Considerations for Commissioners

Biologic and targeted-synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs)

For the treatment of refractory rheumatoid arthritis

Commissioning guidance:

Commissioners may wish to consider the following points relating to the use of bDMARDs and tsDMARDs in patients with rheumatoid arthritis (RA) refractory to prior treatment with tumour necrosis factor-α inhibitors (TNFi) and non-TNFi bDMARDs:

- It was the opinion of the MTRAC committee that a process should be put in place to enable timely access to treatment with bDMARDs and tsDMARDs in patients who need sequential bDMARD treatment. This view is based on specialist advice and opinion from two local Rheumatology centres.
- The published evidence is very limited, but clinical experience suggests benefits in terms of continued improvements and reduced admissions for RA flares for patients receiving fourth/fifth-line bDMARDs or tsDMARDs.
- The choice of therapeutic agent in people with RA is a highly individualized one, and dictated by a range of factors. These can include prior medical history (e.g. Rheumatoid factor status, history of tuberculosis, solid tumour, demyelinating disease), and previous bDMARD history (i.e. adverse effects, lack or loss of efficacy), the patient preference regarding mode and frequency of administration and other health-related quality of life concerns, and other comorbid conditions (e.g. ulcerative colitis), needle phobia, and pregnancy.

Strength of the evidence for efficacy

The strength of the evidence for efficacy in this latter part of the treatment pathway is extremely weak. Data from subsets of participants in three randomised controlled trials has shown numerically greater ACR20 responses* with active treatment *vs*. placebo, but given the very low participant numbers in these groups, the statistical significance of differences between treatment groups is unclear. The Regional Medicines Optimisation Committees (RMOCs) are also considering this area of therapy. A recent newsletter[1] stated "this is a difficult area with a limited evidence base. Limited sequential use of biologics has been covered to varying degrees in NICE guidance although no definitive answer reached due mainly to the lack of evidence."

**proportion of patients showing a 20% or more improvement in tender and swollen joint counts and in 3/5 other criteria: pain, disability, CRP, patient and physician global assessment*

MTRAC considered the commissioning of sequential RA drugs at the request of local commissioners. The guidance will be reviewed after publication of the Regional Medicines Optimisation opinion on the sequencing of biologics.

Description of technology

There are ten bDMARDs licensed for the treatment of RA in the UK. Five are tumour necrosis factor-α inhibitors (TNFis: adalimumab, certolizumab pegol, golimumab, infliximab and etanercept) with biosimilars of three of them (infliximab, etanercept, and adalimumab) also available. Other biologics inhibit interleukins (IL-1: anakinra *[not recommended by NICE except as part of a clinical trial]*; IL-6: tocilizumab and sarilumab), or proliferation of B and T lymphocytes (rituximab and abatacept; a biosimilar of rituximab is also available). All the bDMARDs are administered by injection (intravenous infusion [i.v.], or subcutaneously via syringe or pre-filled pen).

Two tsDMARDs were launched in the UK in 2018. These are janus kinase inhibitors (JAK: tofacitinib and baricitinib), taken as a once or twice daily tablet.

The licensed indications vary across the bDMARDs and tsDMARDs, but all are licensed for use in combination with methotrexate (MTX) in moderate to severe RA when response to conventional DMARDs (csDMARDS, including MTX) is inadequate. Other indications are for use in:

- severe, active and progressive RA in adults not previously treated with MTX (TNFis, abatacept, tocilizumab, and sarilumab),
- as monotherapy where there is intolerance to MTX (adalimumab, etanercept, certolizumab pegol, sarilumab, tocilizumab, baricitinib, and tofacitinib)
- in combination with MTX for moderate to severe RA when response to bDMARDs is inadequate (abatacept, sarilumab, rituximab, tocilizumab, baricitinib, and tofacitinib).

For full details of all products available, see the individual Summaries of Product Characteristics.

Background

RA is a chronic, systemic, autoimmune disorder characterised by synovitis of small and large joints causing swelling, stiffness, pain, and joint destruction[2]. It is best considered as a clinical syndrome with several disease subsets, with different inflammatory cascades leading to synovitis[3]. The disease is progressive and leads to physical disability, but early treatment can delay progression and minimise joint damage[4 5]. RA is also associated with a number of complications and comorbidities such as an increased risk of cardiovascular disease[6], lung disease[7], osteoporosis, anaemia, and infection[8].

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The current treatment paradigm for RA aims to identify and treat patients promptly; research has shown that treatment within three months of onset of the disease (the window of opportunity) can delay progression and minimise joint damage[4]. The treat-to-target strategy detailed in the NICE guideline on the management of rheumatoid arthritis in adults[9] aims to achieve remission or low disease activity (if remission cannot be achieved) through sequential use of conventional DMARDs, then bDMARDS and/or tsDMARDs according to patient need. Regular review at 4-6 week intervals assesses progress against the target and prompts adjustment of the dose or choice of medication as appropriate. The csDMARD methotrexate with or without a bridging glucocorticoid is the first-line treatment, or hydroxychloroquine, sulfasalazine or leflunomide. Following disease progression or an inadequate response to csDMARDs, a second csDMARD can be added in combination, or the use of bDMARD or tsDMARD therapy may be considered. This guidance focusses on later treatment options after failure of TNFi and non-TNFi bDMARD treatment.

Clinical evidence for efficacy and safety

This review included systematic reviews, meta-analyses and phase 3 RCTs that evaluated treatment in people with RA refractory to at least three bDMARDs including TNFi and non-TNFi bDMARDs. Prior treatments were clearly stated in the baseline characteristics, and subgroup analyses were reported that evaluated differences in the results according to the number of bDMARDs already received.

One systematic review[10] evaluated treatment in people with refractory rheumatoid arthritis after failure of bDMARD treatment. Twelve trials were included in the review, eleven evaluated treatment after failure of only one bDMARD and the twelfth included a small subset of participants with multiple bDMARD failures (RADIATE trial, discussed further below). The review concluded that later bDMARD treatment was associated with clinically meaningful and statistically significant benefits (American College of Rheumatology 50% improvement threshold [ACR50: proportion of patients showing a 50% or more improvement in tender and swollen joint counts and in 3/5 other criteria: pain, disability, CRP, patient and physician global assessment)], Health Assessment Questionnaire [HAQ], remission) compared with placebo or csDMARDs in people with RA previously unsuccessfully treated with biologics[10].

Three recently published randomised controlled trials (RCTs) were identified that included some patients at this stage of the treatment pathway. The RCTs compared tocilizumab (RADIATE)[11], tofacitinib (ORAL Step)[12] or baricitinib (RA-BEACON)[13 14] with placebo in people with moderate to severe active RA despite treatment with MTX and at least one bDMARD.

The RCTs included participants with moderate to severe RA according to American College of Rheumatology criteria (>6/68 tender or painful joints, >6/66 swollen joints) and biomarkers for active disease (erythrocyte sedimentation rate [ESR] > 28mm/h or C-reactive protein [CRP] > 66.67 mmol/L (7 mg/L). Participants had a previous inadequate response or unacceptable side effects on one or more TNFi [11 12], or other bDMARD treatment[13 14]. The main outcome measure in all the trials was the American College of Rheumatology ACR20 response rate.

The RADIATE trial (n = 499)[11] compared i.v. tocilizumab 4 or 8 mg/kg every four weeks with i.v. placebo (plus stable MTX 10 to 25 mg weekly) for 24 weeks. Across all participants, both the 8 mg/kg (50.0%) and 4 mg/kg (30.4%) dose groups showed significantly greater ACR20 responses compared with control (10.1%; p<0.001). In people with three previous TNFi treatments, ACR20 responses were 53.8% (14/26), 22.2% (4/18) and 5.6% (1/18) in the tocilizumab 8 mg/kg, 4 mg/kg and placebo groups, respectively, although participant numbers were small in this subset. There was no data on this subset of participants for the reported HAQ or DAS outcome data.

The RA-BEACON trial (n = 527) [13 14] compared baricitinib 2mg or 4 mg oral tablets once daily with placebo over 24 weeks; 27% of participants in this trial had received unsuccessful treatment with three or more bDMARDs and 38% of participants had received at least one non-TNFi bDMARD. The primary outcome, measured after 12 weeks, showed an ACR20 response rate of 55% among participants who received baricitinib 4 mg, compared with 27% of placebo-treated participants (p < 0.001). Participants receiving baricitinib 4 mg also had significant improvements in two of the major secondary measures (the DAS28-CRP and the HAQ-DI score) at week 12 as compared with placebo (p < 0.001 for both comparisons). Subgroup analyses showed little evidence of a heterogeneous treatment effect according to the number of prior biologic DMARDs (<3 *vs.* ≥3), the number of prior TNFi among participants who had received only TNFi-bDMARDs (1 *vs*. >1), or the number of prior bDMARDs that were not TNFi (0 *vs*. ≥1).

The ORAL Step trial (n = 399) [12] compared tofacitinib 5 or 10 mg oral tablet twice daily with placebo over a 6-month period (participants randomised to placebo in first three months were re-randomised to tofacitinib 5 or 10 mg twice daily for a further 3 months). The baseline characteristics showed that 8% of trial participants (32 people) had failed treatment with three or more TNF-inhibitors and 12% of participants (46 people) had received a previous non-TNFi bDMARD (abatacept, rituximab or tocilizumab). In the whole trial population, ACR20 response rates for tofacitinib 5 and 10 mg twice daily were 41.7% (55/132; p=0·0024) and 48·1% (64/133; p<0·0001), respectively, versus placebo, 24·4% (32/131). In participants previously treated with at least three TNFi (data from supplementary appendix), the ACR20 response rate was 22.2% (2/9) in placebo-treated participants, 36.4% (4/11) for tofacitinib 5 mg twice daily treatment and 41.7% (5/12) for tofacitinib 10 mg twice daily. The authors commented that the efficacy of tofacitinib appeared to be lower in the participants receiving at least three TNFis compared with participants treated with one or two TNFi, with the caveat

that very low participant numbers were involved in this subgroup analysis. There was no further information on remission or quality of life for this subset of the participants.

Adverse events

A 2017 systematic review[15] of the safety of DMARDs found that people treated with bDMARDs (both TNFi and non-TNFi) have an increased risk of serious infections, compared with patients on csDMARDs, and that in general there are no differences across bDMARDs. The review included 26 trials, of which 15 focussed on infections, 4 on malignancies, 1 on mortality, 4 on cardiovascular events and 2 on interstitial lung disease. The results of the trials were heterogeneous and meta-analyses were not possible, so results were presented descriptively. None of the trials in the review evaluated biosimilar bDMARDs or JAK inhibitors. The review reported that there is an increased risk of tuberculosis with TNFis, whereas this has not been studied well for non-TNFis. The bDMARD safety guidance from the British Society for Rheumatology[16] advises that until more data are available, the advice given for anti-TNF therapy should be considered.

There does not appear to be an increased risk of herpes zoster with bDMARDs, but viral reactivation (e.g. herpes zoster and herpes simplex) was seen with both tsDMARDs, baricitinib and tofacitinib. Both drugs were also associated with a significant increase in lipid levels during the first few months of treatment.[17]

Based on the results of one study, bDMARDs are not associated with an increased risk of malignancy, with the potential exception of melanoma[15]. The BSR guidance advises, however, that biologic therapies should not be started in patients with clinical signs of, or under investigation for, malignancy (basal cell carcinoma excluded).

Considerations for cost impact

From 2017/18 QOF (quality and outcomes framework) data[18] there were 356,372 patients in England listed on RA registers, giving an overall prevalence of RA of 0.75% in adults over 16. In the Midlands and East of England region there were 115,805 patients with RA recorded in QOF disease registers, giving a slightly higher prevalence of 0.8% than nationally.

The list prices of these products (original and biosimilar versions) are shown online at MIMs (accessed March 2019). Prices paid by the NHS differ from the list, resulting from Patient Access schemes agreed with NICE and commercial arrangements with NHS England. These prices are 'Commercial in Confidence', and not available to the reviewers.

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