Golimumab has been approved for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, while certolizumab-pegol has been approved for Crohn's disease and rheumatoid arthritis. Currently, these two TNF antagonists are of academic interest in the treatment of psoriasis and other dermatoses (Warren and Griffiths, 2010).

## Approved indications of TNF antagonists in dermatology

### Psoriasis

Data from high quality randomized controlled trials show that infliximab, etanercept and adalimumab are highly effective for the management of chronic plaque psoriasis. *Figure 1* shows the efficacy of infliximab for psoriasis.

Infliximab is recommended for use as a 5 mg/kg intravenous infusion at weeks 0, 2, 6 and then every 8 weeks. The evidence shows that it is highly effective for psoriasis and for nail psoriasis. Onset of action is rapid with significant skin improvement within 2 weeks of treatment. Seventy-nine per cent of patients achieve Psoriasis Area and Severity Index (PASI) 75 response (a 75% improvement in clinical severity) by week 10. One study prospectively assessed nail psoriasis and complete clearance of nail disease was achieved in 44.7% of patients at week 50 (Reich et al, 2005; Smith et al, 2005).

Etanercept is recommended as a 25 mg twice-weekly subcutaneous injection. Onset of action is slower than for adalimumab or infliximab, with significant improvement evident between 4 and 8 weeks after initiation. Thirty-four per cent of patients achieved PASI 75 by week 12 with the use of etanercept 25 mg twice weekly (the licensed UK dose). There are no trial data to indicate whether increasing the dose to 50 mg twice weekly in patients who fail to achieve or maintain adequate responses on 25 mg results in improved disease control (Smith et al, 2005).

Adalimumab is recommended as an 80 mg subcutaneous injection at week 0, 40 mg at week 1, then 40 mg every other week for maintenance. Rapid improvement can be seen within 2 weeks of treatment and maximal disease response is achieved between weeks 12 and 16. Sixty-nine per cent of patients achieve PASI 75 at week 12 with adalimumab 40 mg every other week (Gordon et al, 2006).

The integrated data analysed short-term (12 weeks) and long-term (144 weeks) safety of varying etanercept dosage regimens. In the short term ($n$=1965), rates of infectious and non-infectious adverse events were comparable between placebo and etanercept groups. The long-term analysis ($n$=4410) showed that there were no dose-related or cumulative increases in serious infectious events. There was no increase in overall malignancies with etanercept therapy compared with the psoriasis population (Pariser et al, 2011).

Interrupted therapy may result in loss of treatment response. One randomized controlled trial of infliximab showed that patients on continuous therapy at 5 mg/kg every 8 weeks achieved optimal control whereas the majority of patients in whom infliximab was used intermittently had loss of PASI 75 between week 14 and 22 (Menter et al, 2007). Although long-term data on efficacy are limited to 3 years, interrupted therapy should be avoided because of the associated increased risk of infusion reactions and poorer disease control. Methotrexate may be recommended as comedication in certain clinical circumstances, e.g. psoriatic arthropathy or to increase efficacy by preventing the development of drug antibodies. Indeed in a small randomized controlled trial ($n$=59) there were significantly increased numbers of patients 'clear or nearly clear' at 24 weeks of combination of etanercept with continued methotrexate treatment as compared to etanercept with methotrexate tapered up to week 4 (Smith et al, 2005). All patients had been treated with methotrexate ≥7.5 mg/week for at least 3 months before the study.

## Off-label uses of TNF antagonists in dermatology

### Sarcoidosis

The roles of TNF antagonists in sarcoidosis are currently unclear. Uncontrolled series and case reports show favourable outcome of infliximab in sarcoidosis, including those with extensive skin involvement and lupus pernio ($n$>60). However, infliximab has demonstrated only minimal benefit for pulmonary sarcoidosis in a large multicentre randomized controlled trial ($n$=138). Etanercept, on the other hand, is less encouraging as four randomized controlled trials of its use in sarcoidosis demonstrate very limited efficacy. There have been two reports of the successful use of adalimumab to treat cutaneous sarcoidosis (Ramos-Casals et al, 2008).

### Pyoderma gangrenosum

Infliximab is the only TNF antagonist which has undergone a randomized controlled trial in pyoderma gangrenosum. Clinical assessments were performed on 30 patients at weeks 2, 4 and 6. Almost half of the patients improved following a single infusion of infliximab at week 2. Nearly 70% of patients displayed improvement whereas 31% of patients had no response at week 6. This short-term study demonstrates that infliximab is superior to placebo in the treatment of pyoderma gangrenosum but its role in maintaining remission of the disease is unclear. The efficacy of adalimumab in pyoderma gangrenosum has been demonstrated in several cases which either failed to respond to and/or developed infusion reaction to infliximab. One case report has implied that etanercept may not be as effective as either infliximab or adalimumab for the treatment of pyoderma gangrenosum (Brooklyn et al, 2006).

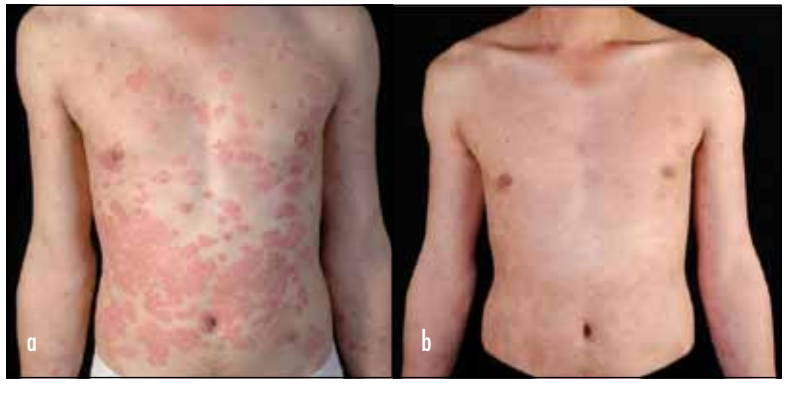
### Pityriasis rubra pilaris

A systematic review of the treatment of pityriasis rubra pilaris type I with TNF antagonists (infliximab, etanercept and adalimumab) suggest that these may be of value in treating type I pityriasis rubra pilaris refractory to immunomodulatory agents. Eighty per cent of patients showed complete response ($n$=15). The most evidence exists for infliximab in combination with acetritin which is the standard treatment for this rare condition (Petrof et al, 2012).

### Hidradenitis suppurativa

Four randomized controlled trials and 65 articles of case series or reports are available from a systematic review of the treatment of severe hidradenitis suppurativa with TNF antagonists. Based on efficacy data, infliximab appears to be the most effective TNF antagonist for the treatment of

***Figure 1. a. A 39-year-old man with extensive chronic plaque-type psoriasis recalcitrant to methotrexate, acitretin and phototherapy (baseline) and (b) showing significant improvement after 16 weeks treatment with infliximab.***



hidradenitis suppurativa. A moderate to good response was found in 82%, 76% and 68% of patients with infliximab, adalimumab and etanercept respectively. Data from randomized controlled trials support the efficacy of infliximab and adalimumab (high dosage) but discourage the use of etanercept for the treatment of severe hidradenitis suppurativa (van Rappard et al, 2012).

**Autoimmune blistering diseases**
Data from one small randomized controlled trial (*n*=8) of etanercept treatment for pemphigus vulgaris suggest that the response to etanercept is heterogenous. The role of TNF antagonists in the management of autoimmune blistering diseases requires further investigation (Fiorentino et al, 2011).

**Systemic lupus erythematosus**
Treatment of systemic lupus erythematosus with TNF antagonists remains controversial as these agents have been associated with increased levels of autoantibodies such as anti-DNA and, less commonly, lupus-like syndromes. Two large randomized controlled trials were designed to evaluate the efficacy and safety of infliximab and etanercept in systemic lupus erythematosus but both were terminated prematurely. One small open-label study (*n*=6) suggests promise for infliximab in the treatment of lupus nephritis and arthritis. Nevertheless, a few cases of severe systemic lupus erythematosus have been reported after treatment of arthritis with TNF antagonists (Lateef and Petri, 2010).

**Behçet's disease**
Arida et al (2011) analysed published data on TNF antagonists for Behçet's disease in 369 patients. There was significantly more information on the therapeutic effect of infliximab than etanercept and adalimumab as 83% of patients received infliximab. The data from only one randomized controlled trial showed that etanercept was effective in suppressing the mucocutaneous manifestations (*n*=20, 4-week trial of etanercept). In 16 open prospective studies of infliximab (*n*=174), organ-specific, clinical responses were evident in 90%, 89%, 100% and 91% of patients with resistant mucocutaneous, ocular, gastrointestinal and CNS involvement respectively. The 13 studies of adalimumab (case reports, case series and retrospective study, *n*=28) showed favourable outcome of adalimumab for the treatment of Behçet's disease (Arida et al, 2011).

**Systemic sclerosis**
A systematic review was performed to evaluate the efficacy and safety of biologic therapies in systemic sclerosis. No randomized controlled trials evaluating the use of TNF antagonists in systemic sclerosis were identified. Forty-nine patients with systemic sclerosis from observational studies of infliximab and etanercept were evaluated. Infliximab and etanercept seem to be safe and effective for inflammatory arthritis but less certain for skin involvement. None of the other biologic agents (antithymocyte globulin, imatinib, rituximab, interferon-γ (IFN-γ), IFN-α, relaxin, delipidated, deglycolipidated *Mycobacterium vaccae*, human anti-transforming growth factor β1 antibody and oral type I collagen) demonstrated reproducible, statistically significant improvement in arthritis, disability index or skin score (Phumethum et al, 2011).

**Primary Sjögren's syndrome**
Randomized controlled trials of infliximab (*n*=130) and etanercept (*n*=28) for the treatment of primary Sjögren's syndrome show no significant difference outcomes when compared with placebo (Ramos-Casals et al, 2008).

**Polymyalgia rheumatica**
A multicentre randomized controlled trial (*n*=51) showed no significant difference between glucocorticosteroid and glucocorticosteroid plus infliximab for the treatment of polymyalgia rheumatica (Ramos-Casals et al, 2008).

**Vasculitis**
From a systematic review of the biologic therapies in systemic autoimmune diseases, infliximab may be considered as a therapeutic option in some antineutrophil cytoplasmic antibodies (ANCA)-related vasculitides such as Wegener's granulomatosis and microscopic polyangiitis, but not for giant cell arteritis. Etanercept, on the other hand, is not effective for the maintenance of remission in patients with Wegener's granulomatosis. In other forms of vasculitides (Churg–Strauss vasculitis, polyarteritis nodosa and cryoglobulinaemia), experience with TNF antagonists is anecdotal (Ramos-Casals et al, 2008).

**Acute and chronic graft *vs* host disease**
On the basis of previous reports, TNF antagonists appear to be most effective for skin and gastrointestinal involvement and less effective for liver involvement in graft *vs* host disease. However, an open-label, phase III trial of infliximab and corticosteroids for the initial treatment of acute graft *vs* host disease revealed no benefit from the addition of infliximab when compared to corticosteroids alone (Graves et al, 2007).

**Miscellaneous**
There are several case series and case reports on the efficacy of TNF antagonists in granuloma annulare, necrobiosis lipoidica, Sweet's syndrome, subcorneal pustular dermatosis, dermatomyositis, adult-onset Still disease, SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, multicentric reticulohistiocytosis, toxic epidermal necrolysis, erythema annulare centrifugum, Hailey–Hailey disease, atopic dermatitis, and multiple familial trichoepithelioma (Graves et al, 2007).

## Biologic therapy targeting interleukin-12 and interleukin-23 cytokines

Ustekinumab is a fully human IgG1 monoclonal antibody which inhibits the actions of interleukin (IL)-12

and IL-23. It binds with high affinity and specificity to the p40 protein, a shared subunit of IL-12 and IL-23. Of relevance to psoriasis, IL-12 induces expression of type 1 cytokines (TNF-α and IFN-γ) while IL-23 stimulates survival and proliferation of a subset of T cells that produce IL-17 (Th17 cells). Recent studies indicate a central role for Th17 and IL-23 in the pathogenesis of psoriasis.

## Approved indications of ustekinumab in dermatology

### Psoriasis

Ustekinumab is a 45 mg or 90 mg subcutaneous injection for patients weighing <100 kg or >100 kg respectively. It is administered at weeks 0, 4 and 16 then 12-weekly. Three large randomized controlled trials demonstrate that ustekinumab is highly effective for psoriasis. Onset of action is evident within 2 weeks of initiation, with 67% and 72% of patients achieving PASI 75 by week 12 for the 45 mg and 90 mg dose respectively. Maximal disease response is achieved between weeks 20 and 24. The ACCEPT trial is the first head-to-head superiority study comparing ustekinumab and etanercept in the treatment of plaque psoriasis. The results show that ustekinumab achieves superior clinical improvement than etanercept 50 mg twice weekly at week 12 (Griffiths et al, 2010).

The integrated data from phase 2, PHOENIX 1, PHOENIX 2 and ACCEPT trials suggest that rates of adverse events are comparable among patients treated with placebo (50.4%), ustekinumab 45 mg (57.6%) or ustekinumab 90 mg (51.6%). No dose response in rates of adverse events, overall infections or serious adverse events was apparent through 3 years. An update on the long-term safety with up to 4 years of continuous use of ustekinumab remains consistent with previous reports (Lebwohl et al, 2011; Reich et al, 2012). However, the British Association of Dermatologists recommends that ustekinumab should be reserved for patients who are resistant to or unsuitable for TNF antagonists.

## Off-label uses of ustekinumab in dermatology

As ustekinumab is a relative new biologic therapy, only sporadic case reports and case series of its off-label uses of have been published.

### Hidradenitis suppurativa

As TNF antagonists are not effective in all patients with hidradenitis suppurativa, ustekinumab has been tried in a small number of patients. Four case reports showed a favourable outcome in three cases and no improvement in one case (Sharon et al, 2011).

### Pityriasis rubra pilaris

Successful treatment of type I pityriasis rubra pilaris with ustekinumab has been reported in two cases, both of which achieved complete remission at week 16 (Ruiz Villaverde and Sanchez Cano, 2010; Wohlrab and Kreft, 2010).

### Pyoderma gangrenosum

Expression of IL-23 is increased in pyoderma gangrenosum. One case report of successful treatment of pyoderma gangrenosum with ustekinumab has been published. The ulcer healed completely after 14 weeks (two injections of ustekinumab) and no relapse occurred over a 6-month follow-up period (Guenova et al, 2011).

### Palmoplantar pustulosis

The open-label trial of ustekinumab for the treatment of palmoplantar psoriasis which included pustular and non-pustular variants did show that five of eleven patients (45.5%) who had palmoplantar pustulosis achieved complete clearance at week 16 of treatment (Au et al, 2012).

### Adult atopic dermatitis

Puya et al (2012) reported successful use of ustekinumab in one patient with atopic dermatitis in addition to allergic contact dermatitis. This patient underwent many systemic treatments including ciclosporin, ultraviolet B therapy, oral prednisone and efalizumab. A significant improvement was found within 2 weeks of initiation and the excellent response was maintained at week 52.

### Allergic contact dermatitis

Studies have suggested a role of Th17 cells in the elicitation phase of contact allergy. A retrospective study of ustekinumab for the treatment of allergic contact dermatitis showed a significant effect in one of five patients (Bangsgaard et al, 2011).

# Biologic therapies targeting B-cells

Rituximab is a potent B-cell depleting chimeric IgG1 antiCD20 antibody. Approved clinical indications are B-cell malignancies (including cutaneous B-cell lymphoma) and rheumatoid arthritis.

## Off-label uses of rituximab in dermatology

### Autoimmune blistering diseases

The majority of 54 patients with autoimmune blistering diseases showed clinical improvement within 3 months of 375 mg/m$^2$ rituximab initiation. Four cases had serious adverse events which were fatal bacterial sepsis, bacterial sepsis, bacterial pneumonia and deep vein thrombosis (Schmidt et al, 2008). It is now the treatment of choice for severe, recalcitrant pemphigus vulgaris.

### Autoimmune connective diseases

Rituximab has been used in patients with systemic lupus erythematosus ($n$=172), cryoglobulinaemia ($n$=88), primary Sjögren's syndrome ($n$=69) and Wegener's granulomatosis ($n$=68) with therapeutic response (>80%) in each disease. Each randomized controlled trial of rituximab for the treatment of severe cryoglobulinaemia ($n$=59) and Wegener's

granulomatosis ($n$=17) showed favourable outcome. Nevertheless, two small trials ($n$<30) of rituximab for primary Sjögren's syndrome did not achieve primary outcome but showed significant improvement in sicca and general symptoms compared with baseline values. Larger controlled trials are needed to establish the efficacy of rituximab in primary Sjögren's syndrome (Ramos-Casals et al, 2010).

*Table 2* outlines the effective uses of biologic therapies in dermatology.

## Miscellaneous biologic therapies

Omalizumab is a recombinant humanized monoclonal antibody that blocks Fc receptor of immunoglobulin E (IgE). It has been approved for moderate to severe persistent asthma in adults and adolescents older than 12 years of age who have a skin test to perennial allergen. There are sporadic cases of successful treatment of omalizumab in atopic dermatitis, chronic urticaria, bullous pemphigoid and hyper-IgE syndrome (Graves et al, 2007).

## The future of biologic therapies

### IL-17 antagonist

IL-17 is an inflammatory cytokine with numerous actions relevant to the pathogenesis of psoriasis. Two phase 2 clinical trials of IL-17 antagonists (ixekizumab and brodalumab) are testament to how effective this approach is. Ixekizumab is a humanized IgG4 monoclonal to IL-17A and brodalumab is a fully human IgG2 monoclonal antibody against the IL-17 receptor. Both approaches showed that 80% of patients achieved PASI 75 within 12 weeks of initiation (Leonardi et al, 2012; Papp et al, 2012).

### Vascular endothelial growth factor

Plasma levels of vascular endothelial growth factor (VEGF) are elevated in patient with psoriasis and correlate with disease severity. Agents that target VEGF directly include a monoclonal antibody (bevacizumab) and a composite decoy receptor for VEGF (aflibercept, Valpha). The use of this approach for psoriasis is encouraged by a case report of the use of bevacizumab for its licensed indication treatment of colon cancer in a patient with concomitant psoriasis. There was clearance of psoriasis. More research is necessary to elucidate the effect of VEGF antagonists in psoriasis (Crawshaw et al, 2012).

It is likely that new biologics which target IL-23 alone and IL-22 will teach us a lot about the underlying mechanisms of skin disease.

### Biologic therapies inducing skin diseases

Paradoxically, biologic therapies can induce skin disease. Psoriasis, atopic dermatitis, sarcoidosis and granuloma annulare have all been reported in patients on TNF antagonists for rheumatological conditions. Cutaneous side effects such as follicultis, xerositis, mucositis and hair

**Table 2. The effective use of biologic therapies in dermatology**

| Drug and indications | | Usual dose range | Evidence level |
|---|---|---|---|
| Infliximab | Psoriasis | 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks | A |
| | Sarcoidosis (cutaneous) | 3–5 mg/kg at weeks 0, 2, 6 and then every 4–8 weeks | C |
| | Pyoderma gangrenosum | 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks if maintenance required | B |
| | Pityriasis rubra pilaris (type I) | 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks | B |
| | Hidradenitis suppurativa | 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks | B |
| | Behçet's disease | 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks | C |
| | Wegener's granulomatosis | 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks | C |
| | Microscopic polyangiitis | 5 mg/kg at weeks 0, 2, 6 and 10 | C |
| Etanercept | Psoriasis | 25 mg or 50 mg twice weekly | A |
| | Behçet's disease | 25 mg twice weekly | B |
| Adalimumab | Psoriasis | 80 mg week 0, 40 mg week 1, then 40 mg every other week | A |
| | Sarcoidosis (cutaneous) | 40 mg every 1–2 weeks | C |
| | Hidradenitis suppurativa | 80 mg week 0, 40 mg week 1, then every 1–2 weeks, 160 mg week 0, 80 mg week 2, then 40 mg every week (better disease response) | B |
| | Behçet's disease | 40 mg every other week | C |
| Ustekinumab | Psoriasis | 45 mg at week 0, 4, then every 12 weeks (or 90 mg if patient's weight >100 kg) | A |
| Rituximab | Autoimmune blistering diseases | 375 mg/m$^2$ monthly | C |
| | Systemic lupus erythematosus | 1 g with a 2-week interval | C |
| | Cryoglobulinaemia | 1 g with a 2-week interval | B |
| | Primary Sjögren's syndrome | 1 g with a 2-week interval | B |
| | Wegener's granulomatosis | 375 mg/m$^2$ at weeks 1, 2, 3, 4, and maintenance at months 4, 8, 12 | B |

abnormalities occur frequently in patients who are treated long term with epidermal growth factor receptor inhibitors for solid tumours. Physicians should be aware of the potential for biologic therapies to induce skin disease (Lee et al, 2007; Osio et al, 2009).

## Conclusions

Over the last decade, biologic therapies have provided a significant translational advance in the management of refractory moderate-to-severe psoriasis. Moreover, off-label uses in skin conditions have increased considerably which promising results for many recalcitrant diseases. There is a need for randomized controlled trials to ascertain the true value of biologics for these miscellaneous conditions. The long-term use of biologic therapies for psoriasis brings with it concern about safety; this can only be truly assessed by the establishment of pharmacovigilance registries. One such, the British Association of Dermatologists Biologic Interventions Registry (BADBIR), currently has more than 3000 patients on biologics under surveillance. **BJHM**

*Conflict of interest: none.*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## KEY POINTS

- Biologic therapies have introduced a significant advance in the management of refractory moderate-to-severe psoriasis in the last decade.
- Tumour necrosis factor antagonists and ustekinumab offer high efficacy for psoriasis and several skin conditions.
- Long-term safety data reveal no serious adverse events or increased risk of malignancy with tumour necrosis factor antagonists and ustekinumab compared with placebo.
- Biologic therapies can also cause various skin diseases such as palmoplantar pustulosis, atopic dermatitis, granulomatous dermatitis and folliculitis.
- Pharmovigilance is warranted to address short- and long-term safety of biologic therapies.
- Understanding the immunopathogenesis of psoriasis will ultimately lead to biologic agents that are still safer and perhaps result in complete clearance of psoriasis.