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Cardiovascular Risk Profile of Antirheumatic Agents in Patients with Osteoarthritis and Rheumatoid Arthritis

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Contents

Abstract

Several new drugs have become available for the treatment of patients with osteoarthritis and rheumatoid arthritis (RA). These agents include selective cyclooxygenase (COX)-2 inhibitors, leflunomide and anti-tumour necrosis factor (TNF)-α antagonists.

COX-2 inhibitors have a more favourable gastrointestinal adverse effect profile than conventional non-steroidal anti-inflammatory drugs (NSAIDs). However, the COX-2 inhibitors are also associated with hypertension, oedema and congestive heart failure, the well-known adverse effects of conventional NSAIDs. Patients with treated hypertension should be monitored regularly when conventional NSAIDs or COX-2 inhibitors are administered. At present, there is a considerable debate regarding the risk of cardiovascular events with the COX-2 inhibitors. The available literature gives no unequivocal answers. This matter can only be solved by an appropriate trial assessing the cardiovascular risk of these agents.

Patients with RA appear to have an enhanced cardiovascular risk which might be related to an unfavourable lipid profile. Corticosteroids induce hypercholest-

erolaemia in patients other than those with RA. It was recently shown that total and high-density lipoprotein (HDL) cholesterol were low in patients with RA who had a high disease activity. Contrary to the expectation, combination therapy with prednisolone rapidly improved the atherogenic index (total/HDL cholesterol). Ongoing studies investigating this topic are underway.

It is not known to what extent corticosteroids induce hypertension in patients with RA. Hence, we advocate blood pressure control for these patients.

A small percentage of patients with RA develop hypertension when taking leflunomide, and no other serious cardiovascular adverse effects have been reported in the literature. Blood pressure monitoring is recommended especially in the first months of treatment.

TNFα antagonists are contraindicated in patients with RA who have congestive heart failure. No specific cardiovascular adverse effects have been reported with the use of these agents in the non-cardiovascular compromised patient. TNFα antagonists are the most powerful anti-inflammatory drugs presently available. As inflammation plays an important role in RA as well as in cardiovascular disease and, in view of the increased cardiovascular risk in RA, it is tempting to expect that suppression of inflammation ultimately will lower the cardiovascular morbidity and mortality in patients with RA.

In the last decade several new drugs have become available for the treatment of patients with osteoarthritis (OA) and rheumatoid arthritis (RA). These drugs have powerful anti-inflammatory and/or disease modifying properties. However, some of them are accompanied by cardiovascular adverse effects. In this review we discuss the cardiovascular risk profile of these new agents and their application in patients with cardiovascular disorders. The focus of this review is on the selective cyclooxygenase (COX)-2 inhibitors, leflunomide and anti-tumour necrosis factor (TNF)-α antagonists. As corticosteroids are also frequently used, we also discuss recent data regarding the effects of corticosteroids on lipid metabolism.

1. Osteoarthritis

OA is a chronic disorder characterised by disintegration of articular cartilage, with reactive phenomena and formation of osteophytes. It is not an inflammatory disorder, albeit that there are sometimes signs of inflammation. The incidence increases with age from about 1% in people younger than 30 years of age to almost 10% of those 40 years of age and to more than 50% in individuals older than 60 years. A large-scale incidence study of symptomatic hand, hip and knee OA showed that OA occurred more frequently in women than in men, especially after the age of 50 years.[1] The incidence of knee OA was twice that of hand or hip OA, and women are twice as likely to have OA than men.

Patients with OA of hip or knee have pain that worsens with weight bearing and improves with rest. Inflammation, if present, is mostly mild and localised in the affected joint. The recommended management of hip or knee OA includes modalities as patient education, weight loss and physical therapy as well as drug therapy.[2]

Paracetamol (acetaminophen), a simple analgesic, is comparably as effective as non-steroidal anti-inflammatory drugs (NSAIDs) in patients with mild-to-moderate pain, whereas for severe pain NSAIDs are superior to paracetamol.[3,4]

COX-2 specific inhibitors might have a place in patients who are at an increased risk of serious gastrointestinal adverse events such as bleeding, perforation and obstruction. These risk factors are age above 65 years, use of oral corticosteroids, prolonged use of maximum dose NSAIDs, serious comorbidity, history of peptic ulcer and of upper gastrointestinal bleeding or use of anticoagulants.[2,5]

Alternatively, the use of a nonselective NSAID and misoprostol or a proton pump inhibitor could be considered.[2,3,6,7]

Tramadol, a centrally acting oral analgesic, is a synthetic opioid agonist that also inhibits reuptake of norepinephrine and serotonin with an efficacy comparable to that of NSAIDs. Tramadol is another option for patients who have contraindications to NSAIDs or to COX-2 specific inhibitors as well as those patients who have not responded to previous drug treatment.[7]

2. Rheumatoid Arthritis

RA is a systemic disease with chronic joint inflammation. It is characterised by symmetrical pain and swelling of the joints, and affects approximately 1% of the population. The chronic synovitis may lead to destruction of cartilage and bone. RA has a wide clinical spectrum which varies from mild joint symptoms to severe joint destruction, accompanied by extra-articular symptoms such as pericarditis, pulmonary involvement, vasculitis and mononeuritis multiplex.[8]

The management of RA consists of co-ordinated multidisciplinary care, e.g. with physical and occupational therapy and drug treatment. Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease-modifying agents.

The pain in RA is caused by joint inflammation and therefore NSAIDs are preferred over analgesics for pain management, in view of their anti-inflammatory effects.[9] Analgesics may be added when NSAIDs alone are not enough for pain relief. However, these agents do not change the course of the disease nor do they prevent joint damage. Therefore, patients with persisting disease activity require (early) treatment with disease modifying antirheumatic drugs (DMARDs).[9]

Evidence is accumulating that DMARDs can reduce or prevent joint destruction.[10] Active RA may cause irreversible joint destruction in the first months of the disease and therefore DMARDs should be initiated early in those patients with disease activity, i.e. persisting joint pain, morning stiffness or fatigue, active arthritis or persisting elevation of C reactive protein or erythrocyte sedimentation rate.[9] In general, early application of DMARDs means within several weeks after the first visit to the rheumatologist.

Conventional DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, gold salts, cyclosporin, azathioprine and penicillamine. Methotrexate is considered the drug of choice with a better long-term efficacy than the other conventional DMARDs.[11] Several investigations have demonstrated that combination DMARD therapy might be more effective than mono-DMARD therapy in patients with early disease.[12]

The place of corticosteroids is a continuing matter of debate because of the adverse effects, particularly with long-term use. There is no doubt that corticosteroids rapidly and effectively suppress the inflammation in RA and their use might be justified for short-term therapy, e.g. for 'bridging therapy' between the initiation of DMARD therapy and it actually being effective.[13]

Recently, leflunomide and TNFα antagonists have become available for the treatment of RA. Leflunomide is a pyrimidine antagonist that blocks the enzyme dihydroorotate dehydrogenase, thereby inhibiting DNA synthesis. It has an efficacy similar to that of methotrexate.[14]

TNFα is a pivotal cytokine in the pathogenesis in RA and TNFα antagonism was shown to be very effective in rapidly controlling disease activity. Although TNFα antagonists appear to be the most effective antirheumatic drugs presently available, long-term safety data are not yet available.[14]

Presently two TNFα antagonists are available for clinical use. Infliximab is a chimeric mouse/human anti-TNFα monoclonal antibody that binds to soluble as well as membrane-bound TNFα. Infliximab is administered intravenously and after the initial infusion it is given at 2, 6 and then every 8 weeks thereafter. Etanercept consists of two human TNFα receptors linked to each other and binds to circulating as well as cell-bound TNFα molecules. Etanercept is given subcutaneously twice weekly.

3. Conventional NSAIDs and Selective COX-2 Inhibitors

The isoenzymes COX-1 and -2 catalyse the conversion of arachidonic acid to thromboxanes and prostaglandins. Thromboxane causes irreversible platelet aggregation and vasoconstriction and smooth muscle proliferation, and it is the major COX-1 product in platelets. Aspirin irreversibly inhibits platelet COX-1 and this activity is responsible for its efficacy in the prevention of cardiovascular disease.

Prostacyclin is a potent platelet aggregation inhibitor, a vasodilator and inhibits smooth muscle cell proliferation, and it is the major COX-2 product in vascular endothelium.

At low doses, i.e. up to 100 mg/day, aspirin does not interfere with prostacyclin biosynthesis. Other NSAIDs inhibit both thromboxane and prostacyclin formation, albeit that the degree of inhibition differs between the individual NSAIDs,[15] whereas COX-2 specific inhibitors suppress prostacyclin synthesis without a concomitant inhibition of thromboxane formation.[16,17] COX-2 is upregulated in foam cells and smooth muscle cells of atherosclerotic plaques,[18] and laminar shear forces may increase COX-2 expression in endothelial cells.[19] The resulting increased production of prostacyclin limits the platelet activation thereby counterbalancing the effects of thromboxane, as part of a homeostatic defence mechanism. Elderly patients using NSAIDs are at the highest risk for developing cardiovascular disease. Hence, the use of specific COX-2 inhibitors might pose an additional increased thrombotic risk to them as a result of a lower prostacyclin synthesis.[20-22]

There is accumulating evidence that the use of the COX-2 inhibitors, celecoxib and rofecoxib, results in a significant decrease of gastrointestinal complications compared with non-selective NSAIDs. Recently, two very large trials investigating this topic were published, the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Celecoxib Long-term Arthritis Safety Study (CLASS).

In the VIGOR trial,[23] rofecoxib in a once daily dose of 50mg was compared with naproxen 500mg twice daily in more than 8000 patients with RA. Patients requiring or who had been treated with aspirin were excluded. The primary end point was confirmed clinical gastrointestinal events. Cardiovascular events were also monitored for a future meta-analysis. However, a separate analysis was not specified in the study protocol.

The median treatment duration was 9 months and the incidence of clinically important upper gastrointestinal adverse effects was 2.1 per 100 patient years in the rofecoxib group and 4.5 per 100 patient years in the naproxen group, (relative risk 0.5; 95% confidence interval [CI] 0.3-0.6; $p < 0.001$). The rate of cardiovascular diseases was 0.8 percent in the rofecoxib recipients and 0.4 in the patients treated with naproxen. This difference was mainly caused by a difference in myocardial infarction and occurred mainly in patients with a high risk of myocardial infarction, for whom low-dose aspirin was indicated (but not given).[23] The relative risk among these patients between the rofecoxib group and naproxen group was 4.89 (95% CI 1.41-16.88, $p = 0.01$) and in the group of patients not requiring aspirin the risk was 1.89 (95% CI 1.03-3.45, $p = 0.04$).[20]

In the CLASS trial, celecoxib 400mg twice daily was compared to either ibuprofen 800mg three times daily or diclofenac 75mg twice daily.[24] More than 8000 patients with either RA or OA with an intended treatment period of at least 6 months were studied. The patients were allowed to take aspirin and 21% of patients actually used aspirin.

No statistical difference was observed in the primary endpoint of ulcer complications with an annualised incidence rate of 0.8% in the celecoxib group versus 1.5% in either NSAID group ($p = 0.09$). Combined with symptomatic ulcers these rates were 2.1 and 3.5%, respectively ($p = 0.02$). No significant differences were observed in the cardiovascular events between the two treatment groups.

The rumour about a possible increase of cardiovascular events with rofecoxib has led to a contin-

uous debate whether or not COX-2 inhibitors are associated with an increased cardiovascular risk.

From a theoretical point of view formation of thromboxane without the simultaneous production of prostacyclin, as a result of the suppression of COX-2, could lead to a prothrombotic state. An increased rate of cardiovascular events was not observed in the CLASS trial. There are several reasons for this discrepancy. An indeed true difference, i.e. induction of cardiovascular events by COX-2 inhibitors, might be masked by the aspirin use in the CLASS trial. Moreover, naproxen in contrast to diclofenac and ibuprofen, the comparator drugs in the CLASS trial, might be cardioprotective,[23] although direct evidence for this interesting hypothesis is lacking. In addition, there is no epidemiological evidence for a cardioprotective effect of NSAIDs (including naproxen).[25] Actually, none of the non-aspirin NSAIDs has been adequately investigated in terms of their potential (preventive) cardiovascular effects.[26] Finally, there is accumulating evidence for an increased cardiovascular risk in patients with RA compared to the normal population. The patients studied in the VIGOR trial were patients with RA whereas predominantly patients with OA were studied in the CLASS trial. Patients with OA are considered to have a cardiovascular risk comparable with the general population and this lower background incidence of cardiovascular events might be another explanation for the observed difference between the two trials.

In summary, there is no convincing evidence for an increased cardiovascular risk when COX-2 inhibitors are used instead of conventional NSAIDs. Obviously, there is a need for sufficiently powered trials that address these topics. Until the results of such studies are available this issue, that is whether there is an increased risk with COX-2 inhibitors when compared to placebo or were the results of the VIGOR trial attributable to antiplatelet effects of naproxen, remains a continuing matter of debate.[27,28]

As well as the arterial side the venous side deserves attention, particularly in patients undergoing major orthopaedic surgery. Theoretically, COX-2 inhibitors could lead to a higher incidence of postoperative venous thromboembolic complications in these patients when COX-2 inhibitors are used instead of conventional NSAIDs, which might offset the lower rate of gastrointestinal complications.[29]

3.1 Hypertension and Congestive Heart Failure

NSAIDs cause little or no elevation in blood pressure in normotensive individuals.[30] The risk for interaction between NSAIDs and antihypertensive medication, with a resulting inadequate blood pressure control, is high and there is evidence for a positive correlation between the use of NSAIDs and blood pressure, especially in those already receiving antihypertensive medication.[31,32] The CLASS study revealed that patients receiving celecoxib experienced less hypertension than patients receiving other NSAIDs, 1.7 versus 2.3%, respectively ($p<0.05$). Data regarding hypertension were not provided in the VIGOR publication but a review about the cardiovascular risk of COX-2 inhibitors indicated that more rofecoxib treated patients than naproxen treated patients developed hypertension in the VIGOR trial; for rofecoxib the mean increase in systolic blood pressure was 4.6mm Hg and a diastolic increase of 1.7mm Hg, for naproxen these values were 1.0mm Hg and 0.1mm Hg, respectively.[20]

Rofecoxib and celecoxib were recently compared in a 6-week double-blind investigation of 810 elderly patients with OA receiving antihypertensive agents.[33] Patients were treated with either rofecoxib 25 mg/day (n = 399) or celecoxib 200 mg/day (n = 411). The primary endpoints were changes in systolic or diastolic blood pressure and the occurrence of oedema. Systolic blood pressure increased significantly in 17 and 11% of the patients randomised to rofecoxib and celecoxib, respectively ($p = 0.03$). Diastolic blood pressure increased in 2.3% in the rofecoxib-treated patients and 1.5% in those receiving celecoxib. Oedema was experienced in 9.5% of the rofecoxib group

and 4.9% of the celecoxib recipients. The clinical relevance of the observed oedema is unclear as another study indicated clearing of oedema in many of the patients treated with rofecoxib when the drug was continued.[34] Moreover, one could argue whether or not the applied dosages were equipotent regarding efficacy as there are some suggestions for a lower efficacy of the investigated dose of celecoxib compared with rofecoxib.[35]

Altogether, data regarding COX-2 inhibitors, hypertension and oedema are not yet conclusive. It is unclear whether these adverse effects occur less frequently with COX-2 inhibitors compared with conventional NSAIDs and whether or not there are true differences between celecoxib and rofecoxib.

The kidney produces both COX-1 and COX-2. In healthy individuals renal prostaglandins play a minor role in maintaining electrolyte balance and renal haemodynamic function, and NSAIDs have no significant effect on renal blood flow. However, when renal perfusion is reduced, for example in patients with congestive heart failure, renal prostaglandins become important for maintaining renal blood flow and for the maintenance of compensated heart failure in these patients with a compromised left ventricular function. NSAIDs reduce renal perfusion in these susceptible patients and recently, it was shown that conventional NSAIDs double the risk of congestive heart failure in elderly patients, particularly in those with a history of cardiac disease.[36]

The NSAIDs, sulindac, meloxicam and nabumetone were introduced for their so-called renal-sparing effects.[37-40] However, convincing clinical evidence regarding the effects of these agents on cardiovascular homeostasis in patients with an impaired left ventricular function is not yet available. COX-2 specific inhibitors probably have the same risk[41] and, recently, both sodium and potassium retention,[42,43] and a decreased glomerular filtration rate were observed in salt-depleted individuals, by several investigators.[44]

4. Corticosteroids

Corticosteroids can be of value in the management of rheumatoid arthritis, and between 15 and 40% of patients with RA use corticosteroids at any one time.[13] Several double-blind trials indicate some advantages of corticosteroid treatment, which is confirmed in meta-analyses.[45,46] However, these studies are limited by a relatively short treatment time and the toxicities of corticosteroids may be cumulative over time. Several large retrospective investigations found corticosteroids to be an independent predictor of adverse outcomes.[13] In addition, corticosteroids induce unfavourable lipid profiles in patient categories other than those with RA.[47,48] Moreover, corticosteroids can cause hyperglycaemia with subsequent detrimental effects on atherogenesis. Therefore, it is commonly stated that corticosteroids should be used minimally, if at all, in patients with RA.

The major cardiovascular adverse events associated with corticosteroids include hypertension and dyslipidaemia. The occurrence of hypertension has not been assessed adequately but has been estimated to be 20%.[49] However, a retrospective investigation in 195 patients with asthma or RA indicated that low dose corticosteroid treatment (prednisone or prednisolone <7.5 mg/day) for more than 1 year failed to show any relationship between blood pressure and dose or duration of therapy.[50] Another, prospective, investigation in 155 patients with early RA showed no influence of corticosteroids in the 76 patients randomised to combination therapy with prednisolone (tapered and stopped after 28 weeks), methotrexate and sulfasalazine (the combination therapy in rheumatoid arthritis [COBRA] study).[51] Altogether, if and to what extent corticosteroids induce hypertension in patients with RA needs to be investigated in appropriate trials.

The enhanced cardiovascular morbidity and mortality in patients with RA might be due to an increased prevalence of risk factors for cardiovascular disease, such as dyslipidaemia. The available literature regarding patients with RA is contradictory and there have been a few reports about lipid

levels in these patients and their relationship with disease activity. One cross-sectional study in 28 patients with RA, with a mean disease duration of 7 years, demonstrated an inverse relationship between disease activity and lipid levels.[52] A subsequent 9 month follow-up study in 11 patients with RA demonstrated normalisation of the lipid levels during antirheumatic treatment after 9 months.[53]

So far no randomised investigations have been reported in patients with early RA. Therefore, we recently studied the effects of prednisolone on total and high-density lipoprotein (HDL) cholesterol levels in patients with RA and the relationship between lipid levels and disease activity.[54] Total and HDL cholesterol levels were determined in stored samples from a previously conducted, 56-week multicentre trial among patients with early RA investigating the value of intensive combination therapy (COBRA); the combination of sulfasalazine, methotrexate (stopped at 40 weeks) and prednisolone (initially 60 mg/day, tapered in 6 weekly steps to 7.5 mg/day and stopped after 28 weeks) was compared to sulfasalazine alone. Contrary to expectation, both total and HDL cholesterol were decreased in these patients with active RA at baseline, and increased on antirheumatic therapy. Although a storage problem with the serum samples can not be totally excluded, this will not influence the observed changes of lipid levels.

Combination therapy with prednisolone rapidly improved the atherogenic index (total/HDL cholesterol), an important prognostic cardiovascular risk factor. Early antirheumatic and especially corticosteroid (combination) treatment may improve the cardiovascular risk in RA, and it appears that the use of corticosteroids is not a risk factor for cardiovascular disease in patients with RA, which is also suggested by other investigators.[55,56]

Presently, additional investigations are being performed to confirm these findings.

5. Leflunomide

In clinical trials, the efficacy of leflunomide was similar to that of methotrexate with a relatively rapid onset of benefit within 1 to 3 months, and leflunomide was approved in The Netherlands for treatment of RA in 2000.

Leflunomide is associated with an overall incidence of hypertension of approximately 6 to 10% as compared to approximately 4% for placebo or other comparators, that is sulfasalazine or methotrexate. Drug-related hypertension occurred in approximately 2 to 4% of the leflunomide-treated patients compared with 2% for the comparator drugs. New onset hypertension is reported in 2% of the leflunomide-treated patients.[57-61]

A retrospective investigation in 99 consecutive outpatients in whom leflunomide was started, revealed a total discontinuation rate of more than 60% (41% due to inefficacy) probably caused by patient selection.[62] Hypertension was observed in 8% of the patients, which is significantly higher than expected from the literature. As this retrospective 'clinical practice' investigation has several methodological limitations, we have initiated a prospective study of the adverse effect profile of leflunomide in patients in whom leflunomide treatment is initiated, with a special focus on cardiovascular risk factors, i.e. hypertension, lipid and homocysteine metabolism.

6. Tumour Necrosis Factor-α Antagonists

Presently, two TNFα antagonists are available for clinical use in patients with RA. No specific cardiovascular problems have been reported with the use of these agents except for incidental allergic reactions.

An interesting potential indication for these agents was recently investigated following the findings that the development of symptomatic heart failure is associated with increased levels of TNFα. Several experimental studies have shown that elevated TNF levels are capable of inducing heart failure with concomitant left ventricular dilatation and dysfunction.[63] Hence, theoretically, inhibition of TNF expression or bioavailability might be beneficial for patients with symptomatic heart failure. Indeed, a double-blind placebo-controlled pilot study in 18 patients with New York

Heart Association (NYHA) class III heart failure with an initial ejection fraction of < 35% revealed an increase in quality-of-life scores, 6-minute walk distance and ejection fraction in those treated with single dose etanercept compared with no changes of these parameters in the placebo-treated patients.[64] No significant adverse effects were encountered in the etanercept patients. Similar findings were found in a larger randomised, placebo-controlled study where 47 patients were treated with biweekly doses of etanercept or placebo for 3 months.[65]

These promising results initiated two large randomised trials in patients with heart failure; one in the US (Randomised Etanercept North American Strategy to Study Antagonism of Cytokine [RENAISSANCE]) and the other one in Europe, Australia and New Zealand (Research into Etanercept: Cytokine Antagonism in Ventricular Function [RECOVER]). The studies had randomised 1500 patients when an interim analysis revealed no likelihood of a difference between etanercept and placebo, and consequently these trials of etanercept were stopped because of lack of evidence.[66] Safety data of these two large trials have not yet been published.

The failure to find a benefit of etanercept in these patients challenges the role of TNF for the remodelling process in heart failure. Alternatively, (the dose of) etanercept was not sufficiently effective or other cytokines are more important for the remodelling process.[66]

Very recently, a phase II trial with infliximab in patients with moderate to severe congestive heart failure, demonstrated a higher incidence of mortality and worsened heart failure in patients treated with infliximab than those receiving placebo. Seven of the 101 infliximab recipients died compared with no deaths among the 49 placebo recipients. Hence, it was advised that patients with congestive heart failure should not be given infliximab, and a clinical alert and a warning was issued by the US Food and Drug Administration.[67]

7. Practical Guidelines for Cardiovascular Patients

Commonly prescribed drugs for OA include paracetamol and NSAIDs, whereas in rheumatoid arthritis besides NSAIDs, second-line antirheumatic drugs are indicated.

7.1 Patients Receiving Oral Anticoagulants

Paracetamol is often the preferred analgesic in patients with osteoarthritis who require anticoagulants. However, administering this drug in high doses and continuous doses may increase the half-life of oral anticoagulants. Therefore, the international normalised ratio (INR) should be monitored in these patients.[68] The statement that selective COX-2 inhibitors could be considered for these patients in view of their lack of antiplatelet effects, appears to be not correct as increased INR values have also been described for the COX-2 inhibitors.

7.2 Patients Receiving Aspirin

When NSAIDs are required in patients receiving aspirin there is at present no convincing evidence that the COX-2 selective agents, as compared with conventional NSAIDs, offer significant benefit. In patients with risk factors for the development for gastrointestinal adverse effects, comedication with misoprostol or proton pump inhibitors should be considered.[28] Formal cost-effectiveness investigations are required to compare the possible treatment modalities in the aspirin-treated patient.

7.3 Patients with Hypertension and/or Congestive Heart Failure

Both conventional NSAIDs and the COX-2 inhibitors are associated with the development of hypertension, oedema and congestive heart failure. The observed differences between the various drugs appear to have a limited clinical significance. Patients with treated hypertension should be monitored regularly when conventional NSAIDs or COX-2 inhibitors are used.

High doses of corticosteroids necessitate blood pressure control. We also recommend monitoring with lower dosages of corticosteroids (up to 20 mg/day prednisone), as the literature is not conclusive regarding hypertensive effects with such dosages.

Leflunomide also requires regular monitoring and control of blood pressure, especially in the first months of treatment. Hypertension in patients receiving leflunomide can sometimes be managed by omitting the NSAIDs from their treatment regimens.

Conventional NSAIDs and the COX-2 inhibitors should be administered with great caution in patients with congestive heart failure in view of their potential to provoke cardiac decompensation in these patients. It has been suggested that corticosteroids with a high mineralocorticoid activity should be avoided in patients with congestive heart failure.[49]

Infliximab should not be used in patients with RA and congestive heart failure. Presently, there are not enough safety data for etanercept in patients with congestive heart failure. The infliximab data suggest a detrimental effect of TNFα antagonism in patients with congestive heart failure. Hence, etanercept should also be considered contraindicated, at least until there are convincing (favourable) safety data available for application of etanercept in this category of patients.

7.4 Remaining Issues

There is some indirect evidence that naproxen might be cardioprotective compared with rofecoxib or other NSAIDs, which is confirmed by a recent meta-analysis. This meta-analysis of 23 investigations conducted with rofecoxib, encompassing a total of 28,000 patients, showed relative risks of 0.84, 0.79 and 1.69 when comparing rofecoxib with placebo, non-naproxen NSAIDs and naproxen for the cardiovascular composite endpoint.[69] Obviously, this investigation is hampered by its retrospective design and it goes without saying that prospective studies with pre-defined cardiovascular endpoints investigating this issue are required for confirmation, in particular, because another retrospective observational cohort investigation failed to indicate a cardioprotective effect for naproxen.[70]

Hopefully, the results of future studies will answer the question whether or not aspirin therapy, when indicated, can be omitted in patients treated with naproxen.

8. Conclusions

The new NSAIDs, that is the COX-2 inhibitors, offer little advantage over conventional NSAIDs in the patient with arthritis with cardiovascular comorbidity. COX-2 inhibitors can be preferred over conventional NSAIDs in patients not requiring aspirin as they are associated with fewer gastrointestinal adverse effects. It is not known whether COX-2 inhibitors can also be preferred over conventional NSAIDs in combination with a gastroprotective agent (misoprostol or a proton pump inhibitor) in patients with risk factors for the development of an NSAID-related gastrointestinal adverse effect. However, equally effective COX-2 inhibitors are preferred in view of the administration convenience and, at least in The Netherlands, substantially lower costs.

Hypertension is the only reported cardiovascular adverse effect for leflunomide, and so far no significant cardiovascular adverse effects have been reported with the use of TNFα antagonists.

Ongoing studies will address the effects of leflunomide and corticosteroids on lipid metabolism and other risk factors for cardiovascular disease in patients with RA. As inflammation plays a pivotal role in RA as well as in cardiovascular disease and the cardiovascular risk appears to be enhanced in RA, it can be expected that effective suppression of inflammation ultimately will lead to a decreased cardiovascular risk in RA. Ongoing investigations are presently investigating these issues.

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