LMMG New Medicine Recommendation

Use of certolizumab (Cimzia®), adalimumab (Humira®), etanercept (Enbrel®), golimumab (Simponi®) or infliximab (Remicade®) as a second anti-TNF (tumour necrosis factor) in psoriatic arthritis (PsA) following discontinuation of first anti-TNF due to an adverse event or primary or secondary inefficacy .

Recommendation: Red

A second anti-TNF is recommended in patients with PsA, who meet the NICE criteria for the use of an anti-TNF, but who have failed their initial anti-TNF either due to adverse events or primary or secondary inefficacy.

The choice of therapy should be based on the most cost effective preparation; taking into account drug administration costs, required dose, product price per dose (taking into consideration any patient access schemes (PAS) that may be in place from the manufacturers) and the level of evidence available for that particular biologic for use second line.

Treatment should be discontinued if a person's disease does not show an adequate response on the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. Healthcare professionals should also consider continuing treatment if a person's skin disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks in the absence of an adequate PsARC response. This assessment should be done by a dermatologist to determine whether continued treatment is appropriate on the basis of the skin response alone.

Summary of supporting evidence:

- There are no randomised controlled trials (RCTs) looking specifically at the sequential use of anti-TNFs in PsA patients who have stopped their initial anti-TNF due to an adverse event or primary or secondary inefficacy. (Primary inefficacy being where there was never a sufficient response and secondary inefficacy being where there was an initial response but it has subsequently diminished).
- Evidence in support of the sequential use of anti-TNFs is limited to observational studies, information contained in biologics registers and a regional audit.
- The two anti-TNFs with the largest body of evidence when used second line are adalimumab and etanercept, with a limited amount for infliximab, golimumab and certolizumab. The main reason for this is due to the timing when different biologics obtained their product license extensions for PsA. Available evidence does not support the clinical efficacy of one anti-TNF over another when used second line.
- Evidence in support of certolizumab second line is from observational studies and the small cohort of patients from an RCT who had previous exposure to an anti-TNF but had not experienced primary failure.
- There is very little data published for the second line use of golimumab in patients with PsA.

- The response rates, for the recommended Anti-TNFs being used second line, have varied quite significantly between the papers reviewed. These have ranged from 19% when using ACR20 to measure success in the DANBIO study, up to 52% when the criteria to measure an "adequate response" has not been stated (as in the North West retrospective study) and 59.3% when using ACR20 in the RAPID PsA trial.
- A Danish study[4] looked at drug survival of an anti-TNF and found that a first anti-TNF is likely to be used for 2.2 years and a second for 1.3 years. In patients who switch, their first anti-TNF is likely to only be used for 0.7 years. Smaller observational studies support this.
- One of the studies found that drug survival is consistently shorter when the drugs are used as a second treatment; also that the survival of the second anti-TNF was better (p=0.007) if the first one was replaced because of an adverse event.
- NICE guidance dating from 2010[1] states that there is insufficient data to make a recommendation on the sequential use of TNF inhibitors in PsA.
- BSR (British Society of Rheumatology) and BHPR (British Health Professionals in Rheumatology) guidelines[2] as well as EULAR (European League Against Rheumatism) recommendations[3] state that a second anti-TNF should be considered if a patient has had to stop the first, but does not recommend one particular anti-TNF over another when prescribing second line.

Due to the current PAS for certolizumab, this would currently be the least expensive choice of preparation, but only for the first year of treatment, at which point it would be the third least expensive anti-TNF. The body of evidence for certolizumab used second line is smaller than for some of the other anti-TNFs available, this is primarily due to its license extension for use in PsA being granted later than the other available biologics.

Details of Review

Name of medicine Certolizumab pegol (Cimzia®), adalimumab (Humira®), etanercept (Enbrel®), golimumab (Simponi®) infliximab (Remicade®)

Strength(s) and form(s):
Certolizumab pegol – 200 mg prefilled syringe
Adalimumab – 40 mg prefilled pen or prefilled syringe
Etanercept – 25 mg prefilled syringe, 25 mg powder and solvent for injection, 50 mg prefilled pen & prefilled syringe
Golimumab – 50 mg prefilled pen or prefilled syringe.
Infliximab – 100 mg vial

Dose and administration: Certolizumab 400mg s/c at weeks 0, 2 & 4, then 200 mg fortnightly s/c thereafter[5], adalimumab 40 mg s/c fortnightly [6], etanercept 50 mg s/c weekly [7], golimumab 50 mg s/c monthly [8] infliximab 5 mg/kg at 0, 2 & 6 weeks and then every 8 weeks.[9] See individual SPC for alternative doses in specialised populations.

BNF therapeutic class / mode of action: Section 10.1.3, Drugs that suppress the rheumatic disease process; cytokine modulators

Licensed indication(s):

- **Certolizumab –** psoriatic arthritis.[5]
- **Adalimumab –**psoriatic arthritis.[6]
- **Etanercept –**psoriatic arthritis.[7]
- **Golimumab –** psoriatic arthritis.[8]
- **Infliximab** – psoriatic arthritis[9]

Proposed use (if different from, or in addition to, licensed indication above):

The application requests the second line use of certolizumab for patients who have failed their first anti-TNF due to primary or secondary inefficacy. The original request also proposed that if a patient were already taking certolizumab that an alternative anti-TNF could be used second line.

Following a review of the currently available evidence the proposed recommendation is for the use of a second anti-TNF, within its licensed indications, only in patients with psoriatic arthritis in whom the initial anti-TNF was discontinued due to primary or secondary inefficacy, or adverse events, but limited to the following anti-TNFs; etanercept, adalimumab, certolizumab, infliximab and golimumab (as detailed in the medicines recommendation above).

Course and cost:

Certolizumab - £7150 1st year due to patient access scheme, £9295 subsequent years.

Adalimumab - £9156 annually.

Etanercept - £9295 annually.

Golimumab - £9156 annually. *(MIMS Oct 2013)*

Infliximab - £10,910 annually (average as based on patients weight)

Current standard of care/comparator therapies: Currently, a PsA patient who fails anti-TNF therapy due to primary or secondary inefficacy has no further treatment options.

Relevant NICE guidance:

NICE TA199 Etanercept, infliximab & adalimumab for the treatment of psoriatic arthritis.[1]

NICE TA220 Golimumab for the treatment of psoriatic arthritis [10]

NICE TA313 Ustekinumab for treating active psoriatic arthritis (not recommending use).[11]

Background and context

This review has been conducted at the request of the Central, North and East Lancashire Rheumatology Alliance. Currently if a patient being treated for PsA has to discontinue treatment with their first anti-TNF due to primary or secondary inefficacy, they have no further treatment options. It has been requested that the evidence for the use of a second anti-TNF in PsA treatment is reviewed.

The anti-TNFs etanercept, infliximab, adalimumab, certolizumab, golimumab and ustekinumab are all licensed for use in patients with PsA.[5-9] A NICE technology appraisal relating to PsA; TA199, covers the use of etanercept, infliximab, adalimumab[1] & golimumab[10]. It should be noted that NICE TA313 specifically does not recommend ustekinumab for PsA.[11]

NICE TA199 recommends etanercept, infliximab & adalimumab; '*for the treatment of active and progressive psoriatic arthritis, based on specific criteria. Treatment choice should be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose).* [1] The guidance also recommends that '*treatment should be discontinued if people's disease does not show an adequate response on the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. Healthcare professionals should also consider continuing treatment if people's skin disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks in the absence of an adequate PsARC response.'* [1]

Golimumab was covered in a later NICE technology appraisal; TA220[10], which recommends its use if in-line with TA199. In relation to sequential use the guidance states *'The Committee concluded that there were insufficient data to make a recommendation on the sequential use of TNF inhibitors in psoriatic arthritis.'*[1]

Certolizumab was not included in either guidance, as at the times of publication the licensed indications for certolizumab did not include PsA. However, LMMG have reviewed certolizumab and have recommended its use in PsA in-line with the NICE guidance TA199 for first line use.[12]

The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics[2] include the recommendation; *'In the case of failure of an anti-TNF treatment either 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.'*[2] This recommendation is based on open-label studies, registry data as well as consensus of opinion of the multidisciplinary working party set up by the BSR to develop the guidelines.

The European League Against Rheumatism recommendations, for the management of psoriatic arthritis with pharmacological therapies,[3] list five overarching principles and 10 recommendations. Recommendation 9 states; *'In patients who fail to respond adequately to one tumour necrosis*

factor inhibitor, switching to another tumour necrosis factor inhibitor should be considered.[3] The document gives this recommendation a 2b level of evidence rating[3] [Individual cohort study (including low quality RCT; e.g., <80% follow-up)][13], a Grade of recommendation of B[3] [consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies][13] and a level of agreement of 8.9±1.8 mean standard deviations.[3]

Summary of evidence

Summary of efficacy data in proposed use:

The majority of evidence supporting the sequential use of anti-TNFs is derived from a Danish Observational Cohort Study[4], the BSR biologics register[14], smaller observational studies and a regional survey from the North West of England.[15]

1) **Assessment of the evidence for the requested use: certolizumab 2nd line if an alternative anti-TNF has been used first line or certolizumab 1st line followed by an alternative anti-TNF 2nd line:**

None of the published evidence covers certolizumab as the first anti-TNF with an alternative anti-TNF second line, primarily because it has only recently had PsA added to its list of licensed indications.[16] There are some data for patients who have been switched from an alternative anti-TNF to certolizumab.

The RAPID-PsA phase III trial, which assessed the effect of certolizumab in PsA,[17] included 409 people with adult onset of PsA for ≥ 6 months duration. They had to have ≥ 3 tender joints, ≥ 3 swollen joints and either erythrocyte sedimentation rate ≥ 28 mm/h or C-reactive protein > upper limit of normal (7.9 mg/L). The trial permitted up to 40% of patients to have received a previous anti-TNF (with a washout period of >3 months before baseline visit). It should be noted that primary failure of a prior anti-TNF was a reason for exclusion. The trial was double-blind placebo controlled to week 24, dose-blind to week 48 then open label to week 216. Patients received either placebo, certolizumab 200 mg every 2 weeks or certolizumab 400 mg every 4 weeks.[17]

19.1% (26 of 136) of patients treated with placebo and 19.8% (54 of 273) treated with certolizumab (combined dose) had received previous anti-TNF treatment.[17] Reasons for the withdrawal of the prior anti-TNF included secondary failure, adverse events and others; including financial and supply problems. Clinical results suggested a similar level of response for patients treated with certolizumab, irrespective of previous anti-TNF exposure.[17] The primary endpoint was ACR20 response at week 12.

The paper summarises that at week 24 for patients who had received prior anti-TNF therapy, of the 54 patients receiving certolizumab, 59.3% achieved an ACR20 response compared to 11.5% of the 26 placebo treated patients ($p<0.001$). This was similar to the outcomes for all patients who achieved an ACR20 response (regardless of prior anti-TNF exposure) which were; 58.0% in the certolizumab pegol 200 mg every 2 weeks group, 51.9% in the certolizumab pegol 400 mg every 4 weeks group, and 24.3% in the placebo group; ($p<0.001$ for both certolizumab pegol dosage groups compared with placebo).

2) Assessment of the evidence for the proposed recommendation; 2nd line use of any one of the following anti TNFs in PsA; etanercept, infliximab, adalimumab, golimumab and certolizumab:

In one paper, patients on the Danish Nationwide DANBIO register were used to assess clinical response and drug survival for patients with PsA who switched anti-TNFs.[4] Patients included had to have a diagnosis of PsA according to the treating rheumatologist. Patients were excluded if they had only received DMARDS, if they had received a biologic as part of a clinical trial, if they were not followed up in the registry after the start of their first anti-TNF or if the first biologic agent received was not marketed to treat PsA.[4] Of the 1422 patients included after meeting these criteria, 548 patients (39%) received treatment with ≥ 2 different biologic drugs during follow-up. 49% of the 1422 patients included were female, with a median age of 48 years and a median follow up time of 2.3 years. Of the 548 patients who started treatment with a second biologic, 245 (45%) continued treatment, 189 (34%) switched to a third biologic and 114 patients stopped without starting a new treatment.[4] The proportion of patients in whom an ACR20 response was achieved within 3-6 months was 47% for the first treatment course; this dropped substantially for subsequent treatment courses.[4] Corresponding rates during the second and third treatment courses were 22% and 18% respectively. This pattern was repeated for ACR50 and ACR70 (33% & 13% for ACR50 and 17% & 5% for ACR70).[4] The proportion of patients who achieved a good response (according to EULAR criteria) were 45% for first line, 19% for second line and 17% for third line. The DAS28 remission was reported as 43%, 34% and 22% for 1st, 2nd and 3rd line biologics respectively.

None of the patients received certolizumab as their first treatment, as in the timeframe covered it was not licensed for PsA and so these patients would have been excluded. However, 3 patients (less than 1%) did receive it as their second treatment course, 7 patients (approx. 4%) for their third treatment course and 6 patients (7%) for subsequent courses.[4] Of the other anti-TNFs used the most common drug sequences were: adalimumab then etanercept (n=155 patients) infliximab then etanercept (n=107), infliximab then adalimumab (n=101), etanercept then adalimumab (n=84) and etanercept then infliximab (n=24). Golimumab was used first line in only 39 patients (3%) and as a second treatment course in a further 24 patients (4%). In the registry, of those included in the paper, the number of patients who used each biologic as a second line treatment were as follows; etanercept 266, adalimumab 188, infliximab 59, golimumab 24 and certolizumab 3.[4]

The paper looks at predictors of drug survival, and found that the type of anti-TNF (current or previous) and the reason for withdrawal of the first anti-TNF were not statistically significant predictors of drug survival.[4] Drug survival was calculated as the number of days that individual patients continued treatment with the drug, with the stop date being the date of the first missed dose. Temporary treatment gaps of ≤ 3 months (e.g. due to infection or surgery etc.) were permitted. The median overall drug survival of a first anti-TNF was 2.2 years (95% CI 1.9-2.5 years). However, drug survival decreased after switching; 1.3 years (95% CI 1.0-1.6 years) for second treatment and 1.1 years (95% CI 0.7-1.5 years) for third treatment.[4] The median drug survival of the first anti-TNF, in patients who switched, was 0.7 years (95% CI 0.6-0.8 years). When looking at predictors of drug survival it was found that survival of the second biologic was longer in men, in patients with fewer tender joints and in patients with lower fatigue score on a

Visual Analogue Scale (VAS).[4] Differences in disease duration, baseline CRP (C-Reactive Protein), HAQ (Health Assessment Questionnaire), DAS28 (Disease Activity Score in 28 joints), swollen joint count, VAS global score, VAS pain score, use of methotrexate or age were not statistically significant when looking at drug survival.[4]

The effectiveness of switching between biologics in PsA has been looked at through data gathered in a large regional survey in the North West of England[15]. This is relevant as it covers the exact population who would be treated by the request. It should be noted that the results were only published in a letter to the editor of the Journal of the Royal College of Physicians, written by the clinicians requesting approval of sequential use. The study looked at PsA patients who started biologic therapy between August 2007 and June 2012. 548 patients across 18 sites in the region were included; 51% female and a median age of 49 years.[15] The majority of patients were prescribed adalimumab and etanercept first line; 64% and 34% respectively. At 12 week assessment, 74% of patients had an adequate response to their initial anti-TNF and 52% of patients had an adequate response to their second line biologic, however the paper does not define the clinical criteria which were required to be met for a patient having had to be considered an adequate response.[15] Of the 94 patients who switched to a second line biologic, 41 did so because of secondary inefficacy, 27 because of primary inefficacy and the rest either weren't reported or were due to adverse events. From these 94 patients who switched to a second biologic, 46 received adalimumab, 36 etanercept, 6 infliximab, 3 golimumab, 1 certolizumab and 2 rituximab. Primary Care Trusts showed significant variation regarding their policy on switching anti-TNFs leading to some Trusts labelling PsA patients as 'Rheumatoid Arthritis with psoriasis'[15] to enable them to use sequential anti-TNFs as sequential use is approved in RA.

Smaller observational studies support the switching of anti-TNFs in PsA. In a 5 year observational study, looking at the switching of anti-TNFs in ankylosing spondylitis and psoriatic arthritis,[18] 7 patients with AS and 15 with PsA received >1 anti-TNF.[18] 10 patients with PsA switched from infliximab to etanercept. A clinical response was seen in 70% of these patients (from a baseline of 10% before etanercept) after 3 months. 57.1% of the 7 PsA patients (5 as a second anti-TNF and 2 as a third) who switched from etanercept to adalimumab showed a clinical response after 3 months, from a baseline of 14.3% before adalimumab.[18] A clinical response was assessed by PsARC (Psoriatic Arthritis Response Criteria). The study drew the conclusion that failure of a first anti-TNF does not preclude the response to another, irrespective of the reason for switching.[18] However the study did note that due to the sample size and design of the study, larger prospective trials were warranted in order to confirm the observations.[18]

A retrospective analysis of patients with PsA who received biologics through Leeds clinics between 2001 and 2006[19] indicated that when considering those patients who switched anti-TNF due to non-response, 4 out of 10 responded to their second-line agent, and 3 of the six who didn't, went on to respond to a third-line agent.[19] In looking at predictors of response, they found similar rates regardless of disease duration, drug used and subtype of disease.[19] Treatment response was assessed using DAS28 but unfortunately, although the paper states that infliximab, etanercept and adalimumab were used, it doesn't specify which and how many were first and second line choices.[19]

An observational study from the British Society of Rheumatology Biologics Register looked at persistence with anti-TNF therapies in patients with PsA.[14] The study included data for 596 biologically naïve PsA patients between 2002 and 2006. Of these, persistence data was available

for 566 patients.[14] 422 patients completed at least 12 months of follow up; 75.5% of whom remained on their initial anti-TNF, 9.5% discontinued due to inefficacy, 10% due to adverse events and 5.0% due to other reasons.[14] The first line anti-TNFs of the initial 566 patients were etanercept n=316, infliximab n=162 and adalimumab n=88, unfortunately the study does not specify which anti-TNFs were used second line.[14] Of the 178 patients who were switched to a second anti-TNF, it was found that persistence with the second course of therapy was lower than with the first course. However, the study pointed out that the numbers were too small to predict the outcome of the second agent or to look at the differences between the anti-TNFs. The paper states the survivor function on a second anti-TNF for switchers was 74% at 12 months, compared to 82% for a first anti-TNF.[14]

An observational study, predominantly looking at RA, was conducted using the Spanish BIOBADASER registry, between February 2000 and September 2004.[20] 4605 patients were registered of whom 10% had PsA. 488 patients received a second anti-TNF, 15 of these had psoriatic arthritis.[20] The study focuses more on the drug survival in patients with RA, however it does still provide useful information. For example, it states that drug survival is consistently lower when the drugs are used as a second treatment and also that the survival of the second anti-TNF was better (p=0.007) if the first one was replaced because of an adverse event.[20] Although the numbers for psoriatic arthritis patients who switched were small, it is still worthwhile to note that of the 15 patients who started a second anti-TNF, 8 failed to remain on their treatment at one year with the survival stated to be 0.81 (95% CI 0.65-0.90).[20] The paper does not state which drugs were used second line specifically for PsA, but does discuss for all indications that etanercept, infliximab and adalimumab were all used as second line biologics, with the majority being switched from infliximab to etanercept. However, it is not clear for the PsA patients which drugs they were switched from to.[20]

A further observational study, which was not fully published and is only available in abstract form, discussed biologic naïve PsA patients in the US[21] participating in the CORRONA registry. The results found that of the 139 patients, 91 (65%) maintained their initial anti-TNF for the 2 years of follow up, 18 (13%) discontinued and 30 (22%) switched.[21] Among those who switched, the proportion achieving and ACR20 at 6 and 12 months was 23% and 29% respectively.[21] It was commented that the distribution of maintainers and switchers were significantly different between IV anti-TNF and SC anti-TNF treatments. For patients receiving the IV formulation (infliximab) there were 85% maintainers, 9% discontinuers and 6% switchers compared to 59% maintainers, 14% discontinuers and 27% switchers in patients receiving the SC anti-TNF therapy (adalimumab, and etanercept) (p=0.012), the factors associated with this are unknown. [21]

There is an observational study looking at the switching of anti-TNF agents in ankylosing spondylitis and PsA versus rheumatoid arthritis.[22] The numbers of patients who switched in the study were low (38%, 115 of 301 patients who had received an initial anti-TNF)[22] and only 21 of these were PsA patients. However these PsA patients showed the best response rate to the second anti-TNF agent (76% adequate response vs. 46% in AS and 33% in RA).[22] The study stated that survival of anti-TNF agents in patients with PsA (p=0.215) seems to be better than in RA. These results need to interpreted with caution due to the small patient numbers. The study did not specify what an adequate response was, neither did it provide details of which anti-TNFs were used first and second line, but that infliximab, etanercept and adalimumab were the therapies used. [22]

Summary of safety data:

The trials for infliximab, golimumab and adalimumab for gaining their PsA license specifically exclude patients who have received previous anti-TNF therapy, so there is no safety data for sequential use from RCTs for these drugs. The etanercept trial does not state whether or not patients who had failed previous biologics had been excluded, so the safety information of sequential use is not known for this trial. Certolizumab has safety data available from an RCT for patients who have received the drug sequentially from the RAPID-PsA trial[17] (for gaining a license for PsA). It is important to note however, that the paper does not differentiate between those who were anti-TNF naive and those who had previous exposure to anti-TNFs when reporting the rates of adverse events (AEs). It was stated that numbers of AEs and infections were similar between all treatment groups (placebo, certolizumab 200 mg and 400 mg) through to week 24, [17] The most common non-infectious AEs were diarrhoea (3.6% in certolizumab vs. 2.9% placebo) and headache (3.6% certolizumab vs. 1.5% placebo).[17] The most common infectious adverse events were nasopharyngitis (8.7% certolizumab vs. 7.4% placebo) and upper respiratory tract infection (7.8% certolizumab vs. 5.1% placebo). The majority of adverse events were considered by the author to be mild or moderate in severity; no serious adverse event occurred in more than one patient[17]

The Danish paper reports the number of patients who stopped their anti-TNF due to AEs (without starting another biologic) were; for the first anti-TNF 79/1422 (5.6%) and for a second anti-TNF as 39/548 (7.1%). To note, the number who discontinued their third anti-TNF due to an AE and did not start another were 15/189 (7.9%). The numbers of patients who experienced an AE and started another anti-TNF were reported as 152/1422 (10.6%) for their first biologic and 43/548 (7.8%) for their second biologic and for those who started a third biologic 12/189 (6.3%) experienced an AE and started a fourth biologic. But the paper does not distinguish between the AEs for the individual drugs.

The EULAR paper, which recommends sequential use of biologics in PsA, states under safety issues that; treatment of patients with PsA should be tailored according to the current manifestations of the disease (such as peripheral joint, skin, axial, entheseal symptoms or dactylitis), the level of current symptoms, clinical findings and prognostic indicators; but also according to the general clinical status (age, gender, comorbidity, concomitant medications, psychosocial factors). For each treatment, a careful choice must be made, taking into account efficacy, safety and cost issues. The paper states their recommendations (one of which is that a second biologic can be considered for patients who fail to respond their first) are based on a balance of efficacy and safety. The paper supporting the EULAR recommendations summarises for biologics that; “overall, there does not appear to be an increased risk of toxicity specific to patients with PsA, although data may still be insufficient both in terms of numbers of patients and duration of follow-up.”

The other observational studies covered in this review, where second line use of anti-TNFs has taken place, do not refer to any safety issues related to sequential use. One of the papers[2] refers to only 3 (5%) of the patients followed up experiencing serious side effects causing cessation or switching of therapy, but then does not go onto report how this number changed as a result of a second biologic. The paper gathering data from the BSR register, looking at the persistence of anti-TNFs in PsA, discusses drug discontinuations due to AEs in detail for first course of treatment, but the information is lacking for AEs experienced for a second course of treatment.

They noted that the presence of baseline comorbidities and the use of infliximab rather than etanercept were associated with significantly higher drug discontinuation rates. The letter to the editor referring to patients from the North West of the UK states that of the 94 patients prescribed a second biologic 20 (3.6%) switched due to AEs. It then states that for those who switched 19 (20%) had an AE to their second biologic. Of note, the 18 who switched to a third biologic none experienced an AE.[15]

The Health Technology Appraisal 'Etanercept, Infliximab and Adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation'[23] looks at the various RCTs and other studies and the adverse events reported for each drug. It summarises that 32 relevant studies were identified for the evaluation of safety of the three biologics reviewed. From the tables summarising adverse events the rates of serious infection were 0.6%-16.2% for etanercept, 0.8%-13.8% for infliximab and 0.4%-5.1% for adalimumab. In terms of rates of malignancy these were etanercept 1%-5.7%, infliximab 0.16%-5.1% and adalimumab 0.1%-1.1%. The rates of activation of TB were etanercept 0%-1.4%, infliximab 0.06%-4.6%and adalimumab 0%-0.4%.[23] It is important to note, as the appraisal does, that the adverse event data are derived primarily from patients with RA or other indications. The generalisability of these findings to patients with PsA remains unclear.[23]

For all the anti-TNFs, despite the lack of evidence relating to safety in second line use for PsA, it is reasonable to conclude that their safety profile would be similar to that seen when used as a first line agent. It is important however, to continue to check individual Summary Product Characteristics for specific adverse events relating to the anti-TNF in question.

Strengths and limitations of the evidence:

- Certolizumab has been requested as the anti-TNF of choice for second line use, however, most of the evidence available currently relates to the anti-TNFs adalimumab and etanercept. The number of patients who received certolizumab, golimumab and infliximab second line in the evidence reviewed is small and should therefore be interpreted with caution.
- There are no randomised controlled trials looking specifically at sequential use of anti-TNFs in psoriatic arthritis patients who have stopped the initial anti-TNF due to primary or secondary inefficacy.
- The evidence available is from observational studies and a small cohort of patients from an RCT who had previous exposure to an anti-TNF (patients who had experienced primary failure to their first anti-TNF were excluded).
- BSR and BHPR guidelines[2] as well as EULAR[3] recommend that a second anti-TNF should be considered if a patient has had to stop their first. However, this is solely based on observational studies and expert opinion.
- No safety data was found relating specifically to the use of a second line biologic; however it would be reasonable to suggest that adverse events would be similar to when a biologic is used first line.
- Several of the studies did not define the outcomes they were using to measure treatment success, and so it is difficult to ascertain whether these were true treatment successes as defined by NICE. In studies which did specify the measures used to define treatment success different studies used different criteria, for this reason it is difficult to quantify the

response rates which can be expected using the NICE recommended PsARC for treatment continuation.

- There are no head to head trials assessing the efficacy of the different biologics in second line use and most studies did not distinguish between the different anti-TNFs.
- Many of the observational studies discussed include only very small numbers of patients with PsA, so individual results should be interpreted with caution.
- All of the studies had small numbers of patients using second line biologics in PsA however, collectively, biologics have been used second line in a number of patients and have demonstrated efficacy, particularly for adalimumab and etanercept.

Summary of evidence on cost effectiveness:

Published evidence on the cost effectiveness of sequential use of anti-TNFs to treat psoriatic arthritis is limited. A Health Technology Appraisal 'Etanercept, Infliximab and Adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation'[23] dating from 2011 and based on evidence collected up until June 2009 does cover it briefly stating:

> '*The second-line use of biologics was explored in a sensitivity analysis. As these results are based on non-randomised comparisons they should be considered with caution. For patients with PsA and mild-to-moderate psoriasis who have failed adalimumab or infliximab as first-line therapy for either adverse events or inefficacy, the ICER (incremental cost effectiveness ratio) for etanercept is <£20,000 per QALY (quality adjusted life years). For patients who have failed etanercept as first-line therapy for either adverse events or inefficacy, the ICER for adalimumab is <£20,000 per QALY and the ICER for infliximab is <£30,000 per QALY.*'[23]

Certolizumab was not included in the TA as its licence was not extended to PsA until after publication.

Prescribing and risk management issues:

The sequential use of anti-TNFs present no additional prescribing or risk management issues to those detailed elsewhere for the use of an initial anti-TNF.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per year (ex VAT)
Certolizumab	400 mg at 0, 2 & 4 weeks then 200 mg every 2 weeks	200 mg/mL 2 x 1 ml syringe = £715	£10 725 1st year (patient access scheme, 1st 12 weeks free which means £7150 cost in 1st year), £9295 subsequent years.
Adalimumab	40 mg Fortnightly	40 mg/0.8mL 2=£704.28	£9156
Etanercept	50 mg Weekly	4 x 50 mg = £715	£9295
Golimumab	5 0mg Monthly	1 x 50 mg prefilled pen/syringe £762.97	£9156
Infliximab	5 mg/kg; administered at weeks 0, 2 and 6, then every 8 weeks. This means that in the first year the number of administrations is eight, and then it alternates between seven and six in subsequent years. The annual cost is based on four vials* used per patient for an average 6.5 administrations, and includes wastage.[24]	1x100mg vial =£419.62	£10910
Costs based on MIMS list prices as of October 2013. This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

There is currently a patient access scheme available for certolizumab meaning that the manufacturer pays for the first 12 weeks of treatment. Treatment is only continued beyond the 12 weeks if the patient is showing a response.
A patient access scheme is also currently in place for golimumab, ensuring that even if a patient requires the 100 mg strength rather than the 50 mg strength, the same price is paid.
It is unknown whether there are other discounts available for the alternative biologics.

Productivity, service delivery, implementation:

Patients that would previously have ceased treatment would be able to receive further anti-TNF therapy. This would mean more patients staying in the service and requiring appointments. However the numbers across Lancashire annually are not likely to be huge so little impact on productivity, service delivery or implementation are anticipated.

Anticipated patient numbers and net budget impact:

The NICE costing statement estimates 1248 people respond to and continue therapy with anti-TNFs in the treatment of PsA each year nationally.[24] Assuming a response rate of 60% a further 832 patients will be initiated on an anti-TNF and not respond to therapy stopping treatment at 12 weeks. Thus, a total of 2080 patients nationally will be initiated on an anti-TNF for psoriatic arthritis each year.

Assuming an England population of 53.5 million the estimated number of patients in Lancashire to respond to and continue therapy with anti-TNFs is 35 patients. The estimated number of patients to be initiated on an anti-TNF who are primary non responders or discontinue due to adverse events to therapy is 24. Therefore the total number of patients being initiated on an anti-TNF each year in Lancashire for psoriatic arthritis is 59.

The application states that they expect 15 to 20 patients per year will be initiated on a second anti-TNF across the Lancashire Health Economy, which closely corresponds to the NICE estimate of non-responders (which only includes primary non-responders and those discontinuing due to adverse events). It is anticipated that this estimate could be lower than the actual numbers of patients requiring second line treatment when secondary non responders are taken into consideration. It should be noted the number will be higher in the first year of approval as there will be a cohort of patients who have previously failed a first line anti-TNF.

Patients achieving ACR20 on a second anti-TNF ranged from approximately 22% in the Danish trial,[4] to an overall figure of 51-58% in the RAPID-PsA trial.[17] This equates to between 5 and 14 patients a year failing their initial anti-TNF but responding to their second.

Certolizumab has an annual cost of £9,295. However, upon initiation, a patient access scheme funds the first 12 weeks (10 doses) at a cost of £3,575 meaning the first year cost per patient is £7150. If certolizumab was used as the second anti-TNF, only successful patients would be charged. Drug survival for a second anti-TNF according to the Danish study is 1.3 years,[4] due to the patient access scheme this would equate to a cost of £9,939 for each patient who responds to treatment a total treatment course cost of £49,692 - £139,139 for the estimated numbers in Lancashire.

If the alternative anti-TNFs were used second-line (adalimumab, etanercept, infliximab or golimumab) the cost of 1.3 years treatment (based on average drug survival[4]) would be £11,903 - £14,183 per patient. For the estimated 5 to 14 patients per year who would respond to treatment in Lancashire this would be £59,514 - £198,562 dependent upon which anti-TNF is used.

The total cost of allowing the anticipated 24 non-responders to receive a second anti-TNF treatment for the average 1.3 years[4] would be £49,692 - £198,562 depending how many patients responded to treatment and which anti-TNF was used first and second line.

Innovation, need, equity:

Currently, should a patient with Psoriatic Arthritis need to cease treatment with their initial anti-TNF this is the end of the treatment pathway. This medicines recommendation gives patients access to an additional step on the treatment pathway.

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Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR
Tel: 01772 644 400 | www.midlandsandlancashirecsu.nhs.uk