Celecoxib for the Treatment of Ankylosing Spondylitis

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Abstract

Ankylosing spondylitis is a debilitating form of chronic inflammatory arthritis which primarily affects the spine. Treatment is based on non-pharmacological therapy, largely exercise, and pharmacological therapy, with non-steroidal anti-inflammatory drugs (NSAIDs) recommended as first-line treatment. One of the most well studied pharmacological treatments for patients with ankylosing spondylitis is the cyclooxygenase-2 selective NSAID celecoxib. This short review highlights the importance of inflammation in the pathology of the disease. Data from randomized, controlled clinical trials of celecoxib in patients with ankylosing spondylitis is reviewed with respect to efficacy and safety. In addition, more recent data from longer-term trials suggest that celecoxib may have disease modifying properties. In addition, more recent data from longer-term trials suggest that celecoxib may have disease modifying properties, with the benefits perhaps being more pronounced in patients with syndesmophytes and elevated inflammation levels indicative of more severe disease. With the benefits perhaps being more pronounced in patients with syndesmophytes and elevated inflammation levels indicative of more severe disease.

Keywords: Ankylosing spondylitis; Celecoxib; Disease modification

Introduction

Ankylosing spondylitis is a form of chronic inflammatory arthritis primarily affecting the spine [1]. The prevalence of ankylosing spondylitis is thought to be between 0.1% and 1.4% [1]. It is a disease of young people, generally presenting around 26 years of age, [2] and being more common in men than women with one study reporting a ratio of males to females of 2.4:1 [3]. Treatment aims to reduce symptoms, maintain flexibility and posture, and retard structural damage [4, 5]. There is no cure but European and North American treatment guidelines recommend physical therapy/exercise in combination with non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 selective inhibitors as first-line treatment [4, 5].

This publication outlines the key role of inflammation in ankylosing spondylitis and reviews the available data on the safety and efficacy of the COX-2 selective inhibitor celecoxib, one of the more extensively studied NSAID treatments for ankylosing spondylitis. Finally, the potential disease modifying properties of celecoxib are discussed.

Inflammation Is A Key Component Of Ankylosing Spondylitis

Ankylosing spondylitis is characterized by inflammatory back pain, caused by sacroiliitis and spondylitis, which can lead to bone fusion of sacroiliac joints, vertebral facet joints and inter vertebral discs and a resulting spinal stiffness and loss of mobility [1]. Chronic inflammation likely leads directly to the stiffness and bone fusion, and control of inflammation early in the disease process may prevent ongoing structural damage [6].

Celecoxib Is An Effective Treatment Option For Patients With Ankylosing Spondylitis

Guidelines

The European League Against Rheumatism (EULAR) guidelines [5] advise that treatment should be tailored according to the current manifestations of the disease, including status and severity of symptoms. Disease monitoring (on an individual basis) should include patient history, clinical parameters, laboratory tests, and imaging, while non-pharmacological treatment should be based on patient education and regular exercise [5]. Ongoing treatment with NSAIDs, including COX-2 selective inhibitors, is recommended as first-line drug treatment with other pharmacological treatments (including analgesics, directed corticosteroid injections, and anti-tumor necrosis factor [TNF] therapy) considered if NSAIDs are ineffective [5]. Surgery may also be considered in more severe, non-responding patients [5].

The American College of Rheumatology (ACR) guidelines [4] are similar, also strongly recommending ongoing treatment with NSAIDs and physical therapy. In the ACR guidelines, anti-TNF therapy is strongly recommended in patients who do not respond to NSAIDs as is surgery for more severe patients, while the guidelines strongly recommended against the use of systemic...
There have been five randomized, controlled trials of celecoxib for the treatment of ankylosing spondylitis (Table 1) [7-11]. The trials demonstrated both significantly improved outcomes compared with placebo and non-inferiority compared with non-selective NSAIDs. There were no reported deaths during active treatment; although, in one trial, one patient died following discontinuation of celecoxib due to lack of efficacy but this was considered unrelated to treatment [8]. Reported serious adverse events with celecoxib included severe decreased blood pressure, severe renal calculi, angina pectoris, dyspnoea, sudden hearing loss, deterioration of ankylosing spondylitis, and familial Mediterranean fever but overall incidence was comparable with controls [7-11].

Overall, celecoxib was well tolerated in these trials and was typically associated with numerically fewer gastrointestinal adverse events than the non-selective NSAID comparators [7-11], consistent with the established superior gastrointestinal safety of COX-2 selective inhibitors [12]. There was also no notable difference in cardiovascular adverse events in the trials, although the trials were of limited duration and in relatively young patients (Table 1) [13]. Being significantly younger and with fewer comorbidities than the majority of other patients treated with celecoxib, ankylosing spondylitis patients would likely be at lower risk of gastrointestinal and cardiovascular complications [13]. Nevertheless, currently available data from patients with osteoarthritis and rheumatoid arthritis supports the view that celecoxib is not associated with an increased cardiovascular risk when compared with non-selective NSAIDs such as ibuprofen and naproxen [14, 15].

An alternative COX-2 selective inhibitor, etoricoxib, has also been examined in a 52 week randomized, controlled trial [16]. This trial included a 6 week placebo controlled period and a 46-week active-comparator controlled period in which etoricoxib at 90 or 120 mg once daily was compared with placebo and naproxen at 500 mg twice daily [16]. At 6 weeks, mean change in pain score was -12.6 with placebo compared with -33.7 with naproxen, and -41.5 and -41.6 with etoricoxib 90 mg and 120 mg, respectively and this improvement was maintained over the 1 year active-comparator phase [16]. The recommended dose of etoricoxib was initially limited to 90 mg/day by health authorities, however recent regulatory activity has led to a reduction in the initial dose of etoricoxib recommended for ankylosing spondylitis in some countries [17]. A starting dose of 60 mg/day is now recommended, with the caveat that some patients may benefit from increasing the dose to 90 mg/day. The labeling further recommends a potential return to 60 mg/day in patients once they are clinically stabilized [18].

### Disease Modification In Ankylosing Spondylitis

There is no cure for ankylosing spondylitis and the use of typical disease-modifying anti-rheumatic drugs (such as sulphasalazine and methotrexate) has not been shown to be effective [1,5]. Initially, NSAIDs were considered to only modify the symptoms of ankylosing spondylitis with no effect on the progression of disease. However, long-term follow-up of patients from one randomized controlled trial of celecoxib [7] demonstrated that continuous treatment with celecoxib (for 2 years) resulted in a reduction in radiological progression when compared with patients receiving treatment on demand [19].

This reduction suggested that NSAIDs may have disease modifying properties in addition to the relief of symptoms. A similar reduction in radiological progression was shown in patients with a high intake of NSAIDs over 2 years, with the effect being most pronounced in patients with elevated C reactive protein (CRP) [20]. Increased levels of CRP are associated with more severe disease and treatment with NSAIDs has been shown to reduce levels of CRP [21].

### Table 1: Efficacy outcomes in clinical trials of celecoxib in patients with ankylosing spondylitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Mean age, range (years)</th>
<th>Duration (weeks)</th>
<th>Celecoxib Dose</th>
<th>Comparator(s) Dose</th>
<th>Mean change in pain intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dougdos, 2001 [8]</td>
<td>246</td>
<td>38-40</td>
<td>6</td>
<td>Celecoxib 100 mg qd</td>
<td>Ketoprofen 100 mg qd</td>
<td>-27</td>
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<td>Placebo</td>
<td>-21</td>
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<td></td>
<td>Placebo</td>
<td>-36.3</td>
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<tr>
<td>Sieper, 2008 [10]</td>
<td>458</td>
<td>45</td>
<td>12</td>
<td>Celecoxib 200 mg qd</td>
<td>Diclofenac 75 mg bid</td>
<td>-29.1</td>
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<td></td>
<td>Placebo</td>
<td>-32.7</td>
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<tr>
<td>Huang, 2014 [9]</td>
<td>219</td>
<td>29</td>
<td>6</td>
<td>Celecoxib 200 mg qd</td>
<td>Diclofenac 50 mg tid</td>
<td>-23.8</td>
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<td>Placebo</td>
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Celecoxib is one of the most well studied NSAID treatments for patients with ankylosing spondylitis with relatively strong evidence for its safety and efficacy. Recent evidence suggests that it also has disease modifying properties. Patients with a high risk of radiographic progression may benefit from the continued use of celecoxib, even after achieving the significant improvements in clinical symptoms commonly recorded in clinical trials of this class of medicines.

Conclusions

Celecoxib is one of the most well studied NSAID treatments for patients with ankylosing spondylitis with relatively strong evidence for its safety and efficacy. Recent evidence suggests that it may also have disease modifying properties. Patients with a high risk of radiographic progression may benefit from the continued use of celecoxib, even after achieving the significant improvements in clinical symptoms commonly recorded in clinical trials of this class of medicines.

Declarations

This publication was sponsored by Pfizer. Cindi Sounthonevat and Chris Walker are employees of Pfizer and Chris Walker holds stock options with Pfizer. Jian Zhu confirms no conflicts of interest.

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