PAPER

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Recent advances in the management of rheumatoid arthritis

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ABSTRACT A truly remarkable transformation in RA management has occurred over the past decade. Patient and physician expectation of treatment effect are now high, and management of inflammatory disease and co-morbidity is more readily tailored to individual patient needs. Therapy in rheumatoid arthritis encompasses symptom-relieving drugs (mainly NSAIDS) and DMARDS that retard progression of the disease. Increasingly, the aim of DMARD therapy is to achieve early and sustained suppression of disease activity. Where this can be achieved NSAIDS could potentially be discontinued. The rapid expansion of available therapies for RA over the past decade is exciting, but necessitates constant re-evaluation of treatment goals and toxicity profiles. It may be that the early use of DMARDS including anti-TNFα drugs will render NSAIDS and corticosteroids unnecessary. Early, sustained and intensive treatment will hopefully improve medium and long-term outcomes in RA. In this review we outline issues that have arisen with the use of NSAIDS and advances in the use of existing DMARDS. In addition, currently available biological agents and those in development are also discussed.

KEYWORDS Please provide up to six keywords (list alphabetically)

LIST OF ABBREVIATIONS American College of Rheumatology (ACR), angiotensin-converting enzyme (ACE), COX-2-specific inhibitors (coxibs), C-reactive protein (CRP), cyclo-oxygenase (COX), disease-modifying anti-rheumatic drugs (DMARDS), erythrocyte sedimentation rate (ESR), *Helicobacter pylori (H. pylori),* interleukin-1 receptor antagonist (IL-1ra), Interleukin 1 (IL-1), Interleukin 6 (IL-6), non-steroidal anti-inflammatory drugs (NSAIDS), proton pump inhibitors (PPIs), rheumatoid arthritis (RA), Scottish Intercollegiate Guidelines Network (SIGN), tumour necrosis factor alpha (TNFα), tumour necrosis factor beta (TNFβ)

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OVERVIEW

SYMPTOM-RELIEVING DRUGS

Non-steroidal anti-inflammatory drugs are used to relieve the symptoms of RA. Both the benefits and potential risks of NSAIDS exert their effect on the formation of prostaglandins from arachidonic acid, through inhibition of the enzyme COX (Figure 1). Three isoforms of COX have been described and NSAIDS affect both COX-1 and COX-2. The NSAIDS that are available differ in their relative inhibition of COX-1 and COX-2. Indometacin (indomethacin), for example, is 80% COX-1 and 20% COX-2 selective and very prone to cause gastrointestinal side-effects. Diclofenac is about 50% of each, whereas the ratio of etodolac and meloxicam is 30:70, COX-1:COX-2 selective. Several COX-2-specific inhibitors, the 'coxibs', are also available.

Efficacy

The benefits of NSAIDS and coxibs are similar. They relieve the local manifestations of inflammation – pain, stiffness, swelling, and tenderness – but not the systemic response to inflammation, as assessed by ESR and CRP.

Toxicity

The potential harm from NSAIDS and coxibs differs. Currently, the two areas considered most important are the gastrointestinal side effects and the effects on the cardiovascular system.

Gastrointestinal complications

Non-steroidal anti-inflammatory drugs, due to prostaglandin synthesis inhibition, can damage the gastrointestinal tract throughout its length. Of greatest concern is the occurrence of bleeding (the commonest complication), perforation, and gastric outlet obstruction. The elderly, especially females with cardiovascular disease,

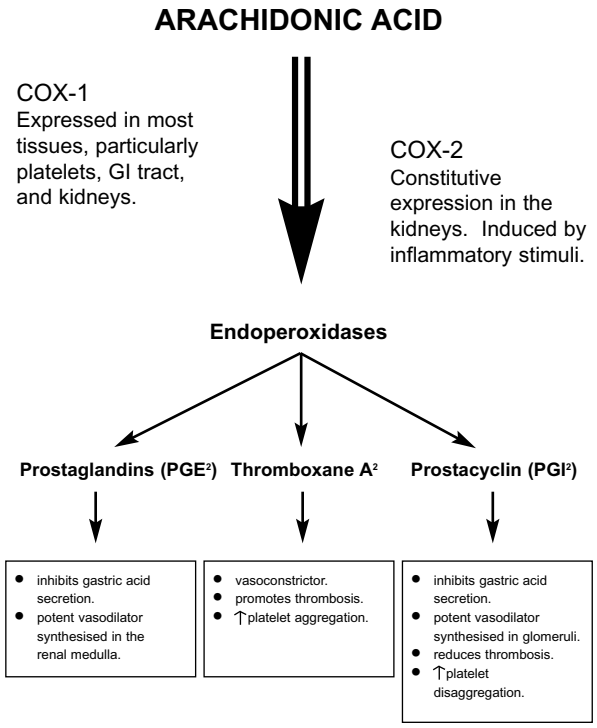

FIGURE 1 The arachidonic acid cascade.

are at greatest risk. Concomitant *H. pylori* infection further increases the occurrence of peptic ulceration and the risk of gastrointestinal bleeding. Coxibs significantly reduce these complications but concurrent aspirin use negates any benefit. Due to the concerns regarding coxibs it is prudent to review how ulceration and gastrointestinal complications can be reduced.

Treatment and prevention

In NSAID-induced upper gastrointestinal tract complications, H-2 blockers, proton pump inhibitors, and misoprostol (a synthetic prostaglandin analogue) can all be effective in reducing symptoms and in the treatment and prevention of ulcers and ulcer-related complications.

H-2 blockers are not recommended in those at risk of NSAID complications. They can heal gastric but not duodenal ulcers and their role in ulcer prevention is limited.

Proton pump inhibitors are the most frequently used agents to relieve NSAID-induced upper gastrointestinal symptoms but no randomised controlled trials evaluating their potential benefit on NSAID-related gastrointestinal complications are available. Proton pump inhibitors are superior to misoprostol in both ulcer healing and prevention.

Misoprostol, a synthetic prostaglandin analogue, has anti-secretory properties and promotes healing of gastric and duodenal ulcers. Its use frequently results in symptoms of gastrointestinal hurry. Studies of preventing ulcer-related complications have been undertaken with misoprostol and its concomitant use prevents perforation and gastric outlet obstruction but not bleeding.

Eradication of *H. pylori* prior to NSAID use reduces ulceration but the benefit on ulcer-related complications is not known and the relationship between *H. pylori* and NSAID-induced ulcers is complex.

Cardiovascular complications

Hypertension

Non-steroidal anti-inflammatory drugs increase supine blood pressure by a mean of 5 mm Hg. The effect on blood pressure is greater with coxibs. Such sustained increases in blood pressure may explain the increased cardiovascular events in RA and osteoarthritis.

Heart failure

Non-steroidal anti-inflammatory drugs cause fluid retention and systemic vasoconstriction which can worsen heart failure. Their interaction with beta-blockers and ACE-inhibitors further limits their use. Coxibs are contra-indicated in NYHA class II–IV heart failure.

Thrombosis

The increased incidence of thrombotic events due to the coxibs was first described with rofecoxib, which has since been withdrawn. This appears to be a class effect, the mechanism of which is not known. Coxibs are contra-indicated in established ischeamic heart disease, cerebrovascular disease, and congestive cardiac failure (NYHA II–IV). It is advised that in those with significant risk for cardiovascular events (hypertension, hyperlipidemia, diabetes mellitus, and smoking) or peripheral vascular disease, the risk:benefit ratio should be considered before prescription of coxibs. Furthermore the risk:benefit ratio for patients taking low dose aspirin for primary prevention of cardiovascular events needs to established, since a clear gastrointestinal safety advantage has not been established when coxibs are combined with aspirin.

A prospective long-term study of naproxen in Alzheimer's disease has been discontinued because of an increased cardiovascular and cerebrovascular event rate. It is not known if this applies to all NSAIDS. Patients on both aspirin and ibuprofen have a higher all cause mortality and cardiovascular mortality. This could be because of competitive inhibition for a shared binding site on COX. It is not clear whether this applies to other NSAIDS.

ADVICE ON SAFE NSAID PRESCRIPTION IN RHEUMATOID ARTHRITIS

1 Only one NSAID should be prescribed.
2 Use the lowest recommended dose and for the shortest possible time.
3 Concomitant aspirin use

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i increases risk of gastrointestinal complications
ii either regularly or immediately prior to ibuprofen use negates its benefit
iii negates any gastrointestinal benefit from the coxibs

It is not known whether this applies to other anti-platelet agents.

4 Avoid use in NYHA II–IV heart failure.
5 Coxibs should not be used in those with, or at high risk of, atheromatous vascular disease. Naproxen also increases cardiovascular disease risk. The case for other NSAIDS is not proven. Monitor blood pressure.
6 Avoid use in renal impairment.
7 Consider *H. pylori* erradication in patients with persistent dyspepsia or prior peptic ulceration.
8 Cautious use in patients on oral corticosteroids.
9 Concomitant misoprostol use reduces the risk of perforation and gastric outlet obstruction but not bleeding.
10 The benefit of proton pump inhibitors in reducing ulcer-related complications is not proven.

DISEASE-MODIFYING THERAPY

Disease-modifying anti-rheumatic drugs modify the local features of RA inflammation as well as its systemic response. Many also reduce radiological progression as well as mortality. Table I shows the available agents, and the monitoring guidelines in the BNF should be followed.

TABLE I Available DMARDs.

DMARD	Dose	Common toxicity
Auranofin	3 mg twice daily	Gastrointestinal Mucocutaneous
Azathioprine	1–2 mg/kg/day	Gastrointestinal Haematological
Ciclosporin A	2·5–4 mg/kg/day	Gastrointestinal Cardiovascular Renal Neurological
Hydroxychloroquine	< 6·5 mg/kg/day	Gastrointestinal Mucocutaneous Ocular
Leflunomide	20 mg/day	Mucocutaneous Gastrointestinal Cardiovascular
Methotrexate	7·5–25 mg/week	Gastrointestinal Haematological Infection
Sulfasalazine	40 mg/kg/day	Gastrointestinal Mucocuteneous Haematological
Sodium aurothiomalate	Intramuscular 50 mg/week Adjusted to response	Mucocutaneous Renal Haematological

Damage, as assessed by plain X-rays, and disability, occur early and are sustained throughout the disease course for RA. Therefore it has been suggested that a window of opportunity exists in early disease and so a delay in initiating DMARD therapy results in a poorer clinical outcome in the short to medium term. The SIGN and ACR guidelines thus advise DMARD use within three months of symptom onset. The choice of initial agent depends on physician familiarity, patient choice, and the presence of co-morbidity.

Efficacy

For DMARD monotherapy, the extent of clinical benefit once optimal dosages are achieved is similar, except for hydroxychloroquine and auranofin which are less effective. Sulfasalazine and methotrexate are the most commonly used drugs. Single agent long-term studies show that this early benefit is not sustained. Rheumatolgists have thus sought to optimise available treatments by using them in combination. Several different combination approaches have been studied.

1 *Sustained DMARD combination therapy.* The combination of methotrexate, sulfasalazine, and hydroxychloroquine compared with sulfasalazine + methotrexate and methotrexate + hydroxychloroquine has been shown to be superior by North American investigators but radiological outcome was not determined. The clinical results have been confirmed in an open single randomised study from Finland in early RA, with radiological benefit that is sustained for three years after treatment initiation.
2 *Step-down combination therapy.* This involves starting treatment with several DMARDS and withdrawing agents as benefit is achieved. A pan-European study compared sulfasalazine monotherapy with oral corticosteroids (prednisolone commenced at 60 mg, tapered every six weeks and withdrawn by week 28) + sulfasalazine (2 g/day) + weekly methotrexate (7·5 mg weekly and withdrawn by week 40). The initial clinical results were promising but the benefit was not maintained at 56 and 80 weeks.
3 *Step-up combination therapy.* This involves combining agents in those with an inadequate response to a single agent and is a more intuitive approach, similar to that used in other chronic disorders such as type II diabetes and hypertension. The first randomised controlled trial of step-up therapy to report benefit was the addition of ciclosporin A to methotrexate non-responders in established RA (the doses of methotrexate were lower than those currently used). No assessment of radiological damage was made. This is not an approach currently used in clinical practice. We have just completed a study comparing the addition of methotrexate to sulfasalazine non-responders after six months of treatment to placebo + sulfasalazine or switching to methotrexate. The initial analyses show encouraging results for combination therapy.

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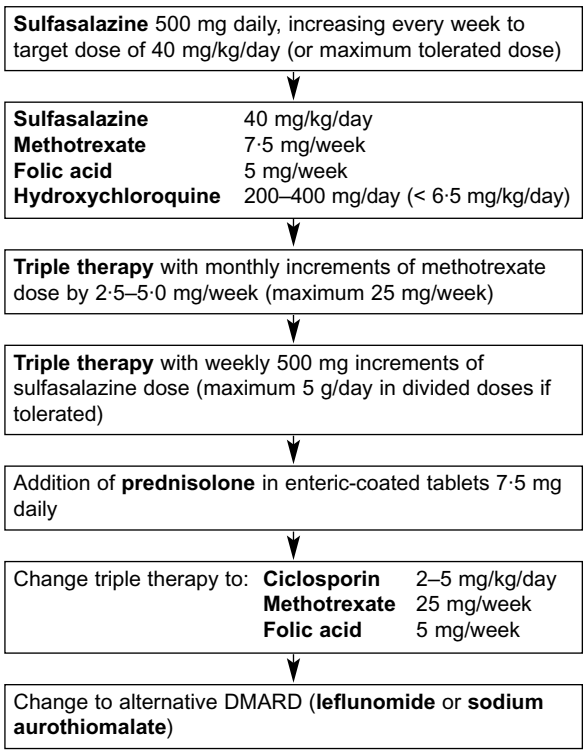

FIGURE 2 Tight control of RA (TICORA) treatment protocol.

4 *Tight control of RA.* Another approach successfully studied in Glasgow in a single blind randomised controlled study has been to try to achieve sustained tight disease control using a predefined treatment strategy (Figure 2) and joint injections. Compared with routine care, patients intensively treated were more likely to be in remission and have good response using a validated composite measure of disease outcome. Benefit was also seen in radiological outcome. Intensively treated patients were more likely to be on combination therapy, received higher methotrexate doses, were less likely to discontinue DMARDS, and on average had a large joint injected with corticosteroid every two months. These clinical results are very similar to what can be potentially achieved with biological agents.

BIOLOGICAL AGENTS

The traditional DMARDS, except sulfasalazine and leflunomide, were studied because of serendipitous observation. A better understanding of the underlying mechanisms of disease, and developments in biotechnology, has resulted in a more targeted approach to suppressing disease activity. A characteristic of rheumatoid synovitis is the presence of synovial cell hyperplasia, consisting of macrophages and fibroblasts. These secrete pro-inflammatory cytokines and matrix metalloproteinases which mediate cartilage degradation. The predominant lymphocytes are CD4+ve T cells, of which some are activated. Plasma cells that secrete rheumatoid factor and B cells are also present.

Synoviocytes and their products

Interleukins 1 and 6 and TNFα are the main pro-inflammatory cytokines produced. TNFα is considered to mediate the proliferative and inflammatory aspects of the disease, whereas IL-1 results in cartilage proteoglycan resorbtion and bone erosion, the destructive aspects of the disease. Interleukin-6 also mediates many of the actions of IL-1 and TNF but also has B cell-stimulating effects. Antagonists to each of these have been developed, the TNFα antagonists being the first to be licensed.

Tumour necrosis factor a antagonists

The NICE guidelines for their use in RA advise that:

All patients must:

1 Satisfy the 1987 criteria of the ACR classification criteria for a diagnosis of RA.
2 Have active RA (DAS28 score >5·1). Measurements of disease activity should be made at two points, one month apart.
3 Have failed standard therapy. Patients must have had adequate therapeutic trials of at least two standard DMARDs (IM gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine, methotrexate, or leflunomide, of which methotrexate must have been one).
An adequate therapeutic trial would be defined as:
- Treatment for at least six months, with at least two months at standard target dose (unless significant toxicity limited the dose tolerated)
- Treatment for less than six months, where treatment was withdrawn because of drug intolerance or toxicity, but normally after at least two months at therapeutic doses
- Criteria for exclusion and withdrawal of therapy are shown in Table 2.

Three licensed agents are available. These are:

1 Infliximab (Remicade®, Schering-Plough). A chimeric IgG monoclonal antibody; its antigen-binding portion is murine and the constant region human. It binds to both soluble and membrane-bound TNFα, lysing cells to which it is bound by complement and antibody-dependent mechanisms. It is given as an intravenous infusion. In RA it is ineffective when given alone; guidelines advocate that it should be used with maximum tolerated methotrexate dose. The advised dosage is 4 mg/kg given at zero weeks, two weeks, six weeks, and every eight weeks thereafter.
2 Adalimumab (Humira®, Abbott Laboratories). This is a recombinant human IgG-1 monoclonal TNFα antibody that neutralises soluble TNF and mediates necrosis of cells expressing TNFα. It is given as a subcutaneous injection. The advised dose is 40 mg

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TABLE 2 Criteria for exclusion or withdrawal of treatment with TNFα antagonists.

Criteria for exclusion		**Criteria for withdrawal of therapy**
Women who are pregnant or breastfeeding	Active infection	Adverse events including: malignancy, severe drug-related toxicity, pregnancy (temporary withdrawal), severe intercurrent infection (temporary withdrawal)
Patients at high risk of infection including: chronic leg ulcers, previous tuberculosis (NB: patients with previous TB may be eligible if they have completed a full course of anti-tuberculous therapy within the modern antibiotic era), septic arthritis of a native joint within the last 12 months, sepsis of a prosthetic joint within the last 12 months, or indefinitely if the joint remains in situ, persistent or recurrent chest infections, indwelling urinary catheter	New York Heart Association (NYHA) grade III/IV congestive cardiac failure	Inefficacy: lack of response, but not within the first 3 months of treatment, a response is defined as improvement in the DAS28 score by > 1·2 or the achievement of a DAS28 score of < 3·2
Malignancy or pre-malignant state excluding: basal cell carcinoma, malignancies diagnosed and treated < 10 years previously	Clear history of demyelinating disease	

once every two weeks which can be increased to weekly in non-responders.

3 Etanercept (Enbrel®,Wyeth) is a fusion protein of the type 2 TNF receptor (p75) joined to the Fc portion of IgG-1, thus binding to soluble TNFα and TNFβ, preventing binding to their respective receptors. It is given as a subcutaneous injection. The licensed dose is 25 mg twice weekly or 50 mg once weekly.

The benefits of the TNFα antagonists are very similar and in the majority truly significant. Initial studies were undertaken in patients with established disease. With all three drugs, studies in early RA have been reported. When used with methotrexate in early disease, radiological progression is halted with all three agents. Table 3 summarises their potential toxicity.

Interleukin receptor antagonists

The IL-1 receptor is naturally down-regulated by IL-1ra. A recombinant form of this protein (Anakinra®,Amgen) has been evaluated in RA. It has a very short half-life and therefore is given as a daily subcutaneous injection. Although licensed, it has not been approved by NICE. There are no IL-6 antagonists licensed for use but these agents are being evaluated.

T cells and their products

T cells can comprise up to 50% of infiltrating cells in rheumatoid synovitis. CD-4+ve cells of the Th1 phenotype which produce interferon-g and IL-2 predominate over the CD-8+ve subset. Most of the CD-4 cells are memory cells, some also express markers which suggest that they mediate B cell help and thus enhance local auto-antibody formation.

Cytotoxic T lymphocyte antigen 4–Ig (CTLA4–Ig, Abatacept®, Bristol-Myers Squibb). T cell activation requires two signals; the first on binding of antigen to the T cell receptor, the second requires the binding of another T cell surface protein, CD-28 to its ligand (CD-80 or CD-86) on antigen-presenting cells. Cytotoxic T lymphocyte antigen 4, a protein normally expressed on T cells, blocks binding to CD-80 or CD-86. CTLA-4 joined to the heavy chain constant region of IgG-1 is a recombinant fusion protein which inhibits the second T cell activation signal and thus T cell activation. In a placebo-controlled study of patients on methotrexate, 10 mg/kg of CTLA4~Ig produced sustained improvements similar to those achieved with TNFα antagonists.

B cells

B cells compromise only a small proportion of cells in rheumatoid synovitis. Their persistence depends on so called nurse cells of thymic origin and T cells. In addition to other mechanisms, immune complexes containing rheumatoid factor stimulate macrophages to produce pro-inflammatory cytokines. Edwards *et al.* postulated that such immune complexes promote B cell persistence in synovium and hence B cell depletion may be of benefit.

Rituximab (Rituxan®, MabThera) is a genetically engineered chimeric CD-20 monoclonal antibody licensed for CD-20+ve B cell non-Hodgkin's lymphoma treatment. CD-20 is expressed on the cell membrane of pre-B and mature lymphocytes but not on stem cells, pro-B lymphocytes, or plasma cells. The mechanism of cytotoxicity due to the antibody is not known. It is given as a slow intravenous infusion. The first case series of treated RA patients also received cyclophosphamide and corticosteroids. The encouraging results have led to several protocols being devised. The short-term results in conjunction with methotrexate are encouraging.

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TABLE 3 Toxicity of anti-TNFα drugs.

Toxicity profile	Anti-TNFα	Management guidelines for use
Immediate	• Infusion reactions with Infliximab - Symptoms include hives, dyspnoea, chest pain and high/low blood pressure - Can occur during or after infusion, up to 12 days after - Delayed reactions may include fever, rash, headache and myalgia/arthralgia	Infliximab should be discontinued in patients who develop infusion reactions
	• Local injection site reactions with Etanercept and Adalimumab - Erythema, itching, pain or swelling - Mean duration of reactions was 3 – 5 days	Local site injections do not necessitate discontinuation
Intermediate	• Tuberculosis - reactivation of latent TB is highest in the first 12 months of treatment	Pre-commencement TB screening Prophylactic anti-TB therapy for those with potential latent TB Patients who develop symptoms of TB should be treated with full anti-TB chemotherapy but may continue with their anti-TNFα therapy if clinically indicated
	• Other serious infections HIV - Effects on anti-TNFα are unknown	Little evidence apart from several case reports on the use of anti-TNFα in patients with HIV, hepatitis B and hepatitis C Anti-TNFα therapy is not currently advised in patients who are HIV positive
	Hepatitis B - Contradictory case reports, some suggesting severe reactivation and others no deleterious effects	Anti-TNFα therapy should be avoided in patients with hepatitis B infection
	Hepatitis C - Initial reports suggest no deterioration in hepatitis or viral load except for a single case of hepatitis C reactivation	Anti-TNFα therapy may be used with caution in patients with hepatitis C
	• SLE syndromes and autoimmunity - Rare cases have been reported - Symptoms resolve within 6 weeks to 14 months of discontinuing anti-TNFα therapy - No evidence that developing autoantibodies while on anti-TNFα therapy increases the risk of developing clinical SLE	If symptoms of SLE-like syndrome develop while on anti-TNFα, therapy should be discontinued and appropriate treatment instituted
	• Congestive cardiac failure / cardiovascular disease - increased mortality in patients with CCF receiving Infliximab prompted warning statements in November 2001 - Etanercept may also adversely affect CCF	Anti-TNFα should not be used in patients with NYHA grade II-IV Can be used in caution in mild CCF (NYHA grade I) Should be discontinued if CCF worsens
	• Demyelination - Several case reports of demyelination which responded to discontinuation of anti-TNFα therapy and treatment for the acute demyelination	Anti-TNFα should not be commenced in patients with clear history of demyelination and best avoided if there is a possible history or strong family history Should be withdrawn if demyelination occurs
Late	• Malignancy - Lymphoma (3-fold higher incidence than general population) - Other malignancies observed include colon, breast, lung and prostate (similar incidence and type compared with general population)	As yet, there is no evidence of an increased risk of solid tumours or lymphoproliferative disease with anti-TNFα therapy Anti-TNFα should be used with caution in those with pre-malignant conditions (Barrett's oesophagus, cervical dysplasia, colonic polyps) and those with previous malignancy

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CORTICOSTEROIDS

The value of long-term low dose oral corticosteroid therapy when used in combination with DMARDS has been unclear. All clinical studies show that the initial benefit of corticosteroids is not maintained beyond the first six months. When used with early and sustained DMARD therapy we have shown that low dose prednisolone confers no radiological advantage. Of particular concern is their toxicity, which includes osteoporosis, hypertension, and increased NSAID gastrointestinal tract toxicity and infections as well as accelerated atherosclerosis. RA patients in observational cohorts on low dose oral corticosteroids have increased mortality. Current guidelines advise that oral corticosteroid use should be balanced against their potential toxicity and account should be taken of any co-morbidity and concomitant drug therapy. Patients should also be advised of potential long-term toxicity.

HIGHLIGHTS

- NSAIDS provide symptomatic benefit in rheumatoid arthritis (RA) – they do not modify the disease process
- COX-2 specific inhibitory NSAIDS, the coxibs, do not provide any additional symptomatic benefit over other NSAIDS. They should be used with caution in those with atheromatous vascular disease or those with cardiovascular system risk factors
- Proton pump inhibitors effectively relieve NSAID-induced upper gastrointestinal symptoms but have no proven benefit in reducing NSAID-related ulcer complications
- Disease-modifying anti-rheumatic drug therapy should be started early in the course of RA
- Tight control of disease activity using combinations of DMARDS may give greater clinical and radiological benefit than conventional therapy
- Anti-tumour necrosis factor A agents are effective in treating established RA, conferring very significant clinical and radiological benefit. They should be used according to NICE and SMC (Scottish Medicines Consortium) guidelines
- Anti-tumour necrosis factor A agents increase the risk of infection, especially tuberculosis. All patients should be screened for latent TB prior to use. Their long-term risks are not known.

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