Selective Cyclooxygenase-2 Inhibitors in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder. Patients present with joint pain, morning stiffness and physical disability. Non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) are the mainstay of treatment in RA. NSAIDs are used to control symptoms of RA but are associated with significant gastrointestinal side effects. With the better understanding of the enzyme cyclooxygenase (COX), new selective COX-2 inhibitors such as celecoxib, rofecoxib, etoricoxib and valdecoxib have been developed in the past few years.

Mechanism of action of selective COX-2 inhibitors

The action of NSAIDs is related to the inhibition of cyclooxygenase, causing a decrease in production of pro-inflammatory prostaglandins. COX exists in two isoforms, COX-1 and COX-2. COX-1 is constitutively made in the stomach, intestine, kidney and platelets. COX-2 is an inducible form involved in inflammation but also found constitutively in kidney and brain. The gastrointestinal (GI) side effects of NSAIDs are thought mediated through the inhibition of COX-1. In order to reduce the GI side effects, selective COX-2 inhibitors have been developed.

Role of NSAIDs in rheumatoid arthritis

NSAIDs play an important role in the treatment of musculoskeletal diseases. Despite the recent advance in DMARDs and other biologic therapies in treatment of RA, NSAIDs are still very useful in managing these patients by providing effective analgesic and anti-inflammatory effects. In addition to provide symptomatic control, RA patients treated with NSAIDs (celecoxib, naproxen) had been shown to have significant improvement in both functional status and overall health related quality of life compared with placebo.\(^1\)

Efficacy of selective COX-2 inhibitors

A systematic review about the efficacy of celecoxib in RA had been performed in 2002.\(^2\) Five randomised controlled trials were included with 4465 participants, three of the studies also enrolled individuals with osteoarthritis (OA). When compared to active comparators (naproxen, diclofenac and ibuprofen), celecoxib control symptoms of RA to a similar degree and the ACR 20 response was significantly better than placebo. Besides, the efficacy and tolerability of etoricoxib in RA patients had been compared with naproxen and placebo in a multinational randomised trial.\(^3\) Total 687 patients had completed 12 weeks of treatment. Etoricoxib and naproxen were similar in efficacy and showed significant improvement in all efficacy endpoints compared with placebo. ACR20 responder response criteria were achieved in 59% in etoricoxib group, 58% in naproxen group and 41% in placebo group. Both drugs were generally well tolerated.

Advantages of selective COX-2 inhibitors

The main advantage of selective COX-2 inhibitors is the reduced GI toxicities. In the Celecoxib Long-term Arthritis Safety Study (CLASS), around 8000 patients with RA or OA were enrolled.\(^4\) Patients were randomised to receive celecoxib 400mg twice per day, ibuprofen 800mg three times per day or diclofenac 75mg twice per day. The annualised incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib against NSAIDs were 0.76% vs 1.45% (P=0.09) and 2.08% vs 3.54% (P=0.02). The decrease in upper GI toxicity with celecoxib was observed among patients not taking aspirin concomitantly. In another study by the VIGOR (Vioxx Gastrointestinal Outcomes Research) study group, 8076 patients with RA were randomised to receive rofecoxib 50mg daily or naproxen 500mg twice daily.\(^5\) Rofecoxib and naproxen had similar efficacy but rofecoxib was associated with less clinical upper GI events. In the review by Deeks et al., the rate of withdrawal due to adverse GI events, incidence of ulcers detected by endoscopy and incidence of serious upper GI events (ulcers, bleeds, perforations, obstructions) were lower in patients taking celecoxib than traditional NSAIDs.\(^6\) Etoricoxib 120mg daily was also shown to have a significantly lower cumulative incidence of endoscopic ulcer than ibuprofen 800mg three times daily in a 12 week study involving 600 patients.\(^7\) A review of data from 28 trials including around 24000 patients, patients on meloxicam 7.5mg daily had significantly lower risk of serious upper GI events than diclofenac, naproxen or piroxicam.\(^8\)

Indications for selective COX-2 inhibitors

Since selective COX-2 inhibitors are useful to reduce the symptomatic ulcer and ulcer complications, they should be considered to use in the high-risk group. Risk factors for ulcer complications include previous history of peptic ulcer/upper gastrointestinal bleeding, advanced age, use of high dose or multiple NSAIDs and concomitant corticosteroid or anti-coagulant.
Side effects of selective COX-2 inhibitors

Selective COX-2 inhibitors may cause increase in blood pressure and peripheral edema as conventional NSAIDs. Besides, the cardiovascular safety of COX-2 inhibitors has raised concern in the past few years. In the VIGOR study, the incidence of myocardial infarction was lower in naproxen group (0.1%) than rofecoxib group (0.4%). A review of the previous trials in 2003 suggested no evidence of increased cardiovascular thrombotic events when rofecoxib compared with placebo or non-naproxen NSAIDs. A subsequent matched case control study of over 50000 elderly patients suggested current rofecoxib use was associated with a higher relative risk of AMI compared with celecoxib or no NSAID use. The result of the APPROVe (Adenomatous Polyp Prevention on Vioxx) trial led to voluntary withdrawal of rofecoxib. This was a prospective randomised trial designed to evaluate the efficacy of rofecoxib 25mg/day in preventing recurrence of colorectal polyps in patients with history of colorectal adenoma. An increased relative risk of confirmed cardiovascular events, such as heart attack and stroke, was noted after 18 months of treatment with rofecoxib comparing with placebo. The exact cause for these results is still uncertain. Selective COX-2 inhibitors are associated with decreased formation of prostaglandin I2 but with little inhibition of thromboxane A2 generation. Prostaglandin I2 cause vasodilatation, inhibit platelet aggregation and preventing proliferation of vascular smooth muscle cells. Thromboxane A2 produces the opposite effects. Therefore, depression of prostaglandin I2 formation might be expected to elevate blood pressure and accelerate atherogenesis. Different COX-2 inhibitors have different COX-2 selectivity and structure. Whether this explain the difference in cardiovascular risk or related to other mechanisms still need to be determined.

Alternatives for selective COX-2 inhibitors

Hooper L et al. recently reviewed the effectiveness of five strategies for the prevention of NSAID induced gastrointestinal toxicities. These included H2 receptor antagonists, proton pump inhibitors (PPI) or misoprostol plus non-selective NSAIDs; COX-2 selective and COX-2 specific NSAIDs. 112 randomised controlled trials were included, five were judged to be at low risk of bias. These trials compared the above strategies with non-selective NSAIDs +/- placebo. They concluded that COX-2 specific, COX-2 selective NSAIDs, misoprostol and probably PPI significantly reduced the risk of symptomatic ulcer. Misoprostol and probably COX-2 specific NSAIDs significantly reduced the risk of serious gastrointestinal complications. However, we should bear in mind that the results do not come from head to head studies of the five gastroprotective strategies. We can consider the use of misoprostol or PPI plus non-selective NSAIDs as alternatives to selective COX-2 inhibitors in patients with high risk of ulcer complications who are also having cardiovascular risk factors.

Conclusion

Selective COX-2 inhibitors have similar efficacy to conventional NSAIDs but with reduced GI toxicities. Despite the withdrawal of rofecoxib due to increased cardiovascular events, selective COX-2 inhibitors are still useful options in RA patients having high risk of GI toxicities. We should consider the use of it on an individual patient basis. Further information on long term usage of these drugs from prospective randomised controlled trials will give us a better idea of their cardiovascular safety profile.

References