Chapter 13

ESTABLISHED AND NEW BIOLOGIC THERAPIES FOR PSORIATIC ARTHRITIS AND PSORIASIS

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ABSTRACT

Psoriatic arthritis (PsA) is part of the group of seronegative spondyloarthropathies (SpA). These diseases share common clinical features such as sacroiliitis, spondylitis, enthesitis, psoriasis, uveitis, and genetic markers. The newly developed biologic treatments aim to target molecular and cellular abnormalities associated with autoimmunity in PsA and psoriasis. There are several biologic agents which are currently used, or are under investigation in both diseases, which creates an opportunity for rheumatologists and dermatologists to share their expertise for patients'

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benefit. Apart from the large body of evidence for efficacy of the licensed biologic therapies in psoriasis and PsA, research efforts are currently put into discovering and testing new molecular targets with therapeutic potential. This chapter will review all the biologic agents ever tested in these two diseases, stratified based on the level of evidence regarding their efficacy. As PsA and psoriasis have a diverse clinical phenotype, it is useful to identify which treatments are effective for a particular clinical manifestation, such as axial and peripheral arthritis, dactylitis, enthesitis, and skin and nail disease. Another aspect of biologic treatment effectiveness which will be explored in this chapter is the impact of these agents on patients' quality of life and functional ability. We propose that by analysing the patient's individual disease phenotype, based on clinical assessments and biomarkers, there is a huge opportunity to optimise the cost-effectiveness of biologic treatments, by facilitating tailored treatment options for patients with PsA and psoriasis.

Keywords: psoriatic arthritis, psoriasis, biologic treatment, small molecule inhibitors, biosimilars, efficacy, safety, cost-effectiveness

INTRODUCTION

PsA is a chronic inflammatory arthropathy, which is characterised by heterogeneous clinical features, and can effect up to 30% patients with psoriasis. The clinical presentation of PsA is variable. Frequently, PsA manifests as a mild, oligoarticular disease, which can progress to a polyarticular arthropathy, developing into a severe, erosive condition in at least 20% of patients [1]. Aggressive disease is associated with poor prognostic factors, such as polyarticular or erosive arthritis at presentation, additional psoriasis with extensive skin involvement, strong family history of psoriasis, and disease onset before 20 years of age [1]. The most common clinical manifestation of PsA are: asymmetrical peripheral oligoarthritis, sacroiliitis, spondylitis, enthesitis (inflammation of the entheses present at the site of the insertion of ligaments and tendons into the bones), dactylitis (sausage-like swelling of the fingers and toes), tenosynovitis (inflammation of the tendon sheath), iridocyclitis, hyperkeratotic and/or pustular rash on the hands and soles (keratoderma blennorrhagica) or psoriasis [2, 3]. Despite being recognised as a distinct entity, the clinical picture of PsA with peripheral involvement can be difficult to distinguish from that of rheumatoid arthritis (RA), which led in the past to a delayed recognition of PsA as a separate disease [4]. In addition, PsA is

associated with increased prevalence of human leucocyte antigen (HLA)-B27 and positive family history of SpA [5, 6].

Several clinical form of PsA were recognised and classified based on the data from large cohort studies and clinical trials [7]:

1. Arthritis affecting predominantly the distal interphalangeal joints (DIPs) (10%)
2. Symmetric polyarthritis (5%-20%)
3. Asymmetric oligoarthritis or monoarthritis (70%-80%)
4. Axial disease: predominant spondylitis associated or not with sacroiliitis (5%-20%)
5. Arthritis mutilans (rare)

Several guidelines have been developed to facilitate the diagnosis and tailored treatment of patients with PsA [8]. Patients experience a decreased quality of life as a consequence of functional impairment, joint pain, cosmetic implications of skin and nail psoriatic changes, and (in some cases) secondary to side-effects to therapy [9]. The prevention of irreversible damage, maintenance of functionality and minimisation of risk of comorbidities are some of the key long term goals for modern therapy in PsA [10]. The progress made by modern therapies had significant impact on improving the quality of life of patients with PsA and psoriasis [11, 12].

One of the major challenges posed by the disease heterogeneity is that of tailoring appropriately the available therapeutic options based on patients' disease phenotype. Conventional disease modifying antirheumatic drugs (DMARDS) used in the treatment of PsA have limited efficacy for certain disease clinical features, such as nail disease, enthesitis or axial involvement, and some are unable to control moderate to severe peripheral joint and skin disease [13]. The development and introduction of biologic treatments in the therapeutic armamentarium of PsA enabled a better control of multiple manifestations of PsA and psoriasis using a single agent, minimising the need for additional therapies.

DISEASE PATHOGENESIS ASPECTS THAT LED TO THE DEVELOPMENT OF SPECIFIC BIOLOGIC THERAPEUTIC TARGETS

Despite the recent evidence of differential expression of some biomarkers in patients with PsA and cutaneous psoriasis [14], the involvement of pro-inflammatory T cell subtypes was considered equally relevant for the immunopathogenesis of both diseases [15]. The newly developed biologic treatments aim to target these abnormalities. It was previously identified that the dermis and epidermis of psoriasis patients is infiltrated with activated cluster of differentiation (CD) 4+ and CD8+ T cells [16], and also that the synovial fluid aspirated from patients with active PsA contained high levels of CD8+ T cells [17]. The tumour necrosis factor (TNF) inhibitors are the most widely used biologic treatment for both diseases, and the scientific rationale is to target TNF, an inflammatory cytokine released by activated T cells and keratinocytes, which has additional role in promoting pro-inflammatory signals associated with psoriasis and PsA pathogenesis [18].

Co-stimulatory molecules have also been explored as potential therapeutic targets, as they play an important role in the uncontrolled activation of T cells, apoptosis of memory T cells, inhibition of co-stimulation of T cells, and in the decrease of the inflammatory gene expression in psoriatic plaques, via a mechanism insufficiently explained [19, 20]. This seems to be the mechanism of action of alefacept, whilst efalizumab promotes the inhibition of lymphocyte activation and recruitment into tissues (both are T cell modulator therapies, which will be discussed in detail below) [21].

The comprehensive 'interleukin (IL)23/T helper (h)17 axis' model of psoriasis, is based on the role of IL23 (secreted by dermal dendritic cells) in inducing Th17 cell activation and release of pro-inflammatory cytokines that acts on keratinocytes, which, in turn, produce more IL23 and other pro-inflammatory cytokines (such as TNF, IL8, S100 molecules), which all sustain and amplify the chronic inflammatory process [22].

Ustekinumab, a recently approved biologic treatment for psoriasis, also interferes with the activation of certain types of T cells (mediated by the blockage of p40 subunit of IL12/23). IL23 is strongly related to the pathogenesis of psoriasis. The intradermal injection of IL23 or over-expression of IL12/23 p40 subunit in mouse keratinocytes was shown to lead to skin lesions resembling psoriasis [23]. IL23 was also found to be highly expressed in human

psoriatic skin lesions [24], therefore the use of this therapy is also supported by immuno-pathogenic evidence. IL23 also plays an important role in the terminal differentiation of the effector Th17 cells. Th17 cells have a central role in maintaining the skin psoriatic plaque inflammation, as the plaques are characterised by an abundant Th17 cell infiltrate [25]. Furthermore, the interest in identifying therapies targeting IL17, which is the signature cytokine of Th17 cells, was supported by the evidence of high levels of expression of IL17 receptor (IL17R) in the synovial tissue of patients with PsA, along with the presence CD4+ IL17+ T cells in their synovial fluid [26]. New therapies targeting IL17A (secukinumab and ixekinumab) or IL17A receptor (IL17A-R) (brodalumab) have already been proven effective in both psoriasis and PsA.

A big progress was also achieved with the introduction of the first oral biologic agent, apremilast, approved by Food and Drug Administration (FDA) in March 2014 for treatment of adults with active PsA, and in September 2014 for the treatment of moderate to severe plaque psoriasis. Apremilast inhibits phosphodiesterase 4 (PDE4), which degrades cyclic adenosine monophosphate (cAMP) into its inactive form AMP, so counteracting the immune cells ability to produce pro-inflammatory cytokines linked to hyperproliferation and altered differentiation of keratinocytes, as found in psoriasis.

THE EFFICACY OF BIOLOGIC TREATMENTS AND NEW SMALL MOLECULES WAS ASSESSED IN NUMEROUS CLINICAL TRIALS, USING SEVERAL OUTCOME MEASURES

ACR (American College of Rheumatology) response is defined as a different percentage improvement in the following core set measures (initially defined to assess response in RA patients) [27]:

1. patient assessment
2. physician assessment
3. pain scale
4. disability/functional questionnaire
5. acute phase reactant (erythrocyte sedimentation rate - ESR or C-reactive protein - CRP)

ACR20 response is achieved if there is a 20% improvement in tender or swollen joint counts, as well as a 20% improvement in at least three of the other

five criteria (ACR50 has a positive outcome if there is a 50% improvement, and ACR70 if there is a 70% improvement).

PASI (Psoriasis Area Severity Index) score is an index used to express the severity of psoriasis, which combines the severity (erythema, induration and desquamation) and percentage of affected area. PASI75 and 90 define a 75% and 90% respectively reduction of PASI score from the baseline assessment [28].

NAPSI (Nail Psoriasis Severity Index) is used to assign the nail, nail bed and nail matrix psoriasis by area of involvement in the nail unit [29].

PsARC (PsA Response Criteria) response is a measurement of response to treatment in patients with PsA, and includes the following assessments [30]:

- 66 swollen joint score
- 68 tender joint score
- Patient global assessment (PtGA)
- Physician global assessment (PGA)

The PsARC response is defined as improvement in ≥ 2 of the 4 tests:

- One of which must be the joint tenderness or swelling score
- No worsening in any of the four measures
- Improvement is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments.

BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) is a patients reported outcome questionnaire consisting of a 1 - 10 scale measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem), in response to six questions asked of the patient pertaining to the five major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Arthralgia (joint pain) or swelling
4. Enthesitis, or inflammation of tendons and ligaments (areas of localized tenderness where connective tissues insert into bone)
5. Morning stiffness duration
6. Morning stiffness severity

The BASDAI score is calculated as a sum of the five major symptom scores (the average of the two scores relating to morning stiffness is taken), which is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease [31].

The Functional Assessment of Chronic Illness Therapy (FACIT-F score) is a collection of collection of health-related quality of life (HRQOL) questionnaires targeted to the management of chronic illness, which is used along with other patients reported outcome measures [29].

EQ-5D (Euro Quol group instrument assessing 5 domains) is a standardised instrument for use of measure of health outcome in 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [32].

DLQI (Dermatology Quality of Life Index) is the first dermatology specific quality of life 10 question validated questionnaire [32].

Short Form 36 (SF-36) health survey is a 36-item, patient-reported survey of patient health.

Biologic Therapies for Psoriasis and PsA

Biologic agents have revolutionised the treatment of psoriasis and PsA. Their introduction began with the various TNF inhibitors that have been proven efficacious, particularly in those patients who were resistant to conventional DMARDs. Numerous randomised control trials (RCTs) have shown their efficacy in the various manifestations of psoriasis, including skin disease, peripheral joint and axial involvement, nail and tendon involvement, and quality of life (Table 1).

TNF Inhibitors

This group of medications has shown remarkable efficacy across a spectrum of disease characteristics.

Etanercept

Etanercept was the first TNF inhibitor to be registered for use in patients with autoimmune diseases. Etanercept is a fusion protein consisting of the p75 receptor bound to the Fc region of human immunoglobulin G1. Several RCTs have proven its efficacy at 12 weeks for several disease outcome measures in PsA and psoriasis, such as PsARC, ACR20, 50 and 70, and PASI75 response

criteria. In addition to improvements in skin and joint symptoms, there was also an improvement in the quality of life (as assessed by DLQI, SF-36 health survey, EQ-5D scores), patient rating of pruritus and PtGA of psoriasis and PGA [33-40]. Etanercept was shown to inhibit radiographic progression at 12, and also 24 months [41, 42]. Whilst one study found no improvement in FACIT-F scores [40], another found a statistically significant improvement at week 12, as well as greater improvement the Hamilton rating scale for depression (Ham-D) and the Beck depression inventory (BDI) in the active treatment group compared to placebo [38]. Improvement in fatigue was correlated with improvement in joint pain in the same study; however improvements in depression had a weaker correlation.

Efficacy of etanercept has also been demonstrated in the paediatric population with psoriasis. One study reported that at week 12, significant improvements in PASI75, PASI50, PASI90 and PGA scores were found [43, 44]. These improvements were maintained up to week 96 [45]. This is an ongoing study of total duration 264 weeks.

The majority of the clinical trials in patients with psoriasis and PsA have used PASI score and ACR response measures as primary outcomes. However, the clinicians' choice of a certain biologic therapy in a particular patient may be guided by the biologic agent's ability to tackle specific manifestations of these diseases, such as axial disease, dactylitis, enthesitis and nail disease.

Etanercept was also found useful in controlling symptoms of AS and led to improvement in 86% of lesions as detected by serial spinal magnetic resonance imaging (MRI) scan, demonstrating its possible benefit for patients with PsA and axial disease [46]. An observational study looking at patients with PsA with axial disease found 72% patients improved clinically as assessed by the BASDAI score [47].

Etanercept is also effective in patients with PsA and enthesitis and dactylitis. Clinical benefits were documented at week 12 and week 24 in a multiple dose study [48]. Interestingly, the higher dose had proven no additional efficacy in treating the enthesitis and dactylitis, but demonstrated improvement of skin lesions.

Nail disease is a common manifestation of PsA causing pain and manual dysfunction, and reduced quality of life. Placebo controlled trial data are limited, but some trials have reported nail disease improvement as secondary outcome. Etanercept has been proven effective in psoriatic nail treatment [49]. Based on the current level of evidence, it has been recommended by the medical board of the National Psoriasis Foundation for use in different clinical subtypes of

psoriasis and PsA, such as isolated nail disease, skin and nail disease, and nail and skin and joint disease [50].

The safety of TNF blockers has been broadly investigated in RCT of patients with RA, SpA (including PsA), and also with psoriasis. The most recognised side-effects, which are common to TNF inhibitor class as a whole, include infections, malignancies, pancytopenia, demyelinating disease and autoimmune hepatitis [41, 51]. Injection site reactions can occur up to approximately 37% of patients [52]. The open label extensions of RCTs and data from national registries have supported the long-term safety of etanercept treatment [53-55]. These showed that the incidence of serious adverse events (such as infections, malignancy or cardiovascular events) did not increase over time. The numbers of adverse events per 100 patient-years of treatment was 96.9 for infections and 0.9 for serious infections, the latter included bronchitis, cellulitis, fasciitis, diverticulitis, enteritis, and viral meningitis. There were no reports of opportunistic infections or tuberculosis reactivation in this study, suggesting an overall acceptable safety of long-term therapy with etanercept. The rate for malignancies was similar to the general population and did not increase with continued exposure to etanercept [53].

The anti-TNF group of medications have found to be safe and effective in numerous rheumatologic and dermatological autoimmune conditions. Etanercept has also been reported to reduce the risk of myocardial infarct (MI) when used in patients with psoriasis in a retrospective cohort study [56]. Patients with PsA or psoriasis were observed for a median of 4.3 years, and grouped in three cohorts: patients treated with anti-TNF for at least two months (n = 1673), patients treated with other systemic treatments or phototherapy (n = 2097), and patients prescribed only topical treatments (n = 5075). The incidence rates for MI was lowest in the anti-TNF cohort, and after adjusting for MI risk factors, the etanercept group had a 50% lower risk of MI compared with the cohort using only topical treatments. Further research is needed to assess the benefits of anti-TNF therapy for the overall cardiovascular risk of patients with psoriasis and PsA as several studies reported controversial results with regard of the increased cardiovascular risk in this patient population [57-59].

Adalimumab

Adalimumab, a human monoclonal antibody with a high affinity for TNF, which is licensed for use in adults with severe psoriasis and PsA, in whom conventional therapies have failed or are not tolerated.

The benefits of this therapy are well-recognised. In the phase III REACH trial, 71% patients achieved PASI75 score in the treatment arm vs. 7% in the

placebo arm [60]. Further studies have shown similar efficacy at week 12 and 16 for ACR20, ACR50, ACR70, and PsARC response criteria, HAQ and the SF-36 health survey, DLQI score, Mental Component Summary Score and FACIT fatigue scale [61-64]. Radiographic progression, as measured by the modified total Sharp score at weeks 24 and 48, was lower in those in treated with adalimumab irrespective of whether they were receiving methotrexate (MTX) at baseline [61, 64].

With regards to conventional treatments, adalimumab has demonstrated its superiority in multiple RCTs. In a study comparing adalimumab and MTX alongside placebo, PASI75 score was reached by 79.6% in the adalimumab group, which was significantly increased compared to 35.5% in the MTX group and 18.9% in the placebo group [65]. Adalimumab and cyclosporine showed similar efficacy in treating skin lesions but when these drugs were combined they showed superiority to monotherapy [66].

Adalimumab has been compared with other TNF inhibitors (infliximab, etanercept and golimumab) in patients with PsA, all of which have demonstrated similar outcomes with regards to ACR measures [67-69]. In addition, some studies reported additional benefit when switching from one anti-TNF drug to another, in case of inadequate response [70, 71].

The ACCLAIM trial reported significant improvement of clinical features of dactylitis and enthesitis in patients treated with adalimumab [72]. One RCT and three observational studies have shown effectiveness of adalimumab in controlling nail disease [65, 73, 74]. The National Psoriasis Foundation has recommended the use of adalimumab in patients with nail disease alone, skin and nail disease, or for patients with a combination of nail, skin and joint disease [50]. Adalimumab was ranked with the ‘highest enthusiasm’ compared to all other drugs recommended for nail psoriasis.

Data regarding the efficacy of adalimumab in axial disease is available from the AS clinical trials [75, 76]; however a recent meta-analysis assessing the efficacy of adalimumab in AS didn’t report any data on patients with concomitant psoriasis or axial PsA [77]. An open label study of adalimumab on patients with AS improved axial disease, regardless of a history of psoriasis [78], demonstrating that axial disease, classified as both AS or PsA with axial involvement, is equally responsive to adalimumab.

In summary, adalimumab has shown clear benefits in joint and skin disease. Studies have shown a clear reduction in disability and increase of quality of life [79, 80]. Adalimumab may also be the drug of choice for patients with dactylitis, enthesitis and nail disease. It may also be of use in patients in whom MTX is

ineffective or other TNF blockers have failed, or in combination with cyclosporine [81].

The precautions relating to its use are similar to those relating to etanercept, as detailed above. The long term safety of adalimumab has been confirmed through open label extension studies [82] and registries [83]. The adverse event rate during the extension was consistent with that in the initial REVEAL trial, with the rate of side-effects declining through the study period [82].

Infliximab

Infliximab is a chimeric monoclonal antibody against TNFα, which has demonstrated benefits in treating psoriasis and PsA. With regard to treatment of psoriasis, the EXPRESS trials showed significant results at 10 weeks, where PASI75 response at week 10 was 80% vs. 3% for placebo ($P<0.0001$) [37]. Significant results were also found for the treatment of nail disease at week 24 [84], and were maintained up to 1 year for skin and nail disease [85]. However, 27% of patients developed antibodies to infliximab by week 66 [37]. In addition, continuous therapy maintained better PASI responses than intermittent therapy as assessed at week 50 in a separate trial for psoriasis [86].

Infliximab has also demonstrated efficacy in treating PsA. In the IMPACT trials, infliximab was efficacious at treating joint disease demonstrated by significant ACR20, ACR50, ACR70 responses vs. placebo at week 24 [87], with responses maintained through 1 year of treatment [88]. Significant findings for the treatment of other manifestations of PsA have also been shown in these trials for enthesitis and dactylitis [87, 88], as well as demonstrating significant radiographic progression of total joint disease in the PsA-modified van Der Heijde - Sharp (vDH-S) score (developed to score radiographic abnormalities in the hands and feet of patients with PsA) at week 24 [89]. Improvements in quality of life were seen, as evidenced by significantly improved HAQ scores and SF-36 questionnaire at week 14 [90].

Infliximab also demonstrated significant results in other patient demographics, as it significantly improved the PASI75 responses in Chinese patients with psoriasis [91], and the ACR20 responses of Japanese patients with PsA [92].

The benefit of infliximab was translated in a significantly greater PASI75 response when compared with MTX (78% in the active group vs. 42% in the MTX group at week 16) [93]. Similar positive results were reported for joint disease (ACR20) and dactylitis in the RESPOND study [94]. In the PSUNRISE trial, 65.4% of patients who had an inadequate response to etanercept had a PGA

score of 0 or 1 (demonstrating clear or almost clear nail disease) at week 10, upon switching to infliximab [95].

Concerning safety, infliximab has many of the same common adverse effects as the other TNF blockers mentioned above. Serious adverse events were present in 6% of patients on infliximab at week 24 in the EXPRESS trial [37], and in a slightly higher proportion when compared to MTX in the RESTORE trial (7% vs. 3%) [93]. In patients switching from etanercept to infliximab, a proportion of 3.7% experienced a severe adverse event [95]. Patients with PsA tolerated well infliximab, whilst adverse events were often higher than placebo, the incidence of serious adverse events was similar [87, 88, 92, 94]. In the IMPACT-2 study, 11.5% of patients had experienced a serious adverse event, and 8.4% stopped treatment due to adverse events, as assessed at week 54 [88].

Whilst infusion-related reactions were found in 16% patients treated with infliximab, it was observed that patients who are concurrently treated with further immunosuppressive agents, such as MTX or azathioprine, were likely to have lower incidence of infusion-related reactions [52]. Most infusion reactions were of mild-moderate nature [86]. Granulomatous infections were more common in patients on infliximab than etanercept; it has been reported at a prevalence of 239 cases of infection per 100,000 patients treated with infliximab, of which tuberculosis was the most common (144 per 100,000). In addition, candidiasis, coccidioidomycosis, histoplasmosis, listeriosis, nocardiosis and nontuberculous mycobacteria infections were significantly more frequent in patients treated with infliximab. The risk of a granulomatous infection, whilst still very low in absolute terms, is 3.25 times greater in patients on infliximab compared to etanercept [96], a proportion of which are attributed to be reactivation of latent granulomatous infection [97].

The major long-term observational study for infliximab for the treatment of psoriasis: P-SOLAR included 12095 patients, who have been followed up for a combined 31818 patient-years. This study reported that, compared to non-biological therapy, the use of biologic agents was not a significant predictor of MACE **(***Mortality* and *Major Adverse Cardiac Events)*, malignancy or death; and no new safety concerns were found when the results were reported in 2013 [98].

Certolizumab

Certolizumab pegol is a PEGylated Fab fragment from a humanized TNFα-inhibitor monoclonal antibody. Initial benefits were found in treating psoriasis, as patients had significantly greater PASI75 responses at week 12 for multiple

doses (75% 200mg, 83% 400mg) of certolizumab, when compared with placebo (7%), P<0.001 [99].

The RAPID trials demonstrated the efficacy of certolizumab in treating joint manifestations associated with PsA, and reported as a significant ACR20 response vs. placebo at week 12 (for multiple active treatment doses and regardless of prior TNF blocker exposure). Some patients experienced significant improvement as early as week 1 of treatment [100], and the response rates were maintained up until week 48 [101]. Significant positive results were also found for dactylitis, enthesitis, and nail disease at week 24 [100]. Radiographic analyses also demonstrated significant inhibition of progression of joint disease vs. placebo at week 24 [102].

Patient reported outcomes were also improved by treatment with certolizumab, as proven by significant improvement of the PGA scores at week 12 in the active treatment arm compared to placebo [99], as well as significant improvement in physical function, as measured by the HAQ-DI scores at week 24 [103]. In addition, the RAPID trial analysed the changes in productivity in the work-place and at home, and found significant productivity improvement as early as week 4, maintained until week 24. The treatment also improved the patient's domestic, family, social and leisure activities, regardless of employment status at week 24 [104].

With respect to the safety of certolizumab in psoriasis, there was no clinically meaningful differences of treatment-emergent adverse events between treatment groups, and most side effects were of mild/moderate severity, with nasopharyngitis, headache and pruritus being the most common [99]. Serious adverse events occurred in 3% of patients on 200 mg certolizumab, in 5% of those on 400 mg certolizumab and in 2% of patients on placebo over 24 weeks [99]. The RAPID-PsA trial reported similar serious adverse events and treatment discontinuation rates at 24 weeks [100]. At week 48, 9.9% of patients had experienced a serious adverse event [101], and by week 96, 17.0% of patients had experienced a serious adverse event, based on the results of the same trial. The most common adverse events were pneumonia, HIV, erysipelas and urinary tract infection, which had led to 9.2% of patients withdrawing from the study by week 96 [105]. Injection site reactions at 24 weeks were reported by 2.2% patients on placebo vs. 4.3% for 200 mg certolizumab, and 9.6% for 400 mg certolizumab groups [100]. A Cochrane review has found statistically significant increase in serious infections and serious adverse events for certolizumab compared to the control groups [106], but this analysis looked at the data on biologic treatments across many autoimmune conditions, rather than just psoriasis or PsA, and was made on indirect comparisons.

Golimumab

Golimumab is another monoclonal antibody against TNFα, originally engineered from a transgenic model in mice. The GO-REVEAL series of trials showed that this treatment was effective in treating PsA, as assessed by ACR20 responses (48% in the treatment arm vs. 9% in the placebo group, P<0.001) [107]. These benefits were sustained, as reported at different time points: at 1 year [108], 2 years [109], and 5 years [110], with a proportion of 31% of patients discontinuing the treatment with golimumab after 5 years. There was also a significant benefit in controlling symptoms of enthesitis and dactylitis, but this was only seen in the higher dose (100mg) golimumab arm when compared to placebo at week 24 [111]. These benefits, along with significant radiographic response, were maintained through 1 year [108], 2 years [109] and 5 years [110].

Similarly to other biologics, quality of life improvements were demonstrated with golimumab as well, as early as week 24 [107] and as far as 5 years into treatment. A proportion of 52% of patients had a clinically meaningful decrease in their HAQ-DI scores (>0.3) [110].

One of the studies looking at the long-term follow up of patients treated with golimumab demonstrated that 6% from the total number of patients developed antidrug bodies at 5 years. A higher proportion of these patients were on golimumab monotherapy (10.0% vs. 1.8% for those who had received baseline MTX treatment) [110].

Through the first 24 weeks of golimumab treatment in the GO-REVEAL study, there was a similar incidence of adverse events for golimumab vs. placebo, of which nasopharyngitis and upper respiratory tract infections (URTI) were the most common. At 24 weeks, 3% of patients taking golimumab and 4% of placebo patients discontinued treatment due to adverse events [107]. At 1 year, 4% of patients taking golimumab had discontinued due to adverse events [108], and this proportion increased 6% at 2 years. However, by this point there had been no serious injection site reactions requiring treatment or resulting in discontinuation of the study medication, and there was no significant increase in the risk of serious infections, MACE, malignancy or mortality [109]. After 5 years of treatment, 21.1% of patients had experienced a significant adverse event, with 12.4% discontinuing the treatment due to the adverse event. The most common significant adverse events were basal cell carcinoma (BCC), MI and cholelithiasis [110]. This indicates that golimumab is well tolerated during long-term treatment.

Cost-effective ness of TNF-α Inhibitors for the Treatment of PsA

Systematic reviews and meta-analyses have assessed the cost-effectiveness of biologics in the treatment of PsA and psoriasis, with emphasis on TNF agents as they are the most used [112, 113]. The National Institute of Health and Care Excellence (NICE), which is the main UK regulatory body that provides national guidance and advice to improve health, recommended etanercept, infliximab, adalimumab and golimumab for the treatment of active and progressive PsA. These recommendations were bases on published studies assessing clinical effectiveness and on economic evaluations [114]. On the basis of the numerous RCTs, it was concluded that there was sufficient evidence with regards to the effectiveness of these therapies for cost-effective treatment of PsA and psoriasis. They noted that all the anti-TNF agents can be used interchangeably, as there is not enough evidence at the moment to indicate differences between the individuals TNF inhibitors.

The committee responsible for the appraisal considered the results of a base case model [114]. This ranked the costs and quality-adjusted life-year (QALY) associated with the TNF inhibitors compared with palliative care. Acquisition costs for etanercept and adalimumab were similar. Infliximab has additional administration costs. Infliximab was the most effective for controlling joint and skin disease, followed by etanercept and adalimumab. Infliximab was found to be the most expensive, again followed by etanercept then adalimumab. Etanercept had the highest probability of being cost-effective (44% probability, if the maximum acceptable amount to pay for an additional QALY was £20,000 and 48% if the maximum acceptable amount to pay for an additional QALY was £30,000) [114].

However, these cost-effectiveness assessments are based on indirect comparisons rather than head to head studies of all the anti-TNF agents. Furthermore, in clinical practice these drugs are used interchangeably. For this reason, NICE recommends that the most cost-effective practice is to start with the least expensive drug, based on local variation and administration costs [114].

A separate analysis looking at golimumab, which was introduced in clinical practice more recently, recommended the use of golimumab under the same circumstances as the other three drugs [115]. Bases on a phase III RCTs the committee concluded that golimumab is clinically effective and cost-effective when compared to placebo. Golimumab was similarly effective as other anti-TNF agents with regard to PsARC and PASI responses. The NICE appraisal concluded that golimumab was not cost-effective when compared to etanercept, but cost-effective when compared with adalimumab and infliximab.

Golimumab is thus recommended for use in active and progressive PsA, providing the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50mg dose. There is also evidence that the TNF blockers are considered cost-effective for treatment of psoriasis in other countries as well [116]. Depending on the health system regulations in different countries, the licensing of these biologic agents depends on their cost-effectiveness analysis. A similar real-life cost analysis in the United States showed that etanercept is the most cost-effective anti-TNF therapy in autoimmune rheumatic diseases, with the exception of psoriasis, for which adalimumab was the most cost-effective [117].

Anti-Interleukin Biologic Therapies

Ustekinumab

Ustekinumab is a human monoclonal antibody directed against the p40 subunit of IL12/23. The PHOENIX1 and PHOENIX2 RCTs recruited patients with psoriasis and both showed significantly greater PASI75 responses at week 12 vs. placebo [118, 119], with responses maintained until week 76. These studies also reported significant benefit in nail disease at week 12, as evidenced by NAPSI scores improvement [120].

Ustekinumab demonstrated efficacy in treating PsA initially in phase II RCTs which showed significant ACR20 response vs. placebo at 12 weeks [121]. This positive outcome was then replicated in the larger PSUMMIT1 and PSUMMIT2 trials, which showed significantly increased ACR20 response at 24 weeks [122, 123], which was maintained through 2 years [124], alongside significant increases in the ACR50 and ACR70 responses [122, 123]. Ustekinumab is also efficacious for treating other manifestations of PsA. Both PSUMMIT1 and PSUMMIT2 RCTs showed significant benefits for enthesitis [122, 123], but only PSUMMIT1 showed significant improvement in the dactylitis scores and spondylitis (as measured by the BASDAI score at week 24) [122], as well as inhibition of radiographic progression (as measured by the PsA-modified vDH-S score at week 24) [125].

Patient reported outcomes have also improved following treatment with ustekinumab as assessed by DLQI and HAQ-DI scores at week 12 [126], and clinically meaningful HAQ-DI scores of 0 or 1, which were maintained up until 2 years of treatment [124].

Ustekinumab is effective in treating patients from diverse demographic backgrounds, as similar results were reported by the LOTUS RCT which

included Chinese patients [127], and the PEARL RCT which recruited Taiwanese and Korean patients with psoriasis [128].

Ustekinumab has been compared to etanercept in a head-to-head, the ACCEPT trial, which found a non-significant increase in PASI75 response in ustekinumab (67.5% for 45mg, 73.8% for 90mg) vs. etanercept (56.8%) at week 12. In addition, whilst the incidence of adverse events and proportion of participants discontinuing the trial were similar, there was a significantly increased amount of injection site reactions in the etanercept vs. ustekinumab groups, which the authors suggested that could be explained by the difference in the frequency of subcutaneous administrations [129].

In all the RCTs assessing patients with psoriasis, ustekinumab was generally well tolerated [118, 119, 129, 130], including in the Chinese [127] and Taiwanese & Korean [128] populations. In the PHOENIX-1 trial, the most common serious adverse events were infections, malignancy and cardiovascular events, including MI and stroke [118], as assessed at 3 years. A proportion of 7.9% of patients on 45 mg and 10.1% of patients on 90 mg ustekinumab had suffered a serious adverse event, with 6.9% and 6.4% of patients respectively discontinuing study participation due to an adverse event [130]. Injection site reactions were rare: the PHOENIX-2 study reported them in 1.0% of ustekinumab treated patients at week 52. At the same time point, 5.4% of patients had developed antibodies to ustekinumab [119].

Similarly, ustekinumab has been well-tolerated by patients with PsA [121, 122], and all injection site reactions reported in the P-SUMMIT-1 trial at week 24 were mild. The P-SUMMIT-2 trial found 1.3% of patients with ustekinumab had experienced a serious adverse event by week 24, with 2.1% of patients discontinuing treatment due to an adverse event [123]. Long-term safety data for ustekinumab was reported by the PSOLAR registry [98], which found that ustekinumab had a lower unadjusted rate of serious infection of 0.93/100 patient years compared to 2.91/100 patient years for infliximab, and 1.91/100 patient years for other biologics. Also, ustekinumab was not associated with increased risk of malignancy, MACE, or mortality [131].

Ustekinumab is recommended in the treatment of severe psoriasis (which is appreciated as having significant impact on patients' quality of life), but only in patients who have failed to get their disease controlled with other treatments such as Psoralen and long wave ultraviolet radiation (PUVA), cyclosporine and MTX [132].

Ustekinumab has also been recommended for the treatment of patients with active PsA, in which TNF inhibitors were not suitable or effective (after a trial period of 24 weeks). Due to the introduction of the patient access scheme, the

treatment with ustekinumab is now considered to be cost-effective. Incremental cost-effectiveness ratio per QALY compared to conventional treatment was calculated by NICE at £21,900 for patients who had not had TNF inhibitors before (not considered cost-effective); £25,400 for people who have had TNF inhibitors and for whom subsequent TNF inhibitors would be appropriate, and £25,300 for people who have failed TNF inhibitors [133].

Secukinumab

Secukinumab is a monoclonal antibody against IL17A, which was shown to be effective for psoriasis, as proven by significantly increased PASI75 responses vs. placebo at 12 weeks in the ERASURE trial [134], JUNCTURE trial [135] and FEATURE trial [136], as well as demonstrating a significant increase in PASI75 response at week 12 in a head-to-head study, in which it was compared to etanercept.

Early phase IIa RCT data showed a significant ACR20 response at week 6 vs. placebo, but non-significant difference when compared to placebo for the ACR50 and ACR70 response criteria [137]. The FUTURE1 and FUTURE2 trials are still pending publication; however, conference proceedings showed a significant improvement in ACR20 response vs. placebo at week 12 [138, 139], alongside achievement of secondary endpoints, which included dactylitis, enthesitis, DAS28-CRP, ACR50, ACR50, PASI75 and PASI90 responses (regardless of prior anti-TNF treatment) [138, 139]. This was maintained up to week 52 in the FUTURE 1 RCT [138].

Significantly less radiographic progression from baseline was achieved by secukinumab when compared to placebo, as assessed at week 24 [140].

Secukinumab is well tolerated in patients who received this treatment for psoriasis [134-136], with the most common adverse events being nasopharyngitis, headache, URTI [134] and diarrhoea [135]. In the FIXTURE-1 trial there were less injection site reactions for secukinumab (0.75%) compared to etanercept (11.1%), and more patients treated with etanercept discontinued their participation in the study because of side-effects. There are also no clinically apparent differences in the types of significant adverse events among various study groups [134].

For the treatment of PsA, rates and types of infection were similar for secukinumab arm vs. placebo [137]. The early reports of side-effects in the FUTURE-1 RCT found that they affected only 8.6% of patients who had received 75mg SC secukinumab and 9% of patients who had received 150mg at any point in the study [138]. The FUTURE-2 trial reported that the overall incidence of adverse events up to week 16 was similar across all the

secukinumab arms, and also were similar to the placebo arm: overall, 3.3% of patients treated with secukinumab experienced severe adverse events compared to 2.0% for patients on placebo [139].

Secukinumab is recommended in the treatment of patients with severe psoriasis, with impact on their quality of life, and in patients who have failed to respond to other treatments for psoriasis, such as PUVA, cyclosporine and MTX. The cost for secukinumab was £52,760 per QALY gained (incremental costs £20807 compared with best supportive care) [141].

Brodalumab

Brodalumab is a monoclonal antibody against IL17A, IL17F and IL23. Brodalumab is effective for treatment of psoriasis. A phase II RCT demonstrated significantly improved PASI75 responses vs. placebo at week 12, as well as significantly increased PASI90 scores at higher doses (140mg and 210mg), when compared to baseline and with the placebo arm [142]. PASI responses were maintained during the open label extension of the study, up to 120 weeks [143].

Brodalumab has also shown efficacy in treating joint disease in patients with PsA. In a phase II RCT, there was significant increase in the ACR20 response at week 12 when compared to placebo; however there was no significant difference in the enthesitis or dactylitis scores secondary to treatment [144]. In addition, BASDAI scores were significantly improved in the brodalumab group, indicating potential benefits for axial involvement in patients with PsA.

Brodalumab was generally well tolerated. In the RCTs of psoriatic patients, the most common reported adverse events were nasopharyngitis, URTI, arthralgia and erythema [142]. The analysis of the open-label extension study after 120 weeks of treatment reported that 8.3% of patients treated with brodalumab had suffered serious adverse events, with 6.2% of patients discontinuing study participation due to adverse events [143]. For the treatment of PsA, the proportion of serious adverse events was similar to placebo (brodalumab 3% vs. placebo 2%) at week 12, and upon analysing the open-label extension study, it was found that 6% of patients taking brodalumab had experienced a serious adverse event by week 52 [144].

Ixekizumab

Ixekizumab is another monoclonal antibody against IL17A, which has demonstrated efficacy in treating psoriasis, as seen by significantly greater PASI75 score improvement compared to placebo at doses of 25mg, 75mg and

150mg at 12 weeks [145], as well as significant improvement in nail disease vs. placebo at the higher doses of 75mg and 150mg [146].

Ixekizumab was well tolerated over 20 weeks, with no patients reporting a serious adverse event. The most common adverse events were nasopharyngitis, URTI, injection-site reaction (only mild-moderate) and headache [145].

Tocilizumab

A randomised trial of tocilizumab in AS showed no clinical efficacy, despite being effective in decreasing the CRP levels [147]. No further clinical trials are planned.

T Cell Modulatory Therapies

Abatacept

Abatacept, a T cell co-stimulation inhibitor, is a fusion protein that binds to CD80 and CD86 interfering with T cell signalling and activation, and hence reducing the inflammatory response.

Abatacept has shown efficacy at 6 months (as assessed by the ACR20, SF-36, psoriatic target lesion response and PASI scores), particularly at a dose of 10mg/kg in an early phase RCT [148]. The treatment with abatacept was associated with additional improvements in radiographic progression, appearance of osteitis, joint synovitis and function, as assessed by HAQ, and was associated with sustained ACR and skin responses at 12 months [148]. Patients in the placebo group, who had switched to abatacept, exhibited similar responses. However, skin response was inconsistent, and TNF naïve patients showed greater responses than those previously treated with anti-TNF medication. This study showed promise for the use of a new biologic agent in the treatment of psoriasis and PsA. Additional case reports provided evidence that abatacept can be a suitable treatment option for refractory cases of PsA and psoriasis [149, 150].

Abatacept has failed to show efficacy in AS in a 24 week open label study [151]. There has been no data to support its use in PsA with axial involvement, dactylitis, enthesitis or nail disease.

The only RCT of abatacept in PsA reported similar safety profile for the 3, 10 and 30/10 mg/kg doses. There were two cases of infection, which was considered drug related, but overall it was reported to be a well-tolerated and safe drug [148].

Apremilast

Apremilast is a phosphodiesterase inhibitor. It acts by targeting PDE4, thereby increasing levels of cAMP which results in decreased levels of pro-inflammatory cytokines.

Treatment with apremilast was shown effective in controlling the symptoms of PsA, as assessed by the ACR20 response in several RCTs [152, 153]. The PALACE studies, a group of large phase III trials, have demonstrated its efficacy by achieving the primary outcome, the ACR20 response at week 16, which was maintained at week 52 in patients treated with 20 mg twice daily (BD) dose [153]. Apremilast was also effective in improving joint function, and symptoms and signs of enthesitis and dactylitis. The level of efficacy of apremilast is comparable to that of TNF inhibitors as assessed in clinical trials, although, it is of note that TNF inhibitors achieved similar results in almost half the time. Axial disease was not investigated in the RCTs of apremilast in PsA.

Apremilast was also proven effective for treatment of psoriasis [154-156]. The multi dose phase IIb RCT of apremilast in psoriasis reported significant improvement in the PASI75 score at week 16 and 32 in both, the 20 mg and 30 mg BD treatment groups [157]. There were also improvements in pruritus, DLQI and physician global assessment of psoriasis. This trial data also supported the role of apremilast in the treatment of nail disease, with a NAPSI50 response index achieved at both week 16 and 32 [157]. Apremilast is recommended by the National Psoriasis Foundation in skin and nail disease, and skin, nail and joint disease, but with less enthusiasm and a lower ranking then adalimumab and etanercept [50]. The treatment with apremilast was recently approved by FDA for use in PsA and psoriasis [158].

Long-term trials have reported apremilast as safe and well tolerated. In a 52-week RCT of apremilast in PsA, the most common adverse effects were diarrhoea and nausea; these were highest within the first 2 weeks of medication administration and most resolved within a month of continued treatment. The incidence of significant adverse events was comparable across all treatment groups [159]. The treatment with apremilast 30 mg BD in patients with moderate-severe psoriasis was also well tolerated in a 52 week RCT, most side-effects being mild or moderate. Their incidence did not increase with longer apremilast exposure [156]. There were no cases reporting reactivation of tuberculosis.

There was recent interest in assessing the cost-effectiveness of apremilast treatment in different health systems in the UK, Spain and Italy [160-162].

Alefacept

Alefacept is a dimeric fusion protein that consists of the extracellular portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human IgG1, which acts as a T cell modulator. Multiple clinical trials have shown efficacy at week 12 for PASI75 and DLQI scores compared to placebo [163-166]. When used in combination with MTX, the treatment was superior in achieving ACR20 and PASI50 responses at week 24 compared to MTX plus placebo [167]. There was also an improvement in HAQ at 12 weeks, but not at 24 weeks. As of yet there is no data to support the efficacy of this treatment in controlling axial disease, dactylitis, enthesitis or nail disease.

Alefacept is safe and well tolerated, with a similar incidence of adverse events reported in the treatment and placebo groups. The most common adverse events were mild and included headache, infection, injection site reactions. There was no evidence of any adverse immunosuppression caused by the treatment with alefacept [164].

Efalizumab

Efalizumab is a recombinant humanized monoclonal antibody, which binds to the CD11a subunit of lymphocyte function-associated antigen 1, and acts as an immunosuppressant by inhibiting lymphocyte activation and cell migration out of blood vessels into tissues. Efalizumab failed to prove superiority in treating PsA when compared with placebo [168]. A large multicentre RCT of efalizumab in patients with moderate-severe psoriasis established initially this treatment efficacy [169], and was followed by numerous other RCTs with similar results [170-172]. Despite the fact that initially the treatment with efalizumab was considered safe in clinical trials [173], further reports showed that efalizumab was associated with serious adverse events such as infections, malignancy and haemolytic anaemia [174, 175]. Some patients experienced worsening of their psoriasis [176]. Progressive multifocal leukoencephalopathy was observed in 3 patients who had exposure greater than 3 years [177, 178]. Efalizumab drug was withdrawn in 2009 in Europe and the United States due to these risks.

B Cell Depletion Therapies

Rituximab

Rituximab consists of a chimeric monoclonal antibody against CD20, which has not demonstrated any significant benefit in treating psoriasis or PsA

and its manifestations in a small, open label trial, despite being well-tolerated [179].

Small Molecule Inhibitors

Tofacitinib

Tofacitinib is a Janus-Kinase inhibitor, taken orally, which has shown to be effective in treating psoriasis, with significantly higher PASI75 responses at week 12 when compared to placebo [180], as well as having significantly better PASI responses for body regions graded separately at week 12 [181].

Tofacitinib was well tolerated by patients with psoriasis: severe adverse events were reported in 2.0% (2mg BD), 4.1% (5mg BD), 0% (15mg BD) tofacitinib in comparison with 10.0% in the placebo patients. Discontinuation rates due to adverse events were 2.0%, 4.1%, 6.1% respectively for tofacitinib different dose regimens compared to 6.0% in patients on placebo, as reported at week 12 [180].

Biosimilars

Biologics have revolutionised the treatment and changed the lives of patients around the world. As their patents are soon to expire, biosimilars, biotechnologically processed drugs designed to have the same active properties as those previously licensed, are set to add to the repertoire of affordable biologic medications. Whilst clinicians and governing bodies welcome biosimilar substitution, there are risks and uncertainties associated with them, largely due to the limited long-term data.

Biologics cannot be replicated exactly, as the molecules are derived from cells using recombinant DNA technology; therefore the biosimilars are not chemically identical. The National Psoriasis Foundation supports the use of biosimilars and has provided a set of recommendations guiding their use [184]. These include ensuring patients are fully informed and educated, ensuring the biosimilar intended for use have been approved as interchangeable by the FDA following adequate documentation of their safety and efficacy. Adequate evidence of their bio-equivalence, including their clinical efficacy and safety must be obtained before we can fully take advantage of the economic benefits without compromising clinical care [185]. Whilst there have been studies reporting positive results of the use of biosimilars in RA and AS, there are no studies to date to assess their efficacy in PsA and psoriasis [186, 187].

Table 1. Biologic treatments used in PsA and psoriasis

Authors	Duration, type of study, treatment, number of patients (N)	Main results
Anti-TNF treatments		
Mease et al. 2005 [61]	24-week RCT of adalimumab vs. placebo (N = 151 + 162).	At week 12, 58% of the adalimumab-treated patients achieved an ACR20 response, compared with 14% of the placebo-treated patients (P<0.001). 59% adalimumab-treated patients achieved a 75% PASI response at 24 weeks, compared with 1% of the placebo group (P<0.001).
Gladman et al. 2007 [182]	48-week open label trial of adalimumab vs. placebo in PsA (N = 151).	At week 48, patients had achieved ACR20, ACR50, and ACR70 response rates of 56%, 44%, and 30%, respectively. The PASI50, PASI75, PASI90, and PASI100 response rates were 67%, 58%, 46%, and 33%, respectively.
Menter et al. 2008 [60]	52-week, RCT of adalimumab vs. placebo in psoriasis patients (N = 1212)	At week 16, 71% of adalimumab and 7% of placebo-treated patients achieved greater than or equal to 75% improvement in the PASI score (P<0.001).
Sauret et al. 2008 [65]	16-week RCT of adalimumab (N = 108), oral MTX (N = 110) and placebo (N = 53) (1:1:1).	At week 16, 79.6% of adalimumab-treated patients achieved PASI 75, compared with 35.5% for MTX (P<0·001) and 18.9% for placebo (P<0·001 vs. adalimumab).
Mease et al. 2000 [33]	12-week RCT trial of etanercept in PsA (25 mg twice-weekly subcutaneous injections) or placebo (N = 60).	At 12 weeks, the ACR20 was achieved by 73% etanercept-treated patients compared with 13% placebo-treated patients (P<0.0001).
Gottlieb et al. 2003 [34]	24-week RCT of etanercept vs. placebo in patients with psoriasis (N = 112).	At week 12, 30% of the etanercept patients and 2% of placebo-treated patients achieved PASI75% (P<0.001), 56% of etanercept patients and 5% of placebo patients at week 24 (P<0.001).
Leonardi et al. 2003 [35]	24-week RCT of etanercept low dose (25 mg once weekly), medium dose (25 mg twice weekly), or high dose (50 mg twice weekly) vs. placebo.	At week 12, there was an improvement from base line of PASI75 in 4% of the patients in the placebo group, 14% of those in low-dose–etanercept group, 34% in the medium-dose–etanercept group, and 49% in the high-dose–etanercept group (P<0.001 for all three). At week 24, PASI75 was achieved in 25% of the patients in low-dose group, 44% in medium-dose group, and 59% in high-dose group.
Mease et al. 2004 [41]	24-week RCT of etanercept vs. placebo in PsA (N = 205).	At 12 weeks, 59% of etanercept patients met the ACR20 compared with 15% of placebo patients (P<0.0001).

Authors	Duration, type of study, treatment, number of patients (N)	Main results
		At 24 weeks, 23% of etanercept patients achieved at least PASI75 (P=0.001).
Tyring et al. 2006 [38]	24-week RCT of 50 mg twice-weekly etanercept or placebo (N = 618).	At week 12, 47% of patients achieved PASI75 compared with 5% (P<0.0001).
Reich et al. 2005 [37]	46-week RCT of infliximab vs. placebo in patients with psoriasis. (N = 378).	At week 10, a significant greater PASI 75 and PASI 90 response in Infliximab vs. placebo was found: 80% vs. 3%, (P<0.0001), and 57% vs. 1%, (P<0.0001), respectively. At week 24: PASI75 and PASI90 responses were maintained in the active group: 82% vs. 4% (P<0.0001), and 58% vs. 1%, (P<0.0001), respectively.
Rich et al. 2008 [84]	50-week RCT of Infliximab vs. placebo in patients with psoriasis. (N = 305).	At week 24, there was a significantly greater nail disease clearance in the infliximab group vs. placebo: 26.2% vs. 5.1%, (P<0.001) and at week 10, significant greater NAPSI % improvement in infliximab vs. placebo: 26.8% vs. -7.7% (P<0.001) was also noted.
Antoni et al. 2005 [87]	50-week RCT of Infliximab vs. placebo in patients with psoriasis and PsA. (N = 104).	At week 16, significantly greater ACR20 response in infliximab vs. placebo groups: 65% vs. 10%, (P<0.001), and significantly greater improvement in dactylitis score from baseline in the Infliximab vs. placebo groups: 85% vs. 29%, (P<0.001) were found. Similarly, significant lower proportion of enthesitis (14% vs. 31%, P=0.021) and significant greater PASI75 response (68% vs. 0%, P<0.001) in the infliximab vs. placebo groups were found at week 16.
Reich et al. 2012 [99]	12-week RCT of certolizumab 200mg, 400mg vs. placebo in patients with psoriasis. (N = 176).	At week 12, significantly greater PASI75 response in certolizumab vs. placebo groups was noted: 75% (200mg) vs. 83% (400mg) vs. 7% (placebo), (P<0.001). Also, at week 12, significantly greater PGA score of clear/almost clear psoriasis was found in the active medication groups: 53% (200mg) vs. 72% (400mg) vs. 2% (placebo).
Mease et al. 2014 [100]	24-week RCT of certolizumab 200mg, 400mg vs. placebo in patients with psoriasis and PsA. (N = 409).	At week 12, the ACR20 response was significantly increased in the certolizumab vs. placebo arms: (58.0% (200mg) vs. 51.9% (400mg) vs. 24.3% (placebo), (P<0.001). At week 24, significantly greater PASI75 response was encountered in the certolizumab group vs. placebo: 62.2% (200mg) vs. 60.5% (400mg) vs. 15.1% (placebo), (P<0.001); there

Table 1. (Continued)

Authors	Duration, type of study, treatment, number of patients (N)	Main results
		were similar findings for enthesitis improvement: -2.0 (200mg). vs. -1.8 (400mg) vs. -1.1 (placebo) (P<0.01, P<0.03, respectively) and dactylitis improvement: -40.7 (200mg) vs. -53.5 (400mg) vs. -22.0 (placebo) (P=0.02 and P<0.01, respectively)
Kavanaugh et al. 2009 [107]	24-week RCT of golimumab 50mg, 100mg vs. placebo in patients with psoriasis and PsA. (N = 405).	At week 14, these was significantly greater ACR20 response in the golimumab vs. placebo groups: 51% (50mg) vs. 45% (100mg) vs.9% (placebo), (P<0.001). At week 24, there was a significantly greater PASI75 response in the golimumab vs. placebo groups: 40% (50mg) vs .58% (100mg) vs. 3% (placebo), (P<0.001).
Kavanaugh and Mease, 2012 [111]	24-week RCT of golimumab 50mg, 100mg vs. placebo in patients with psoriasis and PsA. (N = 405).	At week 24, there was a significant decrease in PsA-modified MASES enthesitis score in the active medication group: 46% (50mg), P<0.001. vs. 52% (100mg), P<0.001. vs. 13% (placebo), and difference in dactylitis score: 66% (50mg), P=0.09. vs. 82% (100mg), P<0.001. vs. 28% (placebo).
IL12/IL23 Inhibition		
Leonardi et al. 2008 [118]	76-week RCT of ustekinumab 45mg, 90mg vs. placebo in patients with psoriasis. (N = 766).	At week 12, significantly greater PASI75 score was recorded in the ustekinumab vs. placebo groups: 67.1% (45mg) vs. 66.4% (90mg) vs. 3.1% (placebo), (P<0.0001). PASI75 score was better maintained at 1 year in the treatment arm vs. patients withdrawn from treatment at week 40, (P<0.0001).
Rich et al. 2014 [120]	76-week RCT of ustekinumab 45mg, 90mg vs. placebo in patients with psoriasis (N = 766).	At week 24, significantly greater NAPSI score was found in the ustekinumab vs. placebo groups: 26.7% (45mg) vs. 24.9% (90mg) vs. 11.8% (placebo), (P<0.001).
Young et al. 2011 [129]	12-week RCT of ustekinumab 45mg, 90mg vs. etanercept in patients with psoriasis (N = 903).	At week 12, PASI75 response improved significantly in the ustekinumab vs. etanercept groups: 67.5% (45mg) vs. 73.8% (90mg) vs. 56.8% (etanercept)

Authors	Duration, type of study, treatment, number of patients (N)	Main results
McInnes, et al. 2013 [122]	52-week RCT of usekinumab 45mg, 90mg vs. placebo in patients with psoriasis and PsA. (N = 615).	At week 24, a significantly greater proportion of patients achieved ACR20 response in the ustekinumab vs. placebo groups: 42.4% (45mg), 49.5% (90mg) vs. 22.8% (placebo), (P<0.0001). At the same time point, there was significant decreased in dactylitis score: 56.6% (45mg) vs. 76.1% (placebo), P=0.005, and 55.8% (90mg)
T cell co-stimulatory blockade		
Mease et al. 2011 [148]	6-month RCT of abatacept vs. placebo at doses of 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 initial doses of 30 mg/kg, followed by 10 mg/kg).	At week 24, ACR20 response was achieved by 19%, 33%, 48%, and 42% in the placebo, the abatacept 3 mg/kg (P=0.121), 10 mg/kg (P=0.006), and the 30/10 mg/kg (P=0.022) groups respectively.
Phosphodiesterase 4-Inhibitors		
Schett et al. 2012 [152]	12-week RCT of apremilast 20 mg BD, 40 mg OD vs. placebo, followed by a 12-week treatment-extension phase.	At week 12, 43.5% of patients receiving apremilast 20 mg (P<0.001) and 35.8% receiving 40 mg (P=0.002) achieved an ACR20 response, compared with 11.8% of placebo.
Kavanuagh et al. 2013 [153]	24-week RCT of apremilast 20 mg BD or 30 mg BD vs. placebo. (N=504).	At week 16, 31% of apremilast 20 mg BD group (31%), and 40% of the apremilast 30 mg BD group achieved ACR20 vs. placebo (19%) (P<0.001).
IL17 Inhibition		
Langley et al. 2014 [134]	52-week RCT of secukinumab 300mg, 150mg vs. placebo in patients with psoriasis (N = 738). 52 week RCT of secukinumab 300mg, 150mg vs. etanercept in patients with psoriasis. (N = 1306).	At week 12, a significantly greater proportion of patients achieved PASI75 score in the secukinumab group vs. placebo: 81.6% (300mg), 71.6% (150mg) vs. 4.5% (placebo), P<0.001. At week 12, a significantly greater proportion of patients achieved PASI75 score in the secukinumab vs. etanercept group: 77.1% (300mg), 67.0% (150mg) vs. 44.0% (etanercept).
Mease et al. ACR 2014 [138]	52-week RCT of secukinumab 75mg, 150mg vs. placebo in patients with psoriasis and PsA. (N = 606).	At week 24, a significant greater proportion of patients fulfilled the ACR20 response criteria in the secukinumab vs. placebo groups: 50.5% (75mg), 50.0% (150mg) vs. 17.3% (placebo), (P<0.0001).

Table 1. (Continued)

Authors	Duration, type of study, treatment, number of patients (N)	Main results
Papp et al. 2012 [142]	12-week RCT of brodalumab 70mg, 140mg, 210mg vs. placebo in patients with psoriasis (N = 198).	At week 12, more patients achieved PASI75 response in the brodalumab groups vs. placebo: 45.0% (70mg), 85.9% (140mg), 86.3% (210mg) vs. 16.0% (placebo), P<0.001.
Mease et al. 2014 [144]	12-week RCT of brodalumab 140mg, 280mg vs. placebo in patients with psoriasis and PsA (N = 168).	At week 12, more patients achieved ACR20 responses in the brodalumab groups vs. placebo: 37% (140mg), vs. 18% (placebo), P=0.03. 39% (280mg) vs. 18% (placebo), P=0.02. However, at week 12, there was no significant difference in the enthesitis and dactylitis scores. At week 12, the Psoriasis Symptom Inventory, BASDAI, SF-36 physical component scores significantly improved in the brodalumab group (280mg) vs. placebo.
Leonardi et al. 2012 [145]	12-week RCT of ixekizumab 10mg, 25mg, 75mg, 150mg vs. placebo in patients with psoriasis and Psa (N = 142).	At week 12, a greater proportion of patients achieved PASI75 score in the ixekizumab vs. placebo groups, except for lowest (10mg) dose: 82.1% (150mg), 82.8% (75mg), 76.7% (25mg) vs. 7.7% (placebo), P<0.001 Similarly, at week 12, a significantly greater PASI90 score was noted for the 25mg, 75mg, 150mg ixekizumab doses vs. placebo.
Langley et al. 2015 [146]	20-week RCT of ixekizumab 10mg, 25mg, 75mg, 150mg vs. placebo in patients with nail psoriasis. N = 58, in patients with scalp psoriasis (N = 105).	At week 20, scalp psoriasis had significantly improved from baseline for the ixekizumab 25 and 75 and 150mg groups vs. placebo. Similarly, NAPSI scores improved significantly in the ixekizumab 75mg and 150mg groups vs. placebo.
IL6 Inhibition		
Sieper et al. 2012 [147]	12-week RCT of tocilizumab vs. placebo in AS (N = 102)	At week 12, the ASAS20 response rates were 37.3% and 27.5% in the tocilizumab group vs. placebo (P=0.2823).
T-Cell Modulators		
Krueger et al. 2002 [163]	24-week RCT of alefacept 7.5 mg IVS. or placebo in patients with psoriasis (N = 553)	At week 24, PASI 75 score was achieved by 28% of alefacept-treated and 8% of placebo-treated patients (P<0.001).
Lebwohl et al. 2003 [164]	24-week RCT of 10 mg or 15 mg of alefacept once weekly for 12 weeks vs. placebo.	At week 24, PASI 75 score improved significantly (P<0.001) in patients receiving 15 mg of alefacept (33%) or 10 mg of alefacept (28%), compared to the placebo group (13%).

Authors	Duration, type of study, treatment, number of patients (N)	Main results
	followed by 12 weeks of observation.	
Mease et al. 2006 [167]	24-week RCT of alefacept and MTX (N = 123) or placebo and MTX (N =62) in patients with psoriasis.	At week 24, 54% of patients in the alefacept plus MTX group achieved an ACR20 response, compared with 23% of patients in the placebo plus MTX group (P<0.001).
Gordon et al. 2003 [169]	24-week RCT of 12 weekly subcutaneous efalizumab, 1 mg/kg (N = 369) vs. placebo (N = 187)	At week 24, 27% of efalizumab-treated patients achieved PASI-75 score vs. 4% of the placebo group (P<0.001).
Menter et al. 2004 [183]	12-week RCT of efalizumab 1.0 mg/kg/week vs. placebo in patients with psoriasis.	At week 12, efalizumab-treated patients showed significant improvement in patient-reported outcomes, as measured by DLQI (P<0.001), psoriasis severity (P<0.001), psoriasis frequency (P<0.001), and psoriasis itch (P<0.001) scores.
Papp et al. 2007 [168]	24-week RC of efalizumab 1 mg/kg weekly or placebo for 12 weeks, followed by 12 additional weeks of open-label efalizumab in PsA patients (N = 115).	At week 12, 28% of efalizumab-treated patients achieved ACR20 response, compared with 19% of placebo patients (P=0.27).
Janus Kinase Inhibitors		
Papp et al. 2012 [180]	12-week RCT of tofacitinib 2mg, 5mg, 15mg vs. placebo in patients with psoriasis. (N = 197).	At week 12, a significant higher PASI75 response was achieved for all active treatment groups vs. placebo: 25.% (2mg), 40.8% (5mg), 66.7% (15mg), 2.0% (placebo), (P<0.0001).
Menter et al. 2014 [181]	12-week RCT of tofacitinib 2mg, 5mg, 15mg vs. placebo in patients with psoriasis. (N = 197).	At week 12, a significantly greater proportion of patients achieved PASI scores in all active treatment groups vs. placebo in all body regions (head/neck, upper limbs, trunk, lower limbs), P<0.001.
Anti-CD20		
Jimenez-Boj et al. 2012 [179]	6-month open label study of rituximab in patients with psoriasis and PsA (N = 9).	At week 24, 56% patients achieved the primary endpoint, which was 30% improvement by PsARC, 33% of patients achieved ACR20 response criteria, 44% improved their dactylitis scores, but there was no improvement in the enthesitis, and also there was no significant difference in the BASDAI score compared to baseline: 6.3+/-2.2; 5.9+/-3.0, P=0.57.

Legend: Legend: ACR20,50,70 – American College of Rheumatology response criteria; AS – ankylosing spondylitis; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BD – twice daily; DLQI – Dermatology Quality of Life Index; MTX – methotrexate; NAPSI – Nail Psoriasis Severity Index; PASI – Psoriasis Area Severity Index; PGA – physician global assessment; PsA – psoriatic arthritis; PsARC – Psoriatic Arthritis Response Criteria; RCT – randomised controlled trial.

General considerations

The biologic therapeutic armamentarium for psoriasis and PsA is rapidly expanding, as proven by the large number of biologic agents and small molecule inhibitors available at present. Even if initially, the majority of these medications were assessed for efficacy in psoriasis, recent data showed that many of them are useful for PsA patients as well. Clinicians have many therapeutic options at present and data about direct comparisons between all these agents are relatively lacking. However, as discussed above, there is evidence from head-to-head RCTs that secukinumab and ustekinumab had greater efficacy than etanercept in treating psoriasis. Alefacept induced sustained treatment benefit for a drug-free follow-up period of 12 weeks in patients with psoriasis (suggesting the possibility of intermittent treatment regimens), and itolizumab (a humanized anti CD6 monoclonal antibody tested only in psoriasis, but no in PsA) was associated with very prolonged drug-free remission [188].

An indirect comparison between the percentage of patients achieving ACR20 response criteria when treated with different biologic agents showed the following figures: ustekinumab 90 mg, 42%; secukinumab 300 mg, 54%; brodalumab 280 mg, 64%: abatacept 10 mg/kg, 48%; apremilast 20 mg daily, 43.5%, which is comparable to infliximab 5 mg/kg, 65%; certolizumab 200 mg e.o.w., 58%; golimumab 100 mg monthly, 61%; adalimumab 58%, etanercept 25 mg twice weekly, 59%). TNF inhibitors, ustekinumab and secukinumab have been effective in controlling symptoms of dactylitis and enthesitis. Patients with PsA and axial involvement also responded to therapy with ustekinumab and secukinumab (in addition to TNF inhibitors), and the nail involvement associated with psoriasis also improved with treatment with apremilast and sekukinumab (along with all the licensed TNF inhibitors).

Table 2. Biologic treatments effectiveness in relation to various disease manifestations (* = level of evidence)

Treatment	Sacroiliitis and spinal disease	Peripheral arthritis	Dactylitis	Enthesitis	Nail involvement	Skin psoriasis
ABATACEPT	NO (*1b) Only AS studies	YES (*1b)				YES (*1b)
ADALIMUMAB		YES (*1a)			YES (*1a)	YES (*1a)
ALEFACEPT						YES (*1a)
APREMILAST		YES (*1a)	YES (*1b)	YES (*1b)	YES (*1b)	YES (*1a)
BRODALUMAB	YES (*1b)	YES (*1b)	NO (*1b)	NO (*1b)		
CERTOLIZUMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
EFALIZUMAB (withdrawn)		NO (*1b)				YES (*1a)
ETANERCEPT	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
GOLIMUMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
INFLIXIMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
ITOLIZUMAB	Planned studies	Planned studies	Planned studies	Planned studies	Planned studies	YES (*1b)
IXEKIZUMAB		Ongoing	Ongoing	Ongoing	Ongoing	YES (*1a)
RITUXIMAB		NO (*1b)	NO (*1b)	YES (*1b)		
SECUKINUMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)		
TOCILIZUMAB	NO (*1b)	YES (*4)				YES (*4)
TOFACITINIB	Ongoing (in AS)	Ongoing	Ongoing	Ongoing		YES (*1a)
USTEKINUMAB	YES (*1b)	YES (*1a)	YES (*1b)	YES (*1b)		YES (*1a)

Table 2 *includes a summary of evidence of efficacy of different biologic treatments for different clinical manifestations in PsA and psoriasis. The data is presented using the Oxford Centre of Evidence-based Medicine classification:*

1a Systematic reviews (with homogeneity) of randomised controlled trials

1b Individual randomised controlled trials (with narrow confidence interval)

1c "All or none" randomised controlled trials

2a Systematic reviews (with homogeneity) of cohort studies

2b Individual cohort study or low quality randomised controlled trials (e.g., <80% follow-up)

2c "Outcomes" Research; ecological studies

3a Systematic review (with homogeneity) of case-control studies

3b Individual case-control study

4 Case-series (and poor quality cohort and case-control studies)

5 Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

The need to optimise the therapy of patients who failed TNF inhibitors is one of the main challenges that clinicians face. In order to maximise their chance to respond to subsequent biologic therapies, different strategies of doses optimisation were employed in clinical trials (e.g., in a clinical trials with secukinumab, the intravenous loading dose and use of the 300 mg monthly dose was associated with best response in PsA patients who failed TNF inhibitors). Recent data from the NOR-DMARD cohort showed that the response to the second TNF inhibitor, in patients with PsA who failed the first anti-TNF, is significantly lower [70]. In consequence, it was hypothesised that switching to another biologic treatment with a completely different mechanism of action is a more suitable option. In comparison with RA, and in both AS and PsA, the retention rates of first anti-TNF treatment and the response to the second TNF inhibitor are higher, although these are decreased compared to the first anti-TNF [189]. Therefore, the switch to the second TNF might therefore be recommended in most cases when no other (biologic) treatments are available.

CONCLUSION

In summary, this chapter highlighted that the number of biologic treatments for PsA and psoriasis increased significantly in the recent years. Also the small molecule inhibitors might be the next treatments licensed for PsA, taking into consideration their cost and oral administration. Given the heterogeneity of

clinical features of both PsA and psoriasis, clinician should tailor the treatment options based on local policies and assessment of individual patient cases. Further research into both prognostic biomarkers and patient stratification is required to allow clinicians the possibility to make better use of the various biologic treatment options available.

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