Sequential biologics in the management of psoriatic arthritis

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Summary

- Up to a third of PSA patients may fail on first-line TNF inhibitor therapy due to inefficacy or adverse events, and ustekinumab is currently the only recommended treatment options for these patients. However, an increasing number of specialists may consider switching to an alternative TNF inhibitor before ustekinumab.

- No randomised controlled trials have specifically investigated the sequential use of biological drugs in the treatment of PsA. The evidence to support the sequential use is limited to registry data, observational studies and regional audits.

- The response rates to sequential treatment varied significantly between these studies, but overall responses were significantly lower during second and third treatment courses. Patients achieving an ACR20 response to a second TNF inhibitor ranged from 22% in the DANBIO study to 53.9% in the RAPID-PsA trial.

- In general, persistence with further courses of therapy was lower than with the first course. The median overall drug survival was 2.2 years with the first TNF inhibitor, 1.3 years for the second, and 1.1 years for the third. In patients who switched, median drug survival with the first TNF inhibitor was only 0.7 years. The TNF inhibitor used, the reason for withdrawal of the first TNF inhibitor, and age were not significant predictors of drug survival.

- Safety data relating to specifically to the sequential use of biological drugs in the treatment of PsA are very limited. In one study the survivor function for discontinuing a second TNF inhibitor due to AEs was lower than that for the initial TNF inhibitor (76% vs. 96% at year one, and 92% vs. 64% at year two, respectively). For these patients, the presence of baseline co-morbidities were associated with significantly higher discontinuation rates.

- Despite the paucity of data relating specifically to second- or third-line TNF inhibitors in PsA, it would seem reasonable to assume that their safety profile would be comparable to that observed when a TNF inhibitor is used as a first-line.

- NICE guidance on biologics recommends that treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and product price per dose).

- The price of some biologics differs substantially from list prices due to locally negotiated procurement discounts and National Patient Access Schemes. The introduction of biosimilars is also leading to a shift in the market and manufacturers are bringing in more ‘value’ added services such as variations of homecare and additional nursing support etc.

- The estimated average annual first year cost per PsA patient ranges from £7,150 to £17,286 including administration costs, but excluding VAT. The estimated average annual maintenance cost per PsA patient ranges from £8,559 to £14,045 including administration, but excluding VAT. However, the exact cost depends on the duration of treatment, together with the number of patients treated with each product and any differences in dosing, scheduling and administration. Regional negotiated procurement discounts may be available and CCGs should contact NTAG if more detail is required.
Introduction and background

Psoriatic arthritis (PsA) is a chronic, inflammatory spondylarthritis which affects up to 40% of patients with psoriasis.\textsuperscript{1} PsA can occur at any age, but the majority of cases occur in the fourth decade of life, and it affects both genders equally.\textsuperscript{2,3} The prevalence of PsA is estimated to be around 0.3 -1% of the population.\textsuperscript{2,4}

Although PsA is generally a chronic and progressive condition, its course may be erratic, with flare-ups and remissions that can result in significant functional, psychological and social morbidity. The skin symptoms of PsA precede the arthritis symptoms in over two thirds of people with the disease. Characteristic skin manifestations include erythematous plaques and scaling which can affect any part of the body, and nail lesions. Articular symptoms range from mild non-destructive synovitis to severe, debilitating, erosive arthropathy.\textsuperscript{1-3,5,6}

Patients with PsA are managed in consultation with specialists in dermatology and rheumatology. The goals of treatment are to relieve pain, reduce inflammation, prevent joint damage, and to improve the signs and symptoms of skin manifestations. Mild PsA can generally be managed with non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, with intra-articular corticosteroid injections when necessary. Topical therapies are used for the skin. Disease modifying anti-rheumatic drugs (DMARDs), including methotrexate, sulfasalazine, leflunomide, azathioprine and ciclosporin are used to reduce joint damage and limit disability. After initial treatment with NSAIDs and DMARDs, most people with non-responsive PsA will be treated with a tumour necrosis factor-alpha inhibitor (TNF inhibitor).\textsuperscript{1-3,5,6} The TNF inhibitors adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are licensed for PsA.\textsuperscript{7-11} In March 2015, two biosimilar infliximab products (Inflectra® ▼ and Remsima® ▼) were approved for use in the UK across all current licensed indications, including PsA.\textsuperscript{12,13} A marketing authorisation application for a biosimilar of etanercept has been accepted by the European Medicines Agency.\textsuperscript{14} If authorised this is also likely to be available for use in all licensed indications.

It has been shown that up to a third of PSA patients may fail on first-line TNF inhibitor therapy due to primary non-response, secondary loss of efficacy, or adverse events.\textsuperscript{15-17} The interleukin 12/23 inhibitor ustekinumab is currently the only recommended treatment options for these patients.\textsuperscript{18} However, an increasing number of specialists may consider switching to an alternative TNF inhibitor before ustekinumab.

This document will review the evidence for the sequential use of biological drugs in the treatment of PsA in patients who have stopped their initial TNF inhibitor.

Guidance and related advice

NICE biologics in PsA

There are currently no NICE guidelines specifically on the management of PsA. The TNF inhibitors etanercept, infliximab and adalimumab are recommended by NICE (TA199) for the treatment of active and progressive PsA in adults when the person has peripheral arthritis with three or more tender joints and three or more swollen
joints, and the PsA has not responded to adequate trials of at least two standard DMARDs, given on their own or together. NICE (TA220) recommends golimumab as an option for the treatment of active and progressive PsA in adults only if it is used as described for other TNF inhibitors in TA199, and only if the manufacturer provides the 100 mg dose at the same cost as the 50 mg dose. The TNF inhibitor certolizumab pegol was not considered appropriate for a NICE TA and is not currently planned into any other work programme. However, in June 2014, NICE published an evidence summary on certolizumab pegol in which they suggest that the likely place in therapy is an additional treatment option to the currently available TNF inhibitors licensed for PsA. The interleukin inhibitor ustekinumab is recommended by NICE (TA340) as an option, alone or in combination with methotrexate, for treating active PsA in adults only when treatment with TNF inhibitors is contraindicated but would otherwise be considered (as described in TA199 and TA220), or the person has had treatment with one or more TNF–alpha inhibitors, and only if the manufacturer provides the 90 mg dose at the same cost as the 45 mg dose.

NICE advise that biologic therapy should be discontinued in people whose PsA has not shown an adequate response to treatment using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks (24 weeks for ustekinumab), where an adequate response is defined as an improvement in at least two of the four criteria (one of which must be joint tenderness or swelling score), with no worsening in any of the four criteria. Patients whose PsARC outcome does not justify continuation of treatment but whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.

**NICE - Sequential use**

NICE TA199 published in 2010 concluded that there were insufficient data to make a recommendation on the sequential use of TNF inhibitors in PsA. However, in TA340 published in June 2015, the Appraisal Committee heard from the clinical experts that the sequential use of TNF inhibitors is established practice in the NHS. Therefore, if patients fail on first-line TNF inhibitor therapy due to inefficacy or adverse events, a second TNF-alpha inhibitor will often be used. Although the availability of second-line TNF inhibitors varies across the UK, the sequential use of TNF inhibitors is extensive. The committee also noted that the 2012 NICE commissioning guide on biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology does not explicitly recommend sequential use of TNF inhibitors in PsA, but considered that both the guide and the published TAs do not preclude this use.

**BSR and EULAR - Sequential use**

The British Society or Rheumatology (BSR, 2012), and the European League against Rheumatism (EULAR, 2011) recommend that in the case of failure of an anti-TNF treatment due to inefficacy or adverse events, an alternative anti-TNF therapy should be considered, and response to treatment assessed as for the first anti-TNF agent. However, they both acknowledge there was insufficient evidence to establish a preference for a particular TNF inhibitor in this situation.
**Clinical evidence**

The majority of evidence supporting the sequential use of TNF inhibitors in the treatment of PsA is derived from several large national registries, observational studies and regional audits. A review of the literature did not find any randomised controlled trials (RCTs) which specifically investigated the sequential use of biological drugs in PsA. The trials used to gain regulatory approval for infliximab, adalimumab and golimumab in PsA specifically excluded patients who had received prior TNF inhibitor treatment. The pivotal trial of etanercept does not state whether or not patients who had failed previous biologics had been excluded, and no such data are reported. The pivotal trial of certolizumab pegol (RAPID-PsA) reports some relevant data from a small cohort of patients who had previous exposure to an alternative TNF inhibitor. However, it should be noted that patients who had experienced primary failure of their initial TNF inhibitor were excluded.

**Danish DANBIO registry (2013)**

An observational cohort study based on the Danish Nationwide DANBIO registry evaluated the clinical response and rates of drug adherence (referred to as drug survival) in patients with PsA who switched TNF inhibitors in routine care. Included patients had to have a diagnosis of PsA according to the treating rheumatologist. Patients were excluded if they had received only DMARDs, if they received biologic agents as part of a clinical trial, if they were not followed up in the registry since start of their first TNF inhibitor, or if the first biological agent received was not marketed to treat PsA. Clinical response was evaluated using the American College of Rheumatology criteria for 20% improvement (ACR20)/ACR50/ACR70, EULAR response criteria for good response, and the 28-joint count Disease Activity Score (DAS28, remission). Drug survival was assessed by Kaplain-Meier analysis and calculated as the number of days that individual patients continued treatment with the drug, with the stop being the date of the first missed dose.

Among the 1,422 patients included, 49% were female and their median age was 48 years. The median follow up was 2.3 years. When the data was censored, 548 patients (39%) had switched to a second biologic drug, 632 patients (44%) were still receiving the original TNF inhibitor, and 242 (17%) had stopped treatment without starting a new anti-TNF drug. The main reasons for switching were lack of efficacy (57%), and adverse events (28%). Of the 548 who started treatment with a second biologic, 245 patients continued treatment, 189 (34%) switched to a third treatment, and 114 patients stopped without starting a new treatment. Switchers were more frequently women (56%), had a shorter disease duration, had higher HAQ, DAS28, and fatigue and pain scores (on a VAS), and had more swollen and tender joints compared to non-switchers when they started the first TNF inhibitor. The main reason for switching to a third biologic was lack of effect (62% of switchers; n=118). Similarly, 57 of the 189 patients (30%) switched to a fourth biologic drug, and 20 of those 57 patients (35%) switched to a fifth biologic drug. The most common drug sequences were; adalimumab then etanercept (n=155), infliximab then etanercept (n=107), infliximab then adalimumab (n=101), etanercept then adalimumab (n=84), adalimumab then infliximab (n=35), and etanercept then infliximab (n=24).

The median overall drug survival of the first TNF inhibitor was 2.2 years (95% CI; 1.9–2.5 years). Drug survival decreased after switching to 1.3 years (95% CI; 1.0–1.6 years).
years) for the second treatment, and 1.1 years (95% CI; 0.7–1.5 years) for the third treatment. In patients who switched, the median drug survival of the first TNF inhibitor was 0.7 years (95% CI 0.6–0.8 years). The type of TNF inhibitor (current or previous), the reason for withdrawal of the first TNF inhibitor, and age were not statistically significant predictors of drug survival.

The response rates were significantly lower during the second and third treatment courses compared to the first (all p<0.05). During the first treatment course, the proportion of patients in whom an ACR20 response was achieved within 3–6 months was 47%. Corresponding rates during the second and third treatment course were 22% and 18% respectively. Similarly, ACR50 response rates during the first, second, and third treatment courses were 33%, 13% and 6%, respectively. ACR70 response rates were 17%, 5% and 2%, respectively. The proportions of patients who achieved a good response according to EULAR criteria were 45%, 19% and 17%, respectively. DAS28 remission was 43%, 34%, and 22%, respectively. No significant differences between drug-drug combinations were found.

**Norwegian NOR-DMARD registry (2013)**

A longitudinal observational study based on data from the Norwegian NOR-DMARD register evaluated the clinical response and drug survival of a second TNF inhibitor in patients with PsA in regular clinical practice. The study included patients with PsA who were starting their first TNF inhibitor, and identified patients who had switched to a second TNF inhibitor (switchers). Three-month responses and three-year drug-survival were compared between switchers and non-switchers, and within switchers. Clinical response was evaluated using ACR responses (20/50/70), EULAR response and DAS28 remission rates. Drug survival was assessed by Kaplan-Meier analysis. Separate response analyses were performed for patients who discontinued due to adverse events, and those who had an inadequate response.

Among the 439 patients included, 95 (22%) were identified as switchers and the remaining 344 were non-switchers. Patients receiving their second TNF inhibitor had significantly poorer three-month responses compared with non-switchers. Three-month ACR20/50/70 responses were 40.0%, 22.5% and 12.5% for switchers vs. 64.4%, 40.0% and 32.2% for non-switchers; EULAR good response: 20.0% vs. 59.1%, and DAS28 remission: 28.2% vs 54.1%, respectively, all p<0.05). When comparing the first and second course of TNF inhibitor of switchers, there was a trend towards poorer responses to the second TNF inhibitor for all outcome measures, reaching statistical significance for EULAR response and change in DAS28. There was no difference in responses to the second TNF inhibitor between patients who previously discontinued due to adverse events (n=35), and those who discontinued due to an inadequate response (n=49). Drug survival of the second TNF inhibitor was significantly poorer than observed in non-switchers (p<0.001). The estimated three-year drug-survival was 36% for the second TNF inhibitor compared with 71% for non-switchers, and 57% for the first TNF inhibitor overall (switchers plus non-switchers). There was no difference in drug survival of the second TNF inhibitor of switchers between patients who previously discontinued due to adverse events and those who discontinued due to an inadequate response.
North West of England survey (2014)²³

A large regional survey in the North West of England assessed compliance with current NICE guidance with regards to sequential TNF inhibitor use and the effectiveness of switching biologics. The results of this study have only been published in an abstract and as a letter to the editor of the JRCP. The study included patients with PsA who started biologic therapy between August 2007 and June 2012. Data on 548 patients were collected across 18 sites in the region. The median age was 48 years, 51% were female and the median time from diagnosis to starting a TNF inhibitor was 4.6 years. At baseline, 72% were on a concomitant DMARD, of which 84% included methotrexate. The majority of patients received adalimumab (64%) or etanercept (34%) first-line.

At 12-week assessment, 74% of patients had an adequate response to their initial TNF inhibitor (response criteria not defined). However, 17% (n=94) of patients switched to a second-line biologic with a further 3% switching between three to four biologics (n=19). The main reasons for switching to a second biologic were secondary loss of efficacy (44%) or primary non-response (29%), and adverse events (21%). Subsequent lines of biologics included TNF inhibitors, but also treatments not currently licensed for PsA such as rituximab and tocilizumab. Of the switchers, 52% responded to a second line biologic therapy and 8% to third or fourth-line therapy, 19% were non-responders, 19% were intolerant and 2% were awaiting follow up to assess response to switching at the time of the survey. There was considerable variation among PCTs regarding their policy for switching TNF inhibitors in patients with PsA, with some Trusts labelling PsA patients as ‘rheumatoid arthritis with psoriasis’ to allow eligibility for second biologic, as sequential use is approved in RA.

Conti et al. (2007)²⁴

A five-year observational study evaluated the clinical response after switching TNF inhibitors in patients with ankylosing spondylitis (AS) and PsA. In total 589 TNF inhibitor naive patients were registered, of whom seven patients with AS and 15 with PsA received more than one TNF inhibitor. Clinical response was evaluated using PsARC at baseline and every three months. The wash-out period between TNF inhibitors was six weeks.

Ten patients with PsA switched from infliximab to etanercept. After 3 months of etanercept, the proportion of PsARC responders increased from a baseline of 10% before etanercept to 70% (p<0.01). Seven patients with PsA switched from etanercept to adalimumab. After 3 months of adalimumab, the proportion of PsARC responders increased from 14.3% (baseline before adalimumab) to 57.1% (p=NS). Patients who switched because of adverse events and those who changed because of inadequate efficacy (primary or secondary) presented a similar clinical response.

Coates et al. (2008)²⁵

A retrospective analysis of patients with PsA who received biologic drugs through Leeds clinics between 2001 and 2006 examined the response to long-term biologic drugs and the outcome from switching agents. A total of 60 patients with a mean age of 46 years and median disease duration of 16 years were included. Clinical response was evaluated using DAS28.
Overall, 90% (n=54) of patients achieved a significant response to a TNF inhibitor agent, using switching in 20% of cases. When considering only those patients who switched for non-response, four of 10 responded to a second-line agent, and three of six to a third-line agent. Looking at possible predictors of response there were no significant differences between responses to treatment with respect to the biologic used, disease duration (from time of diagnosis) and disease subtype.

**BSRB register (2009)**

An observational study based on data from the BSRBR registry assessed persistence with first and second TNF inhibitor therapy in patients with PsA. The study included a total of 596 biologic naïve PsA patients registered between 2002 and 2006. Persistence data were available for 566 patients (95%). Of these, 316 (55.8%) patients commenced treatment with etanercept, 162 (28.6%) with infliximab and 88 (15.6%) with adalimumab. Treating physicians completed six-monthly follow-up questionnaires detailing changes to anti-TNF therapies. Persistence with treatment was examined using Kaplan–Meier survival analysis.

At baseline, the mean age of all patients was 45.7 years, 53% were female and the mean disease duration was 12.4 years. In total, 422 patients had completed at least 12 months of follow-up, 75.5% of who remained on their first TNF inhibitor while 9.5% discontinued due to inefficacy, 10.0% due to adverse events and 5.0% due to other reasons. Multivariate analyses showed that being female and the presence of baseline co-morbidities were the only significant predictors of overall drug discontinuation. In total, 178 patients switched to a second TNF inhibitor, and in general persistence with the second course of therapy was lower than with the first course. The survivor function on the second TNF inhibitor for switchers was 74% at 12 months, and 64% at two years. However, the numbers were too small to study whether the reason for stopping the first course of therapy could predict outcome on the second agent, or to look at differences between the TNF inhibitors.

**Spanish BIOBADASER registry (2006)**

A four-year observational study based on data from the Spanish BIOBADASER registry examined drug survival in patients with different forms of chronic arthritis who switched TNF inhibitors. Between February 2000 and September 2004, a total of 4,706 patients treated with biologics were registered, of whom 10% had PsA. Of the patients with PsA, 289 started treatment with a TNF inhibitor, of which 55 (19%) discontinued. Fifteen of these patients were started on a second TNF inhibitor of which 8 failed to remain on their treatment at one year (HR 0.81 (85% CI 0.65-0.90).

**Chakraverty et al. (2010)**

A two-year observational study based on data from the US CORRONA registry examined the pattern of TNF inhibitor switching and factors associated with switching in patients with PsA. The study which has only been published in an abstract form included biologic naïve PsA patients who were starting their first TNF inhibitor (etanercept, infliximab or adalimumab).

Of the 139 patients who initiated a TNF inhibitor, 91 (65%) maintained their initial TNF inhibitor for two years, 18 (13%) discontinued, and 30 (22%) switched to another.
biologic. Among those patients who switched the proportion achieving a Modified ACR20 at six and 12 months was 23%, and 29%, respectively. The distribution of maintainers and switchers differed significantly between intravenous (IV) and subcutaneous (SC) TNF inhibitors. In patients receiving IV infliximab, 85% maintained their initial treatment, 9% discontinued and 6% switched treatment compared to 59%, 14% and 27% in patients receiving SC adalimumab or etanercept, respectively (p=0.012).

Haberhauer et al. (2010)²⁹
An observational study of patients with rheumatic disease treated in an Austrian outpatient clinic looked at switching of TNF inhibitors in AS and PsA compared to RA. In total 301 patients were initiated on a TNF inhibitor (AS 46, PsA 63 and RA 192), of which 38% received more than one TNF inhibitor (AS 11, PsA 21 and RA 83). The main reasons for the 21 PsA patients switching to a second TNF inhibitor were secondary loss of efficacy (62%), adverse events (24%) and primary non-response (14%). Although the response criteria were not defined, PsA patients showed the best response rate to the second TNF inhibitor (76% adequate response for PsA vs. 46% in AS and 33% in RA, respectively). Of the three PsA patients who were switched to a third TNF inhibitor, two achieved an adequate response.

RAPID-PsA (2014)³⁰
The RAPID-PsA trial which investigated the safety and efficacy of certolizumab pegol in PsA permitted up to 40% of enrolled patients to have received a previous TNF inhibitor, provided there was a washout period of >3 months before baseline visit (28 days in the case of etanercept). However, it should be noted that the exclusion criteria included treatment with more than one TNF inhibitor, or primary failure of a prior TNF inhibitor according to investigator assessment. The trial was double-blind and placebo-controlled to week 24, dose-blind to week 48, and then open label to week 216. Patients were randomised to receive placebo, certolizumab pegol 200 mg every 2 weeks, or certolizumab pegol 400 mg every 4 weeks. The primary outcome was ACR20 response at week 12.

In total 19% (26 of 136) of patients receiving placebo and 19.8% (54 of 273) treated with certolizumab (combined dose) had received previous TNF inhibitor treatment. Reasons for prior TNF inhibitor withdrawal included secondary failure, adverse events, and other reasons including financial and supply problems. At week 24 for patients who had received a prior TNF inhibitor an ACR20 response was achieved in 59.3% of those treated with certolizumab and 11.5% of placebo treated patients (p<0.001). This was similar to the level of ACR20 response at week 24 for all patients treated with certolizumab, irrespective of prior TNF inhibitor exposure (63.8% and 56.3% in the 200 mg and 400 mg groups, respectively).
Safety

The RCTs for infliximab, adalimumab and golimumab specifically excluded patients who had received prior TNF inhibitors, so these studied provide no safety data specifically relating to the sequential use of biological drugs in the treatment of PsA. In the RCT of etanercept, it is unclear whether or not patients who had failed previous biologics were excluded, so no relevant safety data on sequential use can be extracted. The RAPID-PsA trial of certolizumab pegol includes a cohort of patients who received sequential biologic treatment, but the paper does not differentiate between those who were TNF inhibitor naïve and those with previous exposure to a TNF inhibitor when reporting rates of adverse events (AEs). Therefore the safety data on the sequential use of biologics in PsA is limited to that reported in a few of the biologic registers, observational studies and regional audits covered in this appraisal.

The Danish DANBIO registry study reported that the 5.6% (79 of 1,422) of patients stopped their first TNF inhibitor due to AEs without starting another biologic. The corresponding number who discontinued their second TNF inhibitor and did not start another were 7.1% (39 of 548), and for the third TNF inhibitor were 7.9% (15 of 189). The numbers of patients who experienced an AE and switched treatment were 10.6% (152) for their first biologic, 7.8% (43) for their second and 6.3% (12) for the third. The numbers of patients experiencing an AE whilst receiving the fourth, fifth and sixth treatment course are not reported. Additionally, the paper does not report the nature of the AEs or distinguish between the AEs for individual drugs.

In the NOR-DMARD registry study, 37% (35) of the 95 patients who received a second line TNF inhibitor had switched treatments due to an AE. Of those who switched, 23% (22) experienced an AE to their second TNF inhibitor.

The report of the North West of England survey states that of the 94 patients who received a second line biologic, 3.6% (20) had switched treatments due to an AE. Subsequently, 20% (19) of those who switched had an AE to their second biologic. None of the 18 patients who switched to a third biologic experienced an AE.

The observational study by Coates et al, reported that serious side-effects causing cessation or switching of therapy occurred in 3% (2) of the 60 patients receiving their initial TNF inhibitor. Of the 12 patients receiving a second TNF inhibitor, one patient switched to a third drug due to a skin rash. None of the seven patients who switched to a third TNF inhibitor experienced an AE.

The study based on the BSRBR register looking at the persistence of TNF inhibitors in PsA noted that the survivor function for discontinuing the second TNF inhibitor due to AEs was lower than that for the initial TNF inhibitor (76% vs. 96% at year one and 92% vs. 64% at year two, respectively). For discontinuations due to AEs, the presence of baseline co-morbidities were associated with significantly higher drug discontinuation rates.

Despite the paucity of safety data relating specifically to second- or third-line TNF inhibitors in PsA, it would seem reasonable to assume that their safety profile would be comparable to that observed when a TNF inhibitor is used as a first-line.
Dosage and administration

Adalimumab
Adalimumab is administered by subcutaneous injection. A clinical response is usually achieved within 12 weeks of treatment.\textsuperscript{7} Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Certolizumab Pegol
Certolizumab is administered by subcutaneous injection in combination with methotrexate, or as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.\textsuperscript{8} A clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Etanercept
Etanercept is administered by subcutaneous injection. A clinical response is usually achieved within 12 weeks of treatment.\textsuperscript{9} Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Golimumab
Golimumab is administered by subcutaneous injection, alone or in combination with methotrexate.\textsuperscript{10} A clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Infliximab
Infliximab is administered by intravenous infusion in combination with methotrexate, or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.\textsuperscript{11}

Two biosimilar infliximab products (Inflectra®\textsuperscript{▼} and Remsima®\textsuperscript{▼}) are approved for PsA.\textsuperscript{12,13} The dosing regimen, pharmaceutical form, and strength for both biosimilar products are identical to those of the originator infliximab.

Ustekinumab
Ustekinumab is administered by subcutaneous injection, alone or in combination with methotrexate.\textsuperscript{32} Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.
Cost analysis

All biologic agents licensed for treatment of PsA are specified high-cost drugs and are excluded from the national tariff.

NICE guidance recommends that treatment should normally be started with the least expensive drug (taking into account administration costs, required dose and product price per dose), and this may need to be varied for individual patients because of differences in the method of administration and treatment schedules.19,20

On 1st April 2015, a new Commercial Medicines Unit (CMU) contract started in the NTAG area. Under the CMU contract the price of some products differs substantially from list prices due to locally negotiated procurement discounts (see table 1).33 In addition, the advent of biosimilars is leading to a shift in the market and manufacturers are bringing in more ‘value’ added services such as variations of homecare and additional nursing support etc. A new CMU contract which will included the TNF inhibitors is due to start on the 1st of March 2016, so prices may subsequently change.

The costs given below exclude VAT. Depending on whether these drugs are given in hospital or delivered to home will affect whether they are VAT exempt or not.

**Table 1. Comparative unit costs of biologics licensed for the treatment of PsA.**

<table>
<thead>
<tr>
<th>Product</th>
<th>Pack size</th>
<th>List price per pack</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab PFS</td>
<td>2</td>
<td>£704.28</td>
<td>Some areas (e.g. London have a small discount).</td>
</tr>
<tr>
<td>40mg/0.8mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab pre-filled pen 40mg/0.8mL</td>
<td>2</td>
<td>£704.28</td>
<td></td>
</tr>
<tr>
<td>Certolizumab PFS</td>
<td>2</td>
<td>£715.00</td>
<td>The manufacturer provides the first 12 weeks of treatment free through a PAS.</td>
</tr>
<tr>
<td>200mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept vials</td>
<td>4</td>
<td>£357.50</td>
<td></td>
</tr>
<tr>
<td>25mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept PFS</td>
<td>4</td>
<td>£357.50</td>
<td></td>
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<tr>
<td>25mg/0.5mL</td>
<td></td>
<td></td>
<td>There are some Trust level arrangements and homecare.</td>
</tr>
<tr>
<td>Etanercept PFS</td>
<td>4</td>
<td>£715.00</td>
<td>This price will change if biosimilar etanercept is launched.</td>
</tr>
<tr>
<td>50mg/1mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept pre-filled pen 50 mg/1mL</td>
<td>4</td>
<td>£715.00</td>
<td></td>
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<tr>
<td>Golimumab PFS</td>
<td>1</td>
<td>£762.79</td>
<td>100mg dose is provided at the same cost as the 50mg dose through a PAS.</td>
</tr>
<tr>
<td>50mg/0.5mL</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Golimumab pre-filled pen 50 mg/1mL</td>
<td>1</td>
<td>£762.79</td>
<td></td>
</tr>
<tr>
<td>Golimumab pre-filled pen 100 mg/1mL</td>
<td>1</td>
<td>£1,525.94</td>
<td></td>
</tr>
<tr>
<td>Infliximab (Remicade) vials</td>
<td>1</td>
<td>£419.62</td>
<td></td>
</tr>
<tr>
<td>100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (Inflectra) vials</td>
<td>1</td>
<td>£377.66</td>
<td></td>
</tr>
<tr>
<td>100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab (Remsima) vials</td>
<td>1</td>
<td>£377.66</td>
<td></td>
</tr>
<tr>
<td>100mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab PFS</td>
<td>1</td>
<td>£2,147.00</td>
<td></td>
</tr>
<tr>
<td>45mg/0.5mL</td>
<td></td>
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</tr>
</tbody>
</table>
It has not been possible to reliably estimate the number of PsA patients which might be considered for sequential biologic treatment. However, studies have shown that up to a third of PSA patients may fail on first-line TNF inhibitor therapy due to primary non-response, secondary loss of efficacy, or adverse events.15-17

The estimated average annual treatments costs per PsA patient are shown in table 2. However, the exact cost depends on the duration of treatment, together with the number of patients treated with each product and any differences in dosing, scheduling and administration. The estimated costs given below exclude VAT. Drugs given intravenously are likely to be administered in a hospital setting and therefore VAT will apply.

**Table 2. Estimated average annual treatment cost per patient.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>First year cost per patient (including administration)</th>
<th>Annual maintenance cost per patient (including administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>40 mg every 2 weeks by subcutaneous injection.</td>
<td>£9,156</td>
<td>£9,156</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>400 mg in weeks 0, 2 and 4, then 200 mg every 2 weeks, or 400 mg every 4 weeks by subcutaneous injection.*</td>
<td>£7,150</td>
<td>£9,295</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg twice weekly or 50 mg once weekly by subcutaneous injection.</td>
<td>£9,295</td>
<td>£9,295</td>
</tr>
<tr>
<td>Golimumab</td>
<td>50 mg once monthly, on the same date each month by subcutaneous injection.</td>
<td>£9,156</td>
<td>£9,156</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5 mg/kg in weeks 1, 3 and 7, then every 8 weeks given as an intravenous infusion.**</td>
<td>£13,428 (£17,286)</td>
<td>£10,910 (£14,045)</td>
</tr>
<tr>
<td>Inflectra</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remsima</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>45 mg in weeks 1 and 4, then every 12 weeks by subcutaneous injection. Alternatively, 90 mg may be used if body weight &gt;100kg.</td>
<td>£10,735</td>
<td>£9,304</td>
</tr>
</tbody>
</table>

Doses are taken from the relevant summary of product characteristics.7-13,32 The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

* Cost of treatment for first year includes the starting dose, and minus the first 12 weeks of treatment cost (£3,575), through the PAS.

** Based on a 70 kg adult, and assumed that vial wastage occurs. It assumes  for Inflectra® and Remsima® and the full list price of Remicade® (£419.62). The cost of administration for infliximab is £3,858 in the first year and £3,135 in the subsequent maintenance years. The cost is based on 2015/16 enhanced tariff option. Day case: Inflammatory spine, joint or connective tissue disorders (weighted average of major CC (HD23A), intermediate CC (HD23B) and without CC (HD23C).34

These data are confidential to the NHS and commercially sensitive. Local CCGs should contact NTAG if more detail is required.
Points to consider

Over a third of PSA patients may fail on first-line TNF inhibitor therapy due to inefficacy or adverse events. Ustekinumab is currently the only recommended treatment options for these patients. However, an increasing number of specialists are likely to consider switching to an alternative TNF inhibitor before using ustekinumab.

The evidence to support the sequential use is limited to registry data, observational studies and regional audits. The response rates to sequential treatment varied significantly between these studies, but overall the response rates were significantly lower during second and third treatment courses. However, a significant proportion of patients still achieved significant improvements in disease activity, with ACR20 responses ranging from 22% in the DANBIO study to 53.9% in the RAPID-PsA trial.

The safety data relating to specifically to the sequential use of biological drugs in the treatment of PsA are very limited. One study noted that the survivor function for discontinuing the second TNF inhibitor due to AEs was lower than that for the initial TNF inhibitor. Despite the paucity of data relating specifically to second- or third-line TNF inhibitors in PsA, it would seem reasonable to assume that their safety profile would be comparable to that observed when a TNF inhibitor is used as a first-line. The intravenous route is generally associated with more adverse events and patients and physicians may have a preference for a particular route of administration.

Several TNF inhibitors are licensed for the treatment of PsA. Adalimumab, etanercept, golimumab and certolizumab are administered by SC injection, while infliximab requires IV infusion. NICE recommends selecting the least expensive drug, taking into account administration and drug acquisition costs. The price of some biologics differs substantially from list prices due to locally negotiated procurement discounts and National Patient Access Schemes. The introduction of biosimilars is also leading to a shift in the market and manufacturers are bringing in more ‘value’ added services such as variations of homecare and additional nursing support etc.

The estimated average annual first year cost per PsA patient ranges from £7,150 to £17,286 including administration costs, but excluding vat. The estimated average annual maintenance cost per PsA patient ranges from £8,559 to £14,045 including administration, but excluding VAT. However, the exact cost depends on the duration of treatment, together with the number of patients treated with each product and any differences in dosing, scheduling and administration.

NICE TA199 (2010) concluded that there were insufficient data to make a recommendation on the sequential use of TNF inhibitors in PsA. However, TA340 (2015) noted that the sequential use of TNF inhibitors is established practice in the NHS, and that the NICE commissioning guide on biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology and the published TAs did not preclude sequential use. Both the BSR and EULAR recommend switching to an alternative TNF inhibitor in the case of failure due to inefficacy or AEs, but acknowledge there was insufficient evidence to establish a preference for a particular TNF inhibitor in this situation.
Author’s declaration: The author has no relevant interests to declare.

References


7. Summary Product Characteristics. Humira Pre-filled Pen, Pre-filled Syringe and Vial. Date of revision of text: August 2015.


33. Personal communication. Specialist Procurement Pharmacist (north East and North Cumbria). August 2015.