New biologic therapies for the treatment of rheumatoid arthritis (RA) are directed to mediators involved in the pathogenesis of the disease. Robust responses to treatment with the tumour necrosis factor (TNF) inhibitors adalimumab, etanercept and infliximab have improved the outcomes of RA patients in early RA, biologic-free remission and drug-free remission are now achievable, and in both early and established RA treated with TNF inhibitors, two-thirds of patients achieve meaningful clinical responses. However, one-third do not respond and, furthermore, a number of patients who initially respond go on to develop acquired drug resistance or gradual drug failure. In addition, some patients have to discontinue the biologic treatment due to adverse events. All in all, the three-year retention rate of TNF inhibitors is around 65%.

Although all TNF inhibitors have similar efficacy in treating RA, they differ in terms of their effectiveness with regard to other rheumatic diseases. In contrast to the monoclonal antibodies, etanercept is not effective in the treatment of granulomatous disorders such as Crohn’s disease, Wegener’s granulomatosis and sarcoidosis. In RA, reports, case series and observational studies indicate that some patients may respond to one but not to another TNF inhibitor. This is partially supported by data showing that TNF inhibitors differ in terms of their pharmacokinetics and mechanisms of action. The half-life of etanercept is three days, of infliximab 10 days and of adalimumab 13 days. These half-life differences may translate into differences in the extent of TNF neutralisation. In addition, the two monoclonal antibodies – infliximab and adalimumab – have strong affinity for TNF, which may increase the percentage of neutralised TNF molecules. In addition, complexes formed of anti-TNF antibodies and monomeric and trimeric soluble and membrane-associated TNF are far more stable than those formed of the soluble TNF receptor etanercept. Finally, the monoclonal antibodies bind only TNF, whereas etanercept also binds lymphotoxin. Thus, in the absence of therapeutic alternatives in RA, switching TNF inhibitors in patients failing on a first biologic agent has been considered a reasonable therapeutic approach.

In a survey among US rheumatologists, over 94% reported switching patients from one TNF inhibitor to another due to inadequate response or side effects. Additionally, guidelines from the Spanish Society of Rheumatology and the French Society of Rheumatology recommend the use of any TNF inhibitor in patients with inadequate response to a previous one. Nevertheless, the UK National Institute for Health and Clinical Excellence (NICE) has concluded that any diminution in efficacy between first and second TNF inhibitor would take the cost-effectiveness of second use outside the acceptable range.

Despite the biologic rationale for switching TNF inhibitors, there are no conclusive data regarding the outcomes of switching. Furthermore, alternatives to switching exist in RA. These include: combination therapy with traditional disease-modifying antirheumatic drugs (DMARDs); combination of TNF inhibitors with DMARDs other than methotrexate; and the new, recently approved biologics rituximab and abatacept, which have distinct mechanisms of action. The efficacy of TNF inhibitors has been also shown in other rheumatic diseases, including spondyloarthropathies (SpAs) and juvenile idiopathic arthritis. In these conditions, there is only limited information on switching TNF inhibitors.

Switching Tumour Necrosis Factor Inhibitors in Rheumatoid Arthritis

To June 2007, there were 32 relevant reports in the literature on switching from one to a second TNF inhibitor in patients who experienced treatment failure. Most reports were observational studies (n=19), case series (n=10) or prospective cohorts from biologic registries (n=3). Twenty-nine reports refer to RA patients, and four to chronic arthropathies. Thirteen studies give an account of the switch from a monoclonal anti-TNF antibody to etanercept, and from etanercept to a monoclonal anti-TNF
antibody and five from one to another monoclonal anti-TNF antibody. On the whole, the numerous limitations of the design of these kinds of study restrict their value. In addition, the disparate measurements of response across studies prevent comparison.

The available information shows that most patients included were women (83%; range: 60–100), with an average age of 52 years (range: 32–68) and a disease duration of 12 years (range: 3–27). When reported at baseline, mean disease activity score (DAS) was 5.6 (range: 2.4–6.8) and mean Health Assessment Questionnaire (HAQ) score was 1.7 (range: 1.5–1.9). This baseline information is not different from most clinical trials. Disparate measurements of efficacy include numbers of swollen and painful joints, erythrocyte sedimentation rate, blood levels of c-reactive protein, DAS28, DAS44, European League Against Rheumatology (EULAR) response criteria, American College of Rheumatology (ACR) response criteria and HAQ. Efficacy results could be provisionally summarised as follows:

- lack of response to a second TNF inhibitor does not predict response to a second, but the efficacy of a second TNF inhibitor after a first has failed is likely to be inferior;
- patients experiencing loss of efficacy after an initial response are more likely to respond to another TNF inhibitor than patients who initially fail; and
- lack of efficacy of a soluble receptor and of one of the anti-TNF antibodies predicts the lack of efficacy of the third TNF inhibitor.

Nevertheless, in the one randomised open-label study that compares etanercept continuation with switching to infliximab in 28 patients with inadequate response to etanercept, infliximab performed better in terms of percentage of patients reaching ACR20 and ACR50 response criteria and percentage of improvement in DAS28.

Three studies describe retention rates of a second TNF inhibitor as a surrogate of effectiveness. Overall, the probability of retaining a second TNF inhibitor was lower than that of retaining the first one. The probability was influenced by the reason for drug replacement, i.e. drug failure or adverse event. Interestingly, the reasons for stopping a second drug were related to the reasons for stopping the first drug. Although the retention rate of a drug can be taken as a sensible indicator of its effectiveness, parameters other than efficacy and safety – such as co-morbidity, co-medications, costs, availability of other therapies, the expectations of patients and physicians and adherence to treatment – could have an impact on drug survival.

The excess of cardiovascular morbidity and mortality occurring in RA improves with treatment with TNF inhibitors. Whether this additional benefit is retained in patients treated with a second TNF inhibitor due to resistance to a first inhibitor remains to be determined.

Switching from a Tumour Necrosis Factor Inhibitor to a Different Biologic Treatment in Rheumatoid Arthritis

In clinical trials, rituximab in combination with methotrexate provided significant improvements in disease activity in patients with long-standing, active RA with inadequate response to TNF inhibitors. This combination also appeared to be effective in slowing the radiographic progression of long-standing, active RA with inadequate response to TNF inhibitors. In one observational study, rituximab was effective in controlling disease activity in patients resistant to TNF inhibitors in clinical practice. Another observational study suggested that treatment with rituximab may be more effective than switching to an alternative TNF inhibitor in patients with RA in whom active disease persists despite this therapy.

In clinical trials, abatacept produced significant clinical and functional benefits in patients who had an inadequate response to TNF inhibitors. At present, there are no reports on the efficacy of combination therapy with traditional DMARDs, treatment with tocilizumab or combination therapy of TNF inhibitors with DMARDs other than methotrexate in patients failing on TNF inhibitors.

Switching Tumour Necrosis Factor Inhibitors in Other Rheumatic Diseases

There is only limited information on switching TNF inhibitors in other rheumatic diseases. A 54-week, open-label, prospective, follow-up study with etanercept was conducted in 23 patients with active ankylosing spondylitis who were resistant, acquired resistance or were intolerant to infliximab. An Assessments in Ankylosing Spondylitis 20% (ASAS20) response was attained by 17 patients (74%), ASAS50 by 14 (61%) and ASAS70 by nine (39%).

In another study, seven patients with ankylosing spondylitis, six with undifferentiated spondylitis and two with psoriatic arthritis with inadequate response or adverse events with infliximab were treated with etanercept and followed for a mean of 10 months. Eleven patients – including the two with psoriatic arthritis – responded to etanercept.

In the Spanish registry of biologics, BIOBADASER, which included RA and other chronic arthritides, the one-year retention rate of a second TNF inhibitor following switching was significantly better in SpA than in RA. The absence of alternative treatments for SpA may have contributed to the favourable retention rate compared with RA. Another explanation could be the lower rate of adverse events in SpA, which can be explained in part by younger age and fewer co-medications.

Finally, a recent work in a selected population of SpA patients indicates that the failure of a first TNF inhibitor does not preclude response to another. In one study of patients with juvenile idiopathic arthritis, a fairly good response to a second TNF inhibitor was reached at six months. However, the retention rate of the second TNF inhibitor seems worse in these patients than in those with SpA.

Conclusion

Over the last few years, in the absence of therapeutic alternatives disputed clinical evidence supported switching to a second TNF antagonist in patients failing on a first one. Today, newer efficacious biologics such as rituximab and abatacept have been approved for patients failing on TNF antagonists in RA.

Evidence demonstrating that switching between TNF antagonists has a greater effect in terms of effectiveness than switching to a different class of biologic is lacking, but preliminary evidence suggests that this may not be the case. Nevertheless, long-term data on the efficacy, safety, impact on function, quality of life and joint damage and comparative
pharmacoeconomics of these new therapeutic options in clinical practice are needed to address this issue. Such comparative studies and studies with other treatment options – including tocilizumab, co-medication with traditional DMARDs and combination of TNF inhibitors with DMARDs other than methotrexate – should consider disease duration, reason for switching – i.e. toxicity or lack of efficacy (resistance or loss of efficacy) – and impact on co-morbidities.

Competing Interests

IJGR is on the Advisory Boards of Schering-Plough, Wyeth, Bristol Meyers Squibb and Roche, and has received lecture fees from Abbott Laboratories, Wyeth, Roche, Bristol Meyers Squibb and Schering-Plough.

LC: no competing interests.