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Guidelines

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The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics

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Background

PsA is a chronic inflammatory arthropathy affecting up to 40% of patients with skin or nail psoriasis. It is considered a type of seronegative SpA and can cause arthritis, enthesitis, dactylitis and axial inflammation. The use of anti-TNF therapy for the treatment of inflammatory arthritis, including PsA, has revolutionized therapeutic options in rheumatology. The last British Society of Rheumatology (BSR) guidelines for the treatment of PsA were published in 2005 when anti-TNF therapy was not widely available. At that time, only one of the anti-TNF therapies was licensed for the treatment of PsA. Since then, use in PsA has become more widespread, with multiple anti-TNF drugs licensed for the treatment of PsA and approved for therapy by the National Institute for Health and Clinical Excellence (NICE).

However, despite these advances, there are still patients who do not respond to treatment with anti-TNF therapies and there are difficult clinical situations where the risks of such drugs may outweigh the benefits of therapy. For this reason, it was felt that further guidance was required.

Need for updating of guidelines

The previous guidelines for the use of anti-TNF therapies in PsA were published in 2005 [1]. At that time, only one

GUIDELINES

NICE has accredited the process used by the BSR to produce its treatment of psoriatic arthritis with biologics guidance. Accreditation is valid for 5 years from 10 June 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation. For full details on our accreditation visit: www.nice.org.uk/accreditation.

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compound was licensed for use in active PsA in the UK (etanercept), and only one other anti-TNF therapy had evidence for efficacy in PsA (infliximab). There are now four anti-TNF drugs with proven efficacy in PsA and a number of novel compounds in development and undergoing clinical trials that may provide future therapeutic options. There are also accumulating data from longer-term use of these therapies to provide further evidence-based recommendations for treatment choices, monitoring and safety.

Objectives

These guidelines offer systematic and evidence-based recommendations for the prescription of anti-TNF therapies in adult PsA patients to support UK clinicians in their use. The guidelines cover adult patients with PsA affecting all domains of psoriatic disease. They provide a stepwise management plan giving clear advice on treatment, including inclusion/exclusion criteria for treatment, monitoring requirements and how to quantify response to biologics. They provide evidence-based advice for the use of anti-TNF therapies in difficult situations, including pregnancy and significant comorbidities. A review on the use of conventional DMARDs prior to the use of anti-TNF therapies was not undertaken.

These guidelines do not include

(i) Biologic therapies for juvenile idiopathic arthritis.
(ii) Biologic therapies for patients with psoriatic disease confined to the skin.

Target audience

The guidelines have been developed to provide assistance to rheumatologists and other clinicians involved in the prescription of anti-TNF therapies for psoriatic disease. They will also assist specialist nurses and allied health professionals (AHPs) in the application, assessment and monitoring of treatment. The guidelines have been drawn from the evidence base available following a systematic literature review up to July 2011. In areas of insufficient evidence, consensus opinion has been provided and this is clearly documented.

Stakeholder involvement

The guidelines have been developed by a multidisciplinary working party set up by the British Society for Rheumatology (BSR), including rheumatologists, a dermatologist, specialist nurses and a patient representative. Any conflicts of interest among the working party were fully declared. Details of members of this working party and their declared conflicts of interest are included at the end of this article. The guidelines were presented for comment at the BSR Annual Meetings in 2011 and 2012 and were available for open consultation on the BSR website in July 2012 prior to submission for publication. Opinions of key stakeholders, including members of the BSR, British Health Professionals in Rheumatology (BHPR) and Primary Care Rheumatology (PCR) as well as patient members of the Psoriasis and Psoriatic Arthritis Alliance (PAPAA), were also sought.

Rigour of development

Literature review

The evidence used to develop these guidelines was compiled from a systematic and comprehensive literature search, including electronic bibliographic databases (Medline and Embase) and systematic review databases (Cochrane) up to 1 July 2011. Key terms for the search were the following: MeSH terms arthritis, psoriatic, psoriatic arthritis, psoriasis and arthritis or oligoarthritis in combination (independently) with biologic therapy, biologics or any biologic therapy drug name. Inclusion criteria for review were clinical outcomes in adults with PsA, published in English. All titles and abstracts were screened and full papers of relevant material were obtained. Reviews of these articles were conducted to establish current evidence for the following topics: efficacy of anti-TNF therapy, safety of anti-TNF therapy, use of concomitant DMARDs, switching to alternative TNF therapies, use of alternative dosing or routes of administration, use in difficult situations (pregnancy, surgery, hepatitis and HIV infection), optimal outcome measures for assessment of response and future biologic non-TNF therapies in development. These key questions were agreed by the working group prior to the literature search. More recent key publications were also included by members of the working group in rapidly evolving research areas to ensure that the guidelines were relevant at the time of publication.

In relation to efficacy, only randomized controlled trials (RCTs) of high quality were included for peripheral arthritis, whereas in other areas, given the paucity of published data, all data were included. Data from relevant articles were extracted using standardized literature evaluation forms in order to summarize evidence. Evidence on safety was extracted from systematic reviews [2–4] and evidence-based guidelines for related diseases (e.g. RA and psoriasis) published prior to 2011. The systematic literature review identified all relevant articles published after those dates to ensure that no new safety issues were overlooked. Evidence for all aspects of the guidelines was limited to articles published in peer-reviewed medical journals.

Level of evidence

The literature was reviewed and the quality of evidence was graded by the working party according to the Royal College of Physicians' Concise Guidance to Good Practice. Grading of recommendations was as follows:

(i) Grade A: meta-analysis of RCTs or an RCT.
(ii) Grade B: controlled trial or quasi-experimental study or descriptive study.
(iii) Grade C: expert committee recommendation.

Consensus agreement

Following evaluation of the literature as detailed above, draft guidelines were developed by the working party for

presentation at the BSR Annual Meeting in 2011 and 2012. Comments from the wider rheumatology community were invited via the BSR website and were incorporated into later drafts. Final draft guidelines were circulated to all members of the working party for a vote on levels of agreement with each recommendation. Voting was performed anonymously, with possible levels of agreement ranging from 0 (total disagreement) to 10 (total agreement). Results of this vote are included with each specific recommendation.

Implications of guidelines

An audit of patients with PsA was performed to examine how the implementation of these guidelines may impact on patient care and may alter prescribing of biologic therapies. Results of this audit are found after the specific guidelines. A detailed cost-effectiveness analysis was beyond the scope of these guidelines. It is recognized that there may be financial barriers to the implementation of these guidelines.

Review using the AGREE instrument

The AGREE instrument was developed by an international collaboration of researchers and policymakers who seek to improve the quality and effectiveness of clinical practice guidelines. The instrument was used to assess and evaluate these guidelines to lend robustness to the process. Following the development of draft guidelines, these were circulated to four independent reviewers who used the AGREE instrument to assess the quality of the proposed guidelines. The reviewers constituted rheumatologists and dermatologists with a special interest in psoriasis and PsA. Each of the six domains within the AGREE instrument (scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence) was assessed separately. Results can be found at the end of the document.

Results

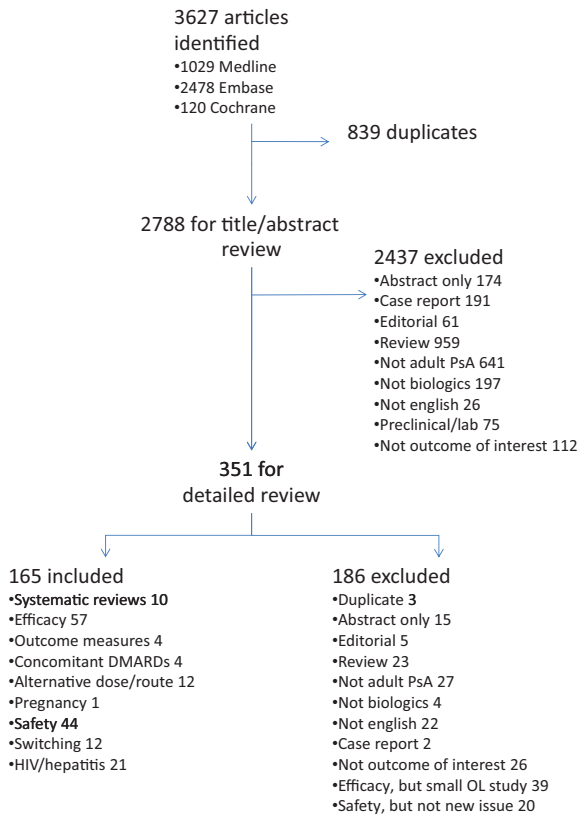
A total of 3627 articles were identified during the literature search in the Medline, Embase and Cochrane databases. Of these, 840 duplicates were excluded, leaving 2787 for further review. By reviewing titles and abstracts, a further 2436 were excluded, leaving a total of 351 articles for review. A detailed flow chart summarizing the systematic review is shown in Fig. 1. There were 20 articles describing the results of nine RCTs that were used to assess efficacy in peripheral joint disease.

Guidelines

New treatment algorithm

Management of PsA is aimed at suppressing inflammation in all domains of the disease, including joints, tendons, entheses and skin involvement. Current practice is aimed at early diagnosis and intervention with DMARDs and anti-TNF therapies to suppress persistent inflammation and improve outcome. Optimal management of all of the domains

Fig. 1 Systematic literature review.



of psoriatic disease is a challenge in the treatment of PsA and will require collaboration between rheumatology and dermatology departments in many cases. In patients with significant joint and skin/nail disease, it is recommended that these departments should work together in either combined clinics or with close collaboration to provide optimal management. Patients with extensive skin psoriasis should be referred to a dermatologist, as they may qualify for biologics for skin involvement alone. Ideally therapies that can address both skin and joint disease should be used in these patients rather than using multiple different drugs [5]. Response to such therapies must be considered in terms of both skin and joint disease when deciding whether to continue with these interventions. See Fig. 2 for the new treatment algorithm.

Treatment of peripheral arthritis (polyarticular disease)

The majority of clinical trials in PsA have focused on treatment of peripheral arthritis in polyarticular disease. A summary of results from RCTs of anti-TNF therapies in PsA is shown in Table 1. The eligibility criteria for entry into the majority of these trials were three or more tender joints and three or more swollen joints, although the trials show far higher median or mean joint counts than the minimum required. Most trials of anti-TNF therapies also required patients to have failed a therapeutic trial of NSAIDs and/or DMARDs to qualify for inclusion. An adequate therapeutic trial of a DMARD is usually defined as failure to tolerate a

Fig. 2 Treatment algorithm for anti-TNF therapy in PsA.

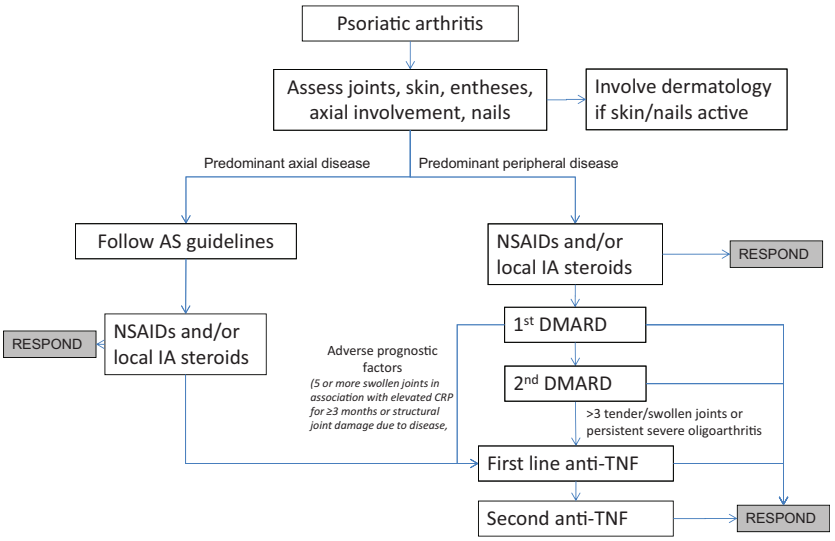


Table 1 Summary of anti-TNF therapy RCTs in peripheral PsA

Drug	*n*	Inclusion	Baseline TJC	Baseline SJC	PsARC, %	ACR20, %	ACR50, %	ACR70, %
Adalimumab 40 mg eow [18]	100	⩾3 TJC and ⩾3 SJC	25.3	18.2	51	39	25	14
Adalimumab 40 mg eow [16]	313	⩾3 TJC and ⩾3 SJC	23.9	14.3	62	52	36	20
Etanercept 25 mg biw [117]	60	⩾3 TJC and ⩾3 SJC	20 (median)	14 (median)	87	73	50	13
Etanercept 25 mg biw [118]	205	⩾3 TJC and ⩾3 SJC	20.4	15.9	72	59	38	11
Golimumab 50/100 mg monthly [19]	405	⩾3 TJC and ⩾3 SJC	22.5	12	73/72	51/45	30/28	12/17
Infliximab 5 mg/kg 8 weekly [21]	104	⩾5 TJC and ⩾5 SJC	23.7	14.6	75	65	46	29
Infliximab 5 mg/kg 8 weekly [20]	200	⩾5 TJC and ⩾5 SJC	24.6	13.9	77	58	36	15

eow: every other week; biw: biweekly; TJC: tender joint count; SJC: swollen joint count.

drug or active disease despite treatment of at least 12 weeks with a target therapeutic dose.

Unfortunately, very little good quality evidence is available to support the use of most synthetic DMARDs in PsA as few RCTs assessing synthetic DMARDs are available. Modest efficacy has been shown for SSZ [6] and LEF [7], with conflicting evidence concerning MTX [8]. A full assessment of evidence for DMARD effectiveness was beyond the scope of these guidelines, which focus on biologic treatments. There is also little evidence to base a judgement on how many DMARDs should be failed before considering biologic therapy. Most anti-TNF trials included patients who were DMARD naïve, those who had failed just one DMARD or those who had failed multiple DMARDs, with little evidence to compare outcome based on previous DMARD stratification. To date, there is only one open-label trial comparing outcomes of MTX-naïve patients starting MTX or anti-TNF therapy [9]. DMARDs are widely used in clinical practice for the treatment of PsA in the UK and anecdotal and observational data support their use. In light of the paucity of evidence, the consensus opinion of the guideline group was that in most cases patients should have had adequate therapeutic trials of two standard DMARDs (either sequentially or in combination) prior to the prescription of biologic therapies. An adequate therapeutic trial is defined either as failure to tolerate a DMARD or active disease despite treatment of at least 12 weeks at target therapeutic dose of a conventional DMARD. The length of treatment constituting a therapeutic trial has been shortened in comparison with the 2005 guidelines to keep the guidelines in line with current advised practice in RA [2].

However, it is recognized that PsA is a heterogeneous disease and that the above approach may be inappropriate in patients with severe progressive disease. Observational cohort studies have identified adverse prognostic factors in PsA that are associated with accelerated joint damage, including a high number of active joints, a high number of previous medications, high inflammatory markers at presentation [10] and current joint damage, that predict ongoing damage at future visits [11]. In patients with active disease and these prognostic factors, treatment with biologic therapies should be considered after failure of one DMARD. This recommendation on the number of DMARDs used prior to anti-TNF

therapies is based on the consensus opinion of the expert committee given the lack of clear evidence.

Trials of anti-TNF therapies have shown a statistically significant difference in the numbers achieving composite arthritis outcome measures, such as the Psoriatic Arthritis Response Criteria (PsARC) and the ACR outcomes, compared with placebo. The PsARC is a response criterion first described in the Veterans Affairs Cooperative Study of SSZ [12]. Response is defined as improvement in two factors (with at least one being a joint score) with worsening of none of the following four factors:

(i) patient global assessment (on a 1–5 Likert scale, improvement defined as a decrease of one category, worsening defined as an increase of one category);
(ii) physician global assessment (as above);
(iii) 68 tender joint count (improvement defined as a reduction by at least 30%, worsening defined as an increase of at least 30%);
(iv) 66 swollen joint count.

The ACR composite outcomes were originally developed for RA but were used widely in clinical trials in PsA due to concerns about relatively high responses as measured by the PsARC in patients receiving placebo. The ACR response criteria require a 20%, 50% or 70% improvement in joint counts (swollen and tender) as well as in at least three of the following five additional domains (physical disability, patient global visual analogue scale (VAS), patient pain VAS, physician global VAS and acute phase response) [13]. Retrospective analyses of pooled data from the anti-TNF RCTs has provided evidence to support the responsiveness of both the PsARC and the ACR outcomes in polyarticular PsA [14], although they may perform less well in other forms of the disease.

Efficacy in most studies was assessed at 12 or 16 weeks. Current guidelines suggest that patients are assessed 12 weeks after the commencement of anti-TNF therapy and that therapy is discontinued in the case of non-response [1]. Recent evidence has shown that although the majority of responders will show some response at 12 weeks, ongoing improvement in joint counts continues beyond this time point [15]. Thus some patients may require a longer therapeutic trial before being categorized as non-responders. After this initial response, anti-TNF treatment should be monitored with assessment of a 68-/66-joint count and PsARC response no less frequently than every 6 months. Anti-TNF therapy should be withdrawn if a prolonged inadequate response is seen on sequential assessments despite 6 months of continuous therapy.

Despite recognized limitations of the PsARC, it remains a feasible tool to assess response and at present it is preferable to the alternatives in assessing response in clinical practice. ACR response criteria perform well but require seven different variables to be measured and calculated, which is less feasible in clinical practice. Due to the heterogeneity of PsA, measures based on 28-joint counts [such as the DAS28 and European League Against Rheumatism (EULAR) responses] are not recommended for individual clinical assessment. Until newer measures of disease activity are further developed and validated (see outcome measures chapter), the PsARC with full 66-/68-joint counts remains the current method for assessing peripheral disease response.

No head-to-head trials comparing the efficacy of the anti-TNF therapies in PsA are available, and direct comparisons of different RCTs are not ideal, as the populations vary between trials. From the data available, there is no convincing evidence of a differential efficacy between the agents in terms of peripheral arthritis response.

Recommendations

(i) Anti-TNF therapy should be considered for those patients with active arthritis (defined as at least three tender and three swollen joints) who have failed treatment with at least two conventional DMARDs (an adequate therapeutic trial is defined either as failure to tolerate a DMARD or active disease despite treatment of at least 12 weeks at the target therapeutic dose of a conventional DMARD, e.g. LEF, MTX, SSZ, ciclosporin). Anti-TNF therapy may be considered for patients who have failed only one DMARD, especially where there is evidence of one or more adverse prognostic factors (adverse prognostic factors defined as five or more swollen joints in association with an elevated CRP persisting for $>$3 months or structural joint damage due to disease) (Grade C). Consensus score 9.6.

(ii) All of the licensed anti-TNF therapies are recommended for use in patients eligible for treatment and the choice of therapy should be left to the treating physician after considering concomitant medical problems, patient preference and cost-effectiveness. For patients requiring rapid control of skin psoriasis, infliximab or adalimumab is preferred in accordance with the British Association of Dermatology (BAD) guidelines [4] (Grade A). Consensus score 9.9.

(iii) Anti-TNF therapies should be continued in patients who have responded after 3 months of treatment. In the case of non-responders, consideration should be given to a further 12 weeks of therapy if there has been a partial response (a partial response is defined as some improvement in swollen or tender joint score and no worsening in physician or patient global score as measured by the PsARC) and then continuing therapy if there has been a full response compared with baseline (Grade B). Consensus score 9.

Oligoarthritis

There is a lack of RCTs investigating the use of anti-TNF therapies in oligoarthritis. Although the inclusion criteria for most clinical trials could have included patients with three or four active joints, the vast majority of patients had polyarticular disease with $\sim$20 active joints. The only large RCT to give information about the proportion of patients with oligoarticular disease was the adalimumab study, in which 25% had an oligoarticular presentation at baseline

[16]. Unfortunately, sub-analyses of the efficacy of adalimumab in this cohort are not available.

At present, there are few therapeutic options for patients with resistant mono- or oligoarthritis with fewer than three joints involved. There are no randomized trials for either standard DMARDs or biologics in the oligoarthritis subtype of PsA. There is some limited evidence for intra-articular anti-TNF therapy (see Alternative dosing/administration of anti-TNF therapies section), but this is based only on case reports and small case series with a significant likely publication bias.

Recommendations

(i) Anti-TNF therapies should be considered in patients with severe persistent oligoarthritis (fewer than three tender/swollen joints), which has a major demonstrable influence on well-being and who have failed treatment with at least two conventional DMARDs and appropriate intra-articular steroids (Grade C). Consensus score 9.2.

Skin

Comprehensive guidelines for the management of psoriasis with biologic therapies are available from the BAD [4] and should be consulted in conjunction with these guidelines. The majority of large RCTs of PsA have reported data on outcomes for skin psoriasis, with impressive results for achieving psoriasis area and severity index (PASI) 50, 75 and 90 responses. There are also significant data to support the use of anti-TNF therapies and ustekinumab in skin psoriasis and three drugs (etanercept, adalimumab and ustekinumab) are currently licensed and NICE approved for the treatment of severe skin psoriasis (PASI $>$ 10) and one drug (infliximab) for very severe skin psoriasis (PASI $>$ 20). In contrast to peripheral arthritis efficacy, there does seem to be evidence of a differential response to anti-TNF in terms of skin psoriasis, despite the acknowledged lack of head-to-head studies. Etanercept (a TNF receptor blocker) consistently shows lower response rates in terms of PASI compared with the monoclonal antibodies. Recently the psoriasis randomized etanercept study in PsA (PRESTA) study compared different doses of etanercept in PsA (50 mg once weekly or 50 mg twice weekly) in an RCT. This showed a significantly higher PASI response with higher-dose etanercept, but no improvement in arthritis outcomes [17].

Enthesitis

Many of the RCTs investigating the use of anti-TNF drugs have used enthesitis as a secondary outcome. In particular, studies of adalimumab [18], golimumab [19], infliximab [20, 21] and etanercept (the PRESTA study only [17]) have included an assessment of enthesitis. All studies, with the exception of the golimumab study, only assessed enthesitis at the plantar fascia and Achilles tendon. The golimumab study also used the Maastricht ankylosing spondylitis enthesitis score (MASES) [19]. All of these studies showed a reduction in the proportion of patients with enthesitis or a reduction in enthesitis score at 3 months [18] or at both 3 and 6 months [17, 19–21] after starting therapy. There are no specific trials investigating enthesitis as the primary outcome in PsA, but the HEEL RCT has shown significant improvement of heel enthesitis in patients with SpA treated with etanercept [22]. This provides some evidence to support the use of anti-TNF therapy in patients with refractory enthesitis. At present, there is not sufficient evidence to support a specific recommendation for the use of anti-TNF therapy for enthesitis in PsA, but research to date appears promising.

Dactylitis

Dactylitis has been assessed as a secondary outcome in studies of adalimumab [18], golimumab [19], infliximab [20, 21] and etanercept (the PRESTA study only [17]) using the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT) dactylitis score, which is based on the number of digits with dactylitis and a tenderness score. Although this is a non-validated scoring system, an improvement in dactylitis was seen following either 3 months [18, 21] or 3 and 6 months [17, 19, 21] of therapy. Given the lack of RCTs investigating dactylitis, as a primary outcome, no specific recommendation is made here regarding treatment for dactylitis, but it is envisaged that dactylitis would be treated with anti-TNF therapy if the patients fulfil the peripheral joint disease activity criteria.

Nail disease

There are few data assessing the impact of anti-TNF therapy on nail disease in PsA, although more studies exist in patients with skin and nail psoriasis [23]. One of the RCTs in PsA (GO-REVEAL—golimumab study) used a measure of the proportion of patients with clinically evident psoriatic nail disease and a Nail Psoriasis Severity Index (NAPSI) score of a target nail to assess the impact of golimumab. Patients showed significant reductions in both measures in both treatment groups compared with placebo, with a numerically greater response in those patients randomized to the 100 mg dose [19]. Two further open-label studies have assessed the impact of adalimumab with a reduction in the Nail Psoriasis Severity Index (NAPSI) seen at the 3- and 6-month time points [24, 25].

Axial disease

No RCTs were identified specifically addressing the treatment of axial PsA with anti-TNF therapies, only one open-label study. In this study, 32 patients with axial PsA were treated with etanercept with good response in patient-reported outcomes, metrology and inflammatory markers [26]. Existing guidelines from the BSR covering the use of anti-TNF therapies in AS and the Assessment in Spondyloarthropathy [Assesment of SpondyloArthritis international Society (ASAS)]/EULAR guidelines for the use of anti-TNF therapies in axial SpA should be consulted [27–29]. In recent revisions to these guidelines, treatment of resistant axial SpA with pre-radiographic disease is now recommended if patients fulfil the ASAS axial SpA classification criteria. Psoriasis is a recognized feature of SpA within these criteria. This is particularly crucial

in axial PsA, as the disease is less likely to be bilateral and to involve the sacroiliac joints, meaning that patients are less likely to fulfil the modified New York criteria for AS.

Recommendations

(i) Anti-TNF therapy should be considered for those patients with active axial PsA according to the 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis (Grade A) [27]. Consensus score 9.8.

Concomitant prescribing with anti-TNF

Many of the RCTs of anti-TNF therapy in PsA used subgroup analysis to compare patients on concomitant MTX with those who were on anti-TNF monotherapy. There was no clear difference between the groups, although these trials were not designed or significantly powered to assess the effect of concomitant therapy.

Registry data from the South Swedish Arthritis Treatment Group have shown that persistence with biologics is increased with concomitant MTX use [30]. Specifically it seemed that the advantage of MTX was related to a lower rate of dropouts for adverse events [31]. Both of these analyses combined all anti-TNF agents and did not assess the drugs independently. Subsequently a smaller analysis of patients treated only with etanercept did not confirm the improved persistence with concomitant MTX [32]. The authors suggested that the advantage of concomitant MTX seen in the Swedish study may have been due to the patients on infliximab (~40% of the registry patients) and that concomitant MTX may be less important with etanercept or adalimumab [32]. Registry data from the British Society for Rheumatology Biologics Register (BSRBR) has shown similar EULAR response rates in patients receiving concomitant MTX, other DMARDs and biologic monotherapy [33].

Ciclosporin is the only DMARD evaluated specifically with anti-TNF therapy. A small open-label study recruited patients on etanercept with ongoing active skin disease and added ciclosporin (3 mg/kg/day) to their etanercept. The majority of patients showed an improvement in skin psoriasis over the 24-week study period, with only one withdrawal due to adverse events [34]. However, the long-term effects of combining anti-TNF therapy and ciclosporin are not known, and the combination is not recommended in dermatological practice.

Outcome measures

As stated above, the PsARC is the current recommendation for response assessment in peripheral arthritis. The ACR response criteria have also been shown to be discriminative in polyarticular PsA [14], but are generally too cumbersome and time consuming for routine clinical practice. Other composite arthritis measures have been validated in PsA. The EULAR responses, based on the DAS and DAS28 scores, have been shown to be responsive in polyarticular disease [34], but there are numerous concerns about their use in the general PsA population [i.e. lack of validity in oligoarticular disease or those with predominant lower limb involvement, remission cut-off validated in RA but not in PsA, global disease activity may be influenced by other aspects of psoriatic disease (such as enthesitis, psoriasis and axial disease), PsA patients show a less linear relationship between disease activity and acute phase response].

The Disease Activity in Reactive Arthritis (DAREA) score was originally developed for use in reactive arthritis [35] but has recently been assessed and validated in two cohorts of PsA patients [36, 37] and the authors have proposed using it in PsA as the Disease Activity in PsA (DAPSA) score. The DAPSA includes joint counts, patient-reported outcome measures (PROMs) and an inflammatory marker and has been shown to be responsive in polyarticular disease. The DAPSA may represent a useful measure of PsA peripheral arthritis activity in the future, as it is feasible for use in clinics and allows a measure of disease state rather than just a response outcome such as the PsARC. However, it is only validated in two datasets and levels of the DAPSA that equate to response, high and low disease activity states, have not been investigated.

There is increasing interest in composite measures of psoriatic disease activity that assess all aspects of the disease rather than just peripheral arthritis. The Composite Psoriatic Disease Activity Index (CPDAI) assesses peripheral arthritis, skin, entheses, dactylitis and axial disease using a grid system with a composite score of disease activity [38]. Cut-offs for active disease have been proposed based on physicians' assessment of the need to escalate therapy. Early work from validation studies performed retrospectively in data from the PRESTA study suggested that this may be more responsive than the DAPSA and could identify the differential response in skin disease between the two doses of etanercept [39]. Further validation of the CPDAI is ongoing.

Criteria to define minimal disease activity (MDA) have also been proposed [40] and validated in PsA [41, 42] and these include individual outcome measures encompassing the key domains in PsA. However, the MDA is a dichotomous measure of disease state and does not allow a response assessment or continuous measure of disease activity.

Work is currently under way within the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Composite Exercise (GRACE) study under the supervision of the GRAPPA group to refine and validate these composite measures further and to develop a novel composite disease activity measure based on patient data collected using similar methodology to the development of the RA DAS. This measure, known as the PASDAS, was initially presented in 2010 and is still in active development. The hope is that work within the GRACE dataset will allow the development and validation of a composite disease activity measure for future use in PsA.

Recommendations

(i) PsARC with 66-/68-joint count is recommended as the clinical response criteria for peripheral PsA and a PASI score should be completed for patients with

significant skin psoriasis [body surface area >10% affected and/or having a major impact on quality of life (e.g. Dermatology Quality of Life Index > 10)] in collaboration with a dermatologist. In the future, following appropriate validation, static composite measures evaluating all aspects of psoriatic disease should ideally be used to assess eligibility and response in PsA (Grade A). Consensus score 9.2.

Safety

No evidence was found for specific contraindications or safety issues over and above those encountered with anti-TNF use in the context of other diseases. Physicians are referred to the BSR guidelines for use of anti-TNF in RA [2] and the BAD guidelines for the use of anti-TNF in psoriasis [4]. A summary of key points is included below.

Infection

Observational studies first raised the possibility that anti-TNF therapy was associated with an increased risk of infection and many registry studies have confirmed an increased risk of infection in RA [43–46]. A review of RCTs in PsA showed only a small increased risk of infection with short-term use in clinical trials [3], but the selection of patients for inclusion in clinical trials may have underestimated the risk in routine clinical practice. Cases of listeriosis and salmonella infection have been reported in patients on anti-TNF therapy [47], identifying a possible risk of food-related infections. Other opportunistic infections, including invasive fungal infections and pneumocystic jiroveci infections, have also been reported in patients on TNF therapy [2].

Recommendations

(i) Anti-TNF therapy should not be initiated or continued in the presence of serious active infection, but can be recommenced once the infection has resolved clinically (Grade B). Anti-TNF therapy should be used with caution in patients at high infection risk after discussing the relative risks and benefits (Grade C). Consensus score 9.8.

(ii) Patients on anti-TNF therapy should be informed of appropriate food hygiene. Patients should also be advised to avoid eating foods that contain unpasteurized milk, uncooked eggs or raw meat (Grade C). Consensus score 8.8.

(iii) There should be a high index of suspicion for the possibility of atypical or opportunistic infections, and treatment should be stopped and advice sought in suspected cases (Grade B). Consensus score 9.7.

Tuberculosis

There is a well-established risk of tuberculosis (TB) associated with anti-TNF therapies that has been documented in many registries. Particularly high rates of TB are seen in countries with a high rate of latent TB infection, with lower rates seen in the UK. Data from the BSRBR and other registries have shown a higher risk of latent TB reactivation with the monoclonal antibody anti-TNF drugs (adalimumab and infliximab) when compared with etanercept [48]. Less data are available for certolizumab and golimumab. The efficacy of screening for TB therapy has been demonstrated by the Spanish registry, which showed a decrease in cases of TB reactivation of 78% following the introduction of routine screening prior to anti-TNF use [49]. Screening guidelines are available from the British Thoracic Society [50].

Recommendations

(i) Prior to starting treatment with anti-TNF therapy, all patients should be screened for mycobacterial infection in accordance with the latest national guidelines. Active mycobacterial infection should be adequately treated before anti-TNF therapy is started. Prior to starting anti-TNF therapy, consideration of prophylactic anti-TB therapy (as directed by the latest national guidelines) should be given to patients with evidence of potential latent disease (Grade B). Physicians should be vigilant for the development of mycobacterial infections throughout treatment with anti-TNF and for at least 6 months after discontinuation (Grade C). If patients develop evidence of mycobacterial infection while on anti-TNF therapy, they should receive a full course of anti-mycobacterial chemotherapy—the anti-TNF therapy may be continued during this time if clinically indicated (Grade C). Consensus score 9.4.

Hepatitis B

Elevated levels of TNF are seen in patients with chronic HBV. TNF may play a role in clearing HBV, leading to the possibility that anti-TNF may enhance viral replication. In animal models, TNF promotes viral clearance of HBV [51]. HBV can be considered in subcategories as below, with each profile carrying differing risk ratios for reactivation with immunosuppressive treatment.

(i) Vaccinated: HBsAg −ve, anti-HBc −ve, anti-HBs +ve
(ii) Resolved: HBsAg −ve, anti-HBc +ve, anti-HBs +/−ve
(iii) Chronic: HBsAg +ve, anti-HBc +ve, anti-HBs −ve
(iv) Occult chronic infection: HBsAg −ve, HBV DNA +ve

Case reports of patients with chronic HBV treated with anti-TNF, including patients with RA, Crohns disease and adult-onset Stills disease, have demonstrated reactivation, including fulminant hepatitis [52]. Three case series of patients with resolved HBV (HBsAg −ve, antiHBc +ve) in PsA have demonstrated no reactivation during anti-TNF therapy without the need for prophylactic antiviral therapy [53–55]. A sub-analysis of 19 patients vaccinated against HBV showed a similar decrease in HBsAb when compared with eight control patients on MTX alone, with only one patient falling below the threshold for protective immunity [55]. A case series of 24 chronic HBV carriers (HBsAg +ve) given anti-TNF for RA, AS or Crohns showed a higher rate of reactivation in those not given antiviral prophylaxis (12 of 16) compared with those who did have prophylaxis (1 of 7) [56]. Cases of HBV reactivation in active HBV carriers have also been demonstrated in other case series of anti-TNF [57] and DMARD use [58] in rheumatic disease.

Hepatitis C

Elevated TNF levels are present in patients with HCV and are associated with a worse prognosis; furthermore, HCV treatments tend to exacerbate the symptoms of PsA and psoriasis [52]. The exact role of TNF in the pathogenesis of HCV is unclear. There are concerns over the use of anti-TNF in patients with PsA and concurrent HCV infection because of the theoretical risks of accelerated hepatic decompensation. Conversely there is evidence that the pathogenesis of hepatocyte destruction and resistance to interferon alpha-2b may be mediated by inflammatory cytokines such as TNF, therefore anti-TNF may be beneficial in cases of HCV [59]. Case report/series evidence currently available in PsA [60–64] and psoriasis [65, 66] suggests that etanercept, adalimumab and infliximab are safe and effective in psoriatic disease with co-existent HCV. However, given the lack of any long-term safety data, close monitoring of HCV DNA and alanine aminotransferase is advised. The same advice is given by EULAR for the use of anti-TNF in rheumatic disease, including PsA [67], and in RA by the BSR [2] and the American Gastroenterology Association [68].

HIV

There is a well-established link between HIV infection and psoriasis and PsA. In the previous BSR guidelines, caution was suggested with the use of anti-TNF in this group due to a lack of data. There is no RCT evidence for the use of anti-TNF therapy in HIV-infected patients with PsA or psoriasis, but a limited number of case reports indicate it is safe and effective in those with well-controlled HIV [52, 69]. The available case report and case series have identified no deterioration in viral load or CD4 count clinically attributable to anti-TNF therapy [70–74]. There is one reported case of recurrent bacterial infections requiring cessation of anti-TNF but no deterioration in viral load or CD4 count [75]. Current guidelines on the use of anti-TNF in psoriatic disease [76, 77], and more widely in other rheumatic disease including PsA and RA [2, 52, 69], are based on case series data. Consensus on the use of anti-TNF in HIV remains the screening of those at risk of HIV prior to treatment [2, 52], optimizing HIV treatment prior to initiating therapy and monitoring viral load and CD4 count [69, 71, 76, 77].

Recommendations

(i) Patients at risk should be screened for HIV, HBV and HCV prior to anti-TNF (Grade C). Consensus score 9.3.

(ii) HIV or HCV infection should not preclude treatment with anti-TNF therapy, although treatment should only be commenced in those with well-controlled disease and with appropriate monitoring under the care of an HIV specialist or hepatologist (Grade B). Consensus score 8.9.

(iii) Anti-TNF therapy in those with chronic HBV should be approached with caution given the potential risk of reactivation and fulminant hepatitis. Anti-TNF therapy should only be commenced in those with well-controlled disease, with appropriate antiviral treatment and regular monitoring in collaboration with a hepatologist. Consideration should be given to vaccinating those at risk of HBV prior to treatment (Grade C). Consensus score 9.5.

Malignancy

Observational and registry data have been reassuring in showing no increase in the rate of overall malignancy related to anti-TNF therapy. Meta-analysis of registry data in RA has shown no increase in overall malignancy (risk estimate 0.95, 95% CI 0.85, 1.05) or lymphoma (risk estimate 1.11, 95% CI 0.70, 1.51) when comparing patients exposed to anti-TNF therapy with those exposed to standard DMARDs [78]. Very little is known about the risk of using anti-TNF therapy in patients with a previous malignancy. These patients are excluded from clinical trials and are generally not considered for treatment with anti-TNF therapy in clinical situations. Data from the German and British registry showed a combined incidence rate ratio of 0.62 (95% CI 0.04, 1.20), but this was based on a small number of cases and selection bias in those treated with anti-TNF therapy following a malignancy is likely to be significant [78].

Registry data in RA have confirmed an increased risk of skin cancer associated with anti-TNF use, both non-melanoma skin cancer and malignant melanoma (MM) [78, 79]. Skin cancers are very common in the general population (60 000 new cases registered in England and Wales each year) and basal cell carcinoma, squamous cell carcinoma (SCC) and MM account for 95% of all cases [80]. People with PsA with significant skin disease may be at further increased risk (in addition to that of anti-TNF therapy) due to self-directed excess ultraviolet (UV) exposure or as a result of phototherapy, particularly PUVA [81]. Long-term immunosuppression with agents such as ciclosporin and AZA may compound this risk, especially for SCC [82, 83]. However, the death rate associated with the majority of skin cancers is very low, as early detection significantly improves both morbidity and mortality and most are completely cured with local, predominantly surgical, measures.

Recommendations

(i) Anti-TNF therapy should be avoided in patients with a current or prior history of malignancy unless the malignancy was diagnosed and treated >10 years ago and/or where the likelihood of cure is high. All patients should be encouraged to participate in national cancer screening programmes appropriate for their age and gender. Patients on anti-TNF should be regularly screened for skin cancers (including melanoma), especially if their background risk is high, and patients who develop suspicious skin lesions while on TNF therapy should be referred for urgent dermatological review and management. Anti-TNF therapy is relatively contraindicated in patients who have had prior treatment with >150 PUVA and/or >350 UVB treatments, especially when this has been followed by treatment with ciclosporin, and should be formally reviewed by a dermatologist where therapy cannot be avoided (Grade C). Consensus score 9.4

Demyelination

There are reports of anti-TNF-associated demyelination in the CNS [84] and peripheral nervous system [85]. The majority of cases resolved with withdrawal of the anti-TNF drug, but some required additional therapy and a few did not achieve a full resolution of their symptoms [86].

Cardiac disease

Concern about cardiac failure as a complication of anti-TNF therapy was raised following adverse experiences in trials of anti-TNF therapies (infliximab and etanercept). Post-marketing surveillance by the Federal Drug Administration (FDA) identified 47 cases of cardiac failure associated with anti-TNF therapies [87], although observational data have not confirmed a clear increase in developing new-onset or worsening cardiac failure with anti-TNF therapy when compared with conventional DMARDs [88].

Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in patients with RA receiving a variety of anti-TNF therapies, but there is an increased risk of ILD in patients with RA. These patients with ILD have a poor prognosis despite withdrawal of anti-TNF therapy, but there is not enough evidence to identify whether the use of anti-TNF therapy impacts the severity of the disease. Any risk of anti-TNF with regard to ILD is likely to be lower in patients with PsA than patients with RA.

Pregnancy

Anti-TNF drugs are classed as risk B by the FDA. There are no systematic data in humans and no observed increased risk in animals. The majority of data are for exposure in cases of RA, but numbers are small (fewer than 150). There is no clear differential risk related to the diagnosis for which anti-TNF is being given, so data are considered here for all TNF exposure. It must be noted, however, that many women were also taking other drugs before or during pregnancy (e.g. MTX), which may impact on feto-maternal risk. The BSRBR reported on 88 live births from a total of 130 pregnancies in patients who received anti-TNF therapy before or during the pregnancy. Those exposed to anti-TNF at the time of conception had a higher rate of spontaneous abortion than those who had ever received anti-TNF therapies (27% *vs* 17%), with the highest rate in those taking concomitant MTX or LEF (33%). A higher proportion of patients exposed to anti-TNF therapy at or after the time of conception opted for termination, possibly related to their concomitant DMARD treatment [89].

Registry data have not shown a clear increased risk of adverse pregnancy outcomes for the fetus, although the small number of cases is a limitation. The main issue that has been raised is of the VACTERL (vertebral anomalies, anal atresia, cardiac defects, tracheo-oesophageal fistula, oesophageal atresia, renal anomalies and limb dysplasia) malformation, which has been flagged as a possible risk [90], but with no convincing evidence.

In terms of breast-feeding, TNF inhibitors (infliximab, etanercept and adalimumab) are known to enter breast milk but are probably digested by the infant gastrointestinal tract. Again, there have been no systematic studies performed.

Recommendations

(i) Anti-TNF agents should ideally be stopped prior to pregnancy and restarted after the end of lactation or delivery if not breastfeeding. Management should be in accordance with BSR safety guidelines for anti-TNF use in RA and the BAD guidelines (Grade C). Consensus score 9.3.

What to do if anti-TNF fails

Switching

Multiple open-label studies and registry data have confirmed the potential benefits of switching anti-TNF therapies in patients with PsA. There are no RCTs of sufficient quality to confirm this benefit. Studies of patients with PsA, taken from cohorts and registries of psoriasis and SpA patients, have generally shown a lower response rate to second and subsequent anti-TNF therapies when compared with a first drug, but nevertheless have shown a significant response [91–97]. Data from larger registries have shown that patients who switch drug due to adverse events have a higher likelihood of persistence with a second therapy than those who switch due to loss of efficacy (either primary or secondary non-response) [93]. At present, there is not enough systematic evidence to identify if switches between certain drugs show better efficacy than others.

Recommendations

(i) 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. Consideration of the possible consequences on the control of skin disease should be given and shared care with a dermatologist when appropriate (Grade B). Consensus score 9.5.

Alternative dosing/administration of anti-TNF therapies

There are few data investigating alternative doses or administration routes of anti-TNF therapies. The Swedish registry reported data on patients with PsA treated with infliximab at a dose of 3 mg/kg every 8 weeks. A higher proportion of patients with PsA required a dose escalation, which is in keeping with the recommended treatment dose of 5 mg/kg every 8 weeks in the UK [30]. However, in Cherouvim's open-label study, the majority of patients with AS and PsA responded well to lower-dose infliximab. Ten of the 13 PsA patients showed a significant response to therapy, with one patient showing no

response at all and two patients showing worsening of response after the initial loading regime [98]. Covelli *et al.* [99] also found a good response to low-dose infliximab in resistant PsA patients, but a relapse was seen in all patients once infliximab was withdrawn.

In 2006 a small open-label study evaluated the use of high-dose etanercept for 12 weeks followed by a standard dose for a further 12 weeks. This was tolerated well and the patients showed a good response in both arthritis and skin psoriasis [100]. Following from this, the PRESTA study compared differing doses of etanercept (50 mg weekly *vs* 50 mg twice weekly) in an RCT over a 12-week period. There was no significant difference in arthritis outcomes, but a higher PASI response was seen with the higher dose of etanercept [17]. The studies of golimumab in PsA used two alternative doses of golimumab, either 50 mg or 100 mg every 4 weeks. The study was not powered to investigate the different doses and showed a significant improvement in psoriatic disease with both doses when compared with placebo. There was a suggestion of a higher response in skin/nail disease with the 100 mg dose [19].

A number of small studies or case reports have investigated the use of intra-articular anti-TNF therapy for monoarthritis. Studies have evaluated the use of infliximab [101, 102], etanercept [103–105] and adalimumab [105] given directly into inflamed joints. The majority of patients showed a good response, although the injections were also often combined with IA steroid in addition to the anti-TNF agent. Some patients showed a lasting benefit for a number of weeks or months, but the longer-term outcome of these patients has not been reported. Efficacy of intra-articular TNF drugs has not been evaluated in a clinical trial and therefore there is not sufficient evidence for a recommendation in this area.

Alternative biologics in testing/development

A number of new biologic therapies beyond anti-TNF have been tested in PsA more recently. The majority of these are unlikely to replace anti-TNF therapies as a first-line therapy, as they have not shown responses equivalent to anti-TNF therapies. There is a need for alternative treatments for patients who fail anti-TNF therapies, but to date, none of these drugs has sufficient evidence to support a recommendation for use.

Rituximab

Rituximab is a chimeric monoclonal antibody that binds to and eliminates CD20 on B cells. CD19-expressing B cells are present in the synovium of patients with PsA, but their functional role has not been established [106]. Partial remission of psoriasis in a patient treated with rituximab for lymphoma was reported in 2005, and rituximab was then used in a patient with PsA who was refractory to standard DMARDs and anti-TNF therapies. This patient had an excellent response to four infusions of rituximab with concomitant oral prednisolone (10 mg/day) and had sustained benefit until 8 months after treatment. A repeat infusion of 1 g rituximab showed repeated benefit and no further radiographic progression has been seen over a 3-year period [107]. Review of the French registry identified eight patients with SpA treated with rituximab, three of whom had PsA. None of the PsA patients responded to the treatment [108]. Most recently, an open-label trial of rituximab in PsA was reported at EULAR 2010 [109]. Twenty patients with PsA received two infusions of 1 g rituximab and 100 mg prednisolone, 14 days apart. Modest responses were seen in most aspects of psoriatic disease (30% achieved ACR20), but with no placebo-controlled arm, it is different to accurately assess the benefit of rituximab. In the absence of phase III data, rituximab should not be considered as a routine part of the treatment of PsA.

Ustekinumab

Ustekinumab, a human monoclonal antibody that binds to the common p40 subunit shared by IL-12 and IL-23, is an approved treatment for psoriasis. Ustekinumab has also been tested in PsA in an RCT of 146 patients with active PsA. This was an active crossover placebo-controlled trial where patients received four injections of 90 mg ustekinumab at weekly intervals and were then followed for 12 weeks. At 12 weeks, 42% of patients on ustekinumab achieved ACR20 compared with 14% of those receiving placebo [110]. Case studies have also confirmed the benefit of PsA with ustekinumab [111]. Provisional evidence therefore suggests that ustekinumab may be moderately effective for PsA. A large phase III programme in PsA is ongoing that is providing further data on its therapeutic utility.

Secukinumab

This is a monoclonal antibody that inhibits the function of IL-17. It has shown promising efficacy in psoriasis phase III studies. One phase IIa study in PsA was reported at ACR 2011 [112]. Twenty-eight patients were randomized to receive secukinumab (two infusions at week 0 and week 3) and were compared to 14 patients treated with placebo. The primary outcome of the ACR20 response at 6 weeks was not met. Numerically superior response rates were seen in actively treated patients who had not previously received a TNF inhibitor agent. No significant safety signal emerged in this short trial. Further studies are required to establish whether secukinumab represents a new treatment modality in PsA.

Abatacept

Abatacept is a fusion protein that inhibits the co-stimulation of T cells via interference with the CD28/CD80/86 pathway. Two case reports in patients who had failed anti-TNF therapy or who had contraindications to its use reported significant improvement in PsA signs and symptoms following regular treatment with abatacept [113, 114]. At ACR 2009, a randomized double-blind study of 170 patients using abatacept in active PsA was reported. Patients receiving 10 mg/kg of abatacept had a significant ACR20 response compared with placebo (48% *vs* 19%, $P = 0.006$), although there was not a significant difference

seen with 3 mg/kg abatacept. Improvement was also seen in the target lesion score of psoriasis and MRI assessment of synovitis. Disappointingly, results were not as good in those patients who had previously failed an anti-TNF drug (ACR20 31% *vs* 56%) [115].

Apremilast

Apremilast is an oral phosphodiesterase-4 inhibitor that has been tested in psoriasis and PsA. A phase II study of 204 patients found a modest effect in arthritis treatment, with a significant difference in ACR20 for both 20 mg bd and 40 mg od doses. A significant difference was not seen in ACR70, with very few patients achieving such a marked improvement in disease activity [116].

TNF antagonist gene therapy

One study to date has highlighted the use of rAAV2-TNFR:Fc, a recombinant adeno-associated viral vector containing the human TNF receptor immunoglobulin (IgG1) Fc fusion (TNFR:Fc) gene. The study was a blinded study with patients with inflammatory arthritis including PsA randomized to receive intra-articular injections of escalating dose concentrations of the gene or placebo at a ratio of 3:1. Injection site reactions occurred in 14% of cases and were dose dependent. Only one case of septic arthritis occurred, but was felt to be unrelated to the gene therapy. There was a reduction in patient reported global VAS scores for the target joint, but this was not significant when compared with placebo [117].

Auditing potential impact of the guidelines

An audit was undertaken at the Royal National Hospital for Rheumatic Diseases in Bath to assess the potential impact of changing the eligibility criteria from those in the 2005 BSR guidelines. The old (2005) and proposed new (2012) eligibility criteria were applied to 100 PsA patients. Cases were selected sequentially from 3 months of clinics between September and December 2011 from the hospital's longitudinal PsA cohort. Only patients who had been on at least one DMARD in the past were included. Case notes were reviewed over the prior 5 years to avoid calendar bias. In 66 cases (two-thirds) the new guidelines would not have resulted in any change to management over the last 5 years. In 21 cases (one-fifth) the new guidelines would have resulted in an opportunity to commence an anti-TNF drug not possible under the old guidelines. Twelve patients were on anti-TNF for joint disease and in 10 cases they would have been eligible for anti-TNF therapy at an earlier time point (mean 32 months). The lower eligibility criteria proposed in these guidelines will therefore result in an opportunity to commence anti-TNF at an earlier stage and the audit provides evidence that this may increase the number of people on anti-TNF in a secondary care cohort.

AGREE instrument evaluation

The AGREE instrument was used to assess and evaluate these guidelines by four independent reviewers including rheumatologists and dermatologists with a special interest in psoriasis and PsA. Results for each of the six domains within the AGREE instrument (scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence) are presented in Table 2. Scores for all domains were high (range 73–98%) and all the reviewers' comments were taken into account with the final revision of the guidelines. All the reviewers scored a high overall rating for the guidelines and recommended the guidelines for use.

Audit tools

An audit pro forma to assess compliance with these guidelines is available to download from the BSR website (http://www.rheumatology.org.uk/resources/audit.aspx).

Updating

The working party acknowledges that there are still areas without high-quality evidence on which to base the recommendations. These guidelines cover a rapidly evolving area of therapeutic intervention. Therefore the working party recognizes that as more evidence becomes available and more anti-TNF therapies are licensed, the guidelines will have to be updated, including updating of the systematic literature review. The working party

Table 2 Scoring of the guidelines by four independent reviewers according to the AGREE II instrument

Domain (maximum score)	Appraiser				Overall domain score (%)
	1	2	3	4	
1. Scope and purpose (21)	21	20	19	18	92
2. Stakeholder involvement (21)	21	20	17	17	87
3. Rigour of development (56)	55	52	47	46	87
4. Clarity of presentation (21)	21	21	19	17	92
5. Applicability (28)	26	22	20	18	73
6. Editorial independence (14)	14	14	13	14	98
Overall assessment (7)	7	6	6	6	
Recommended for use	Yes	Yes	Yes	Yes	

recommends that this should occur within the next 3–5 years, with updated guidelines published.

Working party members and conflicts of interest

The working party was established by the BSR and was set up without any funding or input direct from manufacturers of the TNF inhibitors. Members of the working party were asked to declare any relationships with the manufacturers of biologic therapies. The working party included:

(i) David Chandler, Chief Executive, the Psoriasis and Psoriatic Arthritis Alliance, St Albans, UK, served as patient representative on the committee;

(ii) Laura C. Coates, Rheumatology Clinical Lecturer, NIHR Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK, completed the literature search, reviewed relevant literature, produced the initial draft of the paper and assisted in preparation and final approval of the manuscript;

(iii) Philip S. Helliwell, Rheumatology Senior Lecturer, NIHR Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK, served on the committee, reviewed relevant literature and participated in preparation and final approval of the manuscript;

(iv) Eleanor Korendowych, Consultant Rheumatologist, Royal National Hospital for Rheumatic Diseases, Bath, UK, served on the committee, reviewed relevant literature and participated in preparation and final approval of the manuscript;

(v) Stuart Kyle, Consultant Rheumatologist, North Devon District Hospital, Barnstaple, UK, served on the committee, reviewed relevant literature and participated in preparation and final approval of the manuscript;

(vi) Neil J. McHugh, Consultant Rheumatologist, Royal National Hospital for Rheumatic Diseases, Bath, UK, convened and chaired the working group, reviewed relevant literature and participated in preparation and final approval of the manuscript;

(vii) Iain B. McInnes, Muirhead Professor of Medicine and Director of Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK, served on the committee, reviewed relevant literature and participated in preparation and final approval of manuscript;

(viii) Susan Oliver, Nurse Consultant Rheumatology, Barnstaple, Devon & Minerva Health Centre, Preston, UK, served on the committee, reviewed relevant literature and participated in preparation and final approval of the manuscript;

(ix) Anthony Ormerod, Reader in Dermatology and Honorary Consultant Dermatologist, University of Aberdeen, Aberdeen, UK, served on the committee, reviewed relevant literature and participated in preparation and final approval of the manuscript;

(x) Catherine Smith, Consultant Dermatologist, Guys and St Thomas' Hospital, London, UK, served on the committee, was the lead author on BAD guidelines, reviewed relevant literature and participated in preparation and final approval of manuscript;

(xi) Deborah Symmons, Professor of Rheumatology and Musculoskeletal Epidemiology, University of Manchester, Manchester, UK, served on the committee, advised on the section on safety and participated in the preparation and final approval of the manuscript;

(xii) William Tillett, Research Fellow, Royal National Hospital for Rheumatic Diseases, Bath, UK, served on the committee, reviewed relevant literature, undertook the guideline audit and participated in preparation and final approval of the manuscript;

(xiii) Nicola Waldron, Psoriatic Arthritis Nurse Specialist, Royal National Hospital for Rheumatic Diseases, Bath, UK, served on the committee and participated in preparation and final approval of the manuscript.

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