An update on DMARDs and biologics

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Introduction
The National Institute for Health and Clinical Excellence (NICE) rheumatoid arthritis (RA) management guidelines and the Department of Health commissioning pathway for inflammatory arthritis provide evidence-based approaches for the management of these diseases. Good functioning of the interface between primary and specialist care is imperative in ensuring high-quality care for patients with inflammatory arthritis, whether this is in early or established disease. It is important that colleagues in primary care are kept up to date with this rapidly evolving field.

When a patient develops the first signs of an inflammatory arthritis, the main priority is symptom relief, with pain being the cardinal sign of inflammation that patients most want help with. However, it has become increasingly clear that for inflammatory arthropathies such as RA simply treating the symptoms with non-steroidal anti-inflammatory drugs (NSAIDs) or analgesics is inadequate, because features of the disease that lead to damage to the joints, and then to disability, will carry on unchecked.

In addition to symptom-relieving drugs, patients also need disease-modifying drugs that have been demonstrated to slow down or stop the damaging
aspects of the disease. These drugs are in two classes:

1. **conventional disease-modifying anti-rheumatic drugs (DMARDs),** some of which are well established and have been available for decades (such as methotrexate, sulfasalazine and gold injections) and with leflunomide being the newest, receiving approval for use in 1998. Conventional DMARDs can work very effectively if introduced early in the course of the disease, and if escalated to therapeutic doses as quickly as possible. However, it takes time before they start to work (weeks or months), we do not know precisely how they work, and they can have potential side-effects that need close monitoring. They are a lot cheaper than biological therapies.

2. **biological drugs**, such as anti-tumour necrosis factor (anti-TNF) and anti-B-cell therapy, which act highly specifically on cells or molecules that are important in driving the disease process, and have been developed against the background of an increasing understanding of the pathogenesis of inflammatory arthritis. Infliximab and etanercept were the first anti-TNF drugs, available for clinical use in the late 1990s (though not approved by NICE until 2002). Newer anti-TNF agents have emerged since, as well as other biological therapies that block other pathways that are important in inflammatory arthritis. Anti-TNFs can be rapidly effective in just over 60% of RA patients. They are much more expensive than conventional DMARDs, which has limited their uptake in many countries. Not all biological therapies have been deemed by NICE to be cost-effective and currently the anti-interleukin-1 (anti-IL-1) drug anakinra is therefore not available in the NHS. The anti-TNF drugs (infliximab, etanercept, adalimumab and certolizumab pegol) have been approved by NICE, together with rituximab (an antibody directed against B-lymphocytes) for patients who fail on anti-TNF. With the exception of certolizumab pegol, which is subject to separate guidance, NICE is now recommending (in its June 2010 draft guidelines) the use of a second anti-TNF if the first one fails, provided that patients are intolerant of, or there are contraindications to, rituximab or methotrexate. They are also recommending that abatacept (a T-cell inhibitor) and tocilizumab (anti-IL-6) be made available to the same group of patients.

In putting this article together, we sought advice from GPs on the topics that would be of greatest relevance to them. The following areas were suggested and are addressed below:

- the tendency to use combinations of conventional DMARDs in early active RA
- guidance about the use of steroids in early disease and for flares
- some observations on leflunomide, which still seems relatively unfamiliar to many GPs
- what GPs need to know about biological therapies
- advice on vaccination for RA patients.

**Combination therapy in rheumatoid arthritis and the use of steroids**

The NICE guidelines recommend that for patients with newly diagnosed active RA, a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) should be offered as first-line treatment as soon as possible, ideally within 3 months of the onset of persistent symptoms. This recommendation is based on a number of trials in early RA, and therefore only applies to patients who have RA and not other undifferentiated inflammatory arthritis, where the evidence for the optimal approach is less well established. A systematic review in 2005 showed that combination therapy was more efficacious than monotherapy, and a health economic analysis commissioned for the NICE guidelines demonstrated that combination therapies were more cost-effective than monotherapies, with the added cost of additional drugs being outweighed by the additional efficacy. For the majority of rheumatologists, methotrexate is the favoured anchor drug to which other DMARDs are added, because patients have a greater tendency to stay on this drug longer than other DMARDs (due to a combination of better tolerability and equal efficacy). Because conventional DMARDs take time to work, steroids are a useful way of dampening down the symptoms of inflammatory arthritis and buying some time for the delayed DMARD onset of action. Steroids are used in many of the highly efficacious published regimens. They can be used orally or intramuscularly for a polyarthritis, or intra-articularly if a small number of joints are affected. There is evidence that steroids not only are effective at rapidly diminishing the symptoms of inflammatory
arthritis, but also are disease-modifying. However, the symptomatic benefit that steroids give tends to diminish over time, and the advantages of steroids begin to be outweighed by the well-documented disadvantages. The NICE guidelines emphasise the need to try to avoid the long-term use of steroids wherever possible.

What does this mean for GPs?

1. GPs may see more patients with early active RA on combinations of DMARDs. The monitoring requirements for these patients are no greater than they are for the individual drugs. It was reported in 2005 that, overall, combination DMARD therapy resulted in more withdrawals for toxicity than monotherapy; however, commonly used combinations such as methotrexate with sulfasalazine or with hydroxychloroquine were associated with similar toxicity to monotherapy. GPs need to maintain vigilance for side-effects in any patient on DMARDs, whether on monotherapy or combination therapy, and liaise closely with their specialist unit if they have concerns.

2. The NICE guidelines recommend fast escalation of DMARDs to a clinically effective dose. A recent systematic review on the best dosing strategy to optimise rapid and early response and minimise toxicity suggested a starting dose of 15 mg/week and escalating by 5 mg/month to 25–30 mg/week. GPs may see patients on higher doses of oral methotrexate than are recommended in the British National Formulary (20 mg/week). In patients who develop side-effects on oral methotrexate parenteral administration can diminish gastrointestinal problems, and GPs may witness increasing use of this approach. All patients should receive folic acid supplementation while on methotrexate; this reduces gastrointestinal side-effects. There is no strong evidence to guide when this should be given, but most rheumatologists give this 1–2 days after methotrexate. Sometimes folic acid is given daily to patients who have troublesome nausea on methotrexate.

3. In an ideal world GPs would not need to use steroids in early RA, because they would be able to fast-track such patients to a local specialist unit where the patient could be rapidly assessed without steroids masking the physical signs, giving the specialist team a better chance of making a diagnosis and assessing the disease activity and severity. However, the National Audit Office Report published in 2009 showed that rapid access to a specialist team is not universal across the UK. If for any reason there are delays in accessing a specialist team, and a patient is really struggling with a polyarthritis, the authors of the Report recommend the use of intramuscular steroids (methylprednisolone or triamcinalone acetonide 80–120 mg) rather than oral steroids, which can be difficult to withdraw. In patients with established disease, a polyarticular flare can also be treated with intramuscular steroids in either primary or specialist care. If steroids are needed to be used it is always useful if this can be communicated to the specialist team so that DMARDs can be reviewed to determine whether alterations may improve disease control.

Leflunomide

Randomised controlled trials have demonstrated the clinical efficacy of leflunomide as monotherapy for active RA, and it appears to be as efficacious as methotrexate. Although leflunomide has been prescribed for more than a decade for RA and psoriatic arthritis, many GPs still approach this drug with high levels of caution. Some local GPs in the authors’ experience seem happy to monitor methotrexate, but not leflunomide. Is there any evidence to support this concern?

- Originally the recommendation for commencing leflunomide was to give 3 days of 100 mg loading dose followed by 20 mg daily. However the side-effects associated with this approach have meant that most rheumatologists have now abandoned this.
- Leflunomide is less popular as a DMARD in the UK compared to methotrexate and sulfasalazine, so GPs may be less familiar with it.
- Leflunomide has a long half-life, so when serious side-effects occur washouts are advocated with colestyramine or activated charcoal. These wash-out regimens are not pleasant for the patient, and understandably raise concerns about the drug.
- The risk of developing hypertension from leflunomide use is 10%, so monitoring of blood pressure is an additional requirement to blood-test monitoring.
However, on balance side-effects with leflunomide are similar in rate and severity to those seen with methotrexate, so there is no good reason why once a patient is established on this drug it should not be included in shared-care protocols.

**Anti-TNF and other biological therapies**

Biological therapies are always prescribed from secondary care. It is estimated that currently about 6% of all RA patients in the UK are on biological therapy, so GPs will have contact with patients who are exposed to these drugs. It is important that GPs are aware which of their patients are on biological therapies for an inflammatory arthritis so that they can be vigilant for important side-effects.

Generally biological therapies are well tolerated. Common side-effects are of rashes and constitutional symptoms. These are often mild and self-limiting and often do not lead to drug discontinuation. Of greater concern are serious adverse events that may relate to anti-TNF therapy. Because TNFα is important physiologically in acting against infection and tumour development, there are understandable concerns that blocking this cytokine may lead to increases in sepsis and malignancy. The evidence for both infection and cancer risk of anti-TNF drugs is contradictory but on the whole reassuring, and suggests:

- a slight increased risk of overall serious infection, perhaps twofold, particularly in the early stages of administration (first 3–6 months). Anti-TNF may also suppress the acute-phase response so that patients may not feel particularly unwell or have fevers even in the presence of severe infections. Patients on biological therapies who feel non-specifically unwell should be considered to have sepsis until proven otherwise, and should be referred to the specialist team.

- definite vigilance is required for tuberculosis. All patients receive pre-screening with histories, chest x-rays and skin testing where appropriate with anti-tuberculosis prophylaxis when necessary. However, all patients continue to need monitoring closely thereafter for the emergence of acute or chronic infections.

- no overall increased risk of cancer, but concerns over non-melanomatous skin cancers, and possible greater risks for patients with previous tumours. All patients should be encouraged to monitor their skin closely, and report any new lesions.

On balance, anti-TNF drugs have revolutionised the quality of life for many patients with inflammatory arthritis. Although the advantages of these drugs far outweigh their disadvantages, we cannot be complacent regarding the close monitoring of patients on anti-TNF.

On a practical note, as noted above biological therapies are prescribed from secondary care and therefore do not appear on the patient’s list of medications held by the practice and easily viewed on the prescribing screen of the computerised record. The omission of this information could lead to problems in the management of these patients (e.g. ensuring that anti-TNF is stopped during infections). The Primary Care Rheumatology Society has suggested adding a message on the prescribing screen of computer records to alert the GP to the fact that the patient is on a biologic (Warburton L, pers com). Also, in Summary Care Records the information regarding use of a biological therapy is not accessible to healthcare workers needing records out of hours. Each practice should consider how to make this information more readily available in such circumstances.

**Vaccinations**

For all patients who are on immunosuppressive medication (e.g. methotrexate, leflunomide, steroids – even in low doses – and biological agents), immunisations (pneumococcal, annual influenza and now swine flu vaccination) are recommended as in the BSR guidance. Wherever possible patients are encouraged to have these prior to commencing anti-TNF or rituximab treatment because biological therapies may decrease the effectiveness of the vaccine.

**Conclusion**

We have covered many aspects of disease-modifying drugs and biological therapies in this issue of Hands On. This field of medicine is changing so rapidly that a further update will inevitably be required again soon. However, an understanding of the issues covered in this report will enable GPs to manage their patients with inflammatory arthritis and any potential problems arising from their drug therapies.
Key points

• NICE has recommended early referral for all patients with suspected inflammatory arthritis
• Combinations of DMARDs are also recommended and will be used much more widely
• There is no evidence to suggest that side-effects will increase with combination treatment
• Leflunomide is a newer DMARD with similar efficacy to methotrexate
• 6% of RA patients in the UK are currently on biological therapies
• Biologics can mask the effects of infection such as temperature and systemic upset, so extra vigilance from GPs is necessary
• The risk of serious infection is increased perhaps twofold in patients on biologics
• Each GP practice should ensure that their clinical record clearly states that the patient is on a biological therapy

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Useful resources and further reading

DMARDs

BSR guidance


NICE guidance


Combination therapy compared to monotherapy


Leflunomide compared to methotrexate


ANTI-TNF THERAPY


VACCINATIONS

BSR guidance


OTHER

Dosing of methotrexate


Folate supplementation


Access to specialist referral


Arthritis Research UK drug information sheets

Patient information sheets on individual DMARDs and biologics, revised annually and accessible via: http://www.arthritisresearchuk.org/arthritis_information/arthritis_drugs__medication.aspx.
Tackling Osteoarthritis in Sport
A conference to investigate the prevention and management of osteoarthritis following sport or exercise

21st and 22nd October 2010
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