Tenidap: not just another NSAID?

The paradigm—The concept of rheumatoid arthritis (RA) treatment is based on the therapeutic pyramid, treatment beginning with non-steroidal anti-inflammatory drugs (NSAIDs), and then agents such as antimalarias, intramuscular gold, penicillamine, sulphasalazine, methotrexate, and azathioprine being added sequentially, ultimately progressing to other cytotoxic agents or experimental treatments. This approach draws on the inference that there is little toxicity with the treatments at the pyramid base, but that toxicity increases on ascending the pyramid.

Toxicity of NSAIDs—However, the assumption that NSAIDs are not associated with significant toxicity is no longer acceptable. Substantial evidence now links gastrointestinal and acute renal toxicity to NSAIDs and, more recently, studies of patients in chronic renal failure have implicated NSAIDs, especially when they are taken continuously over a period of years as is required in RA.1–5 Previously, much of this damage was believed to be the result of use of analgesics.4 In addition, there is concern about the effects of NSAIDs on blood pressure, as a sustained increase of 5–10 mm Hg in the diastolic blood pressure over several years substantially increases the risk of cardiovascular morbidity.5

Efficacy of NSAIDs in RA—Over the past 10 years, an increasing choice of NSAIDs has been available. The debate on which is the drug of choice is unresolved. In efficacy trials, there is no clear leader, yet clinical experience and patient preference indicate grounds for distinction. This has been attributed to as yet undefined variations in individual patient response.

Previous experiences with NSAIDs indicated that any claim of superior efficacy of a new agent must be viewed sceptically. Tenidap is said to combine the immediate benefits of an NSAID, with a favourable influence on the acute phase response and a reduction in the radiological progression of RA, without significant additional toxicity.6 Should we remain sceptical, or does its availability mark a turning point for the treatment of RA?

Analogies—a useful way forward?—Before the available efficacy and toxicity data for tenidap in RA can be discussed, it is necessary to establish an understanding of what we are endeavouring to achieve with second line or disease modifying treatments. We suggest that a useful working analogy can be drawn with insulin dependent diabetes, in which tight glycaemic control significantly reduces the number of patients who progress to develop serious end organ damage.7

Although such an analogy is initially appealing, there is an important distinction to be made. Rheumatologists use several measures, rather than one, of outcome in clinical trials of RA. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for example, suggest several disparate measurements, some of which are not entirely a function of the inflammatory process and may be open to influence by both observer and patient biases.8 9 The use of several rather than one outcome measure also acts to diffuse rather than focus on the primary aim of drug treatment—prevention and slowing of end organ damage.

As most rheumatologists accept that limiting progression of erosions and, if possible, preventing erosions are important outcomes, these must then be the goals of drug treatment in RA. Erosive damage and its progression are more strongly associated with C reactive protein (CRP) activity than either clinical or functional indices.10–13 The ability to decrease CRP or erythrocyte sedimentation rate (ESR) is also an important differentiating feature between first and second line drugs. The major aim of second line treatment therefore should be suppression of the acute phase response.

Returning to the diabetes analogy, control of inflammation as assessed by CRP can substitute for glycaemic control, and joint failure as the end organ damage to be prevented. Using a simple measurement such as CRP that is readily available, provides the additional benefit that we can compare trials more easily, and gives the ‘working’ rheumatologist a uniform standard to which to relate in their practice. CRP test kits for rapid clinic use are also available, and perhaps we should be applying such technology in the same way that blood sugars or blood pressure are monitored. This does not imply that function or global assessment should be neglected, as they are also important in overall patient care, but the control of inflammation must be the only expected benefit of drug treatment.

Achieving tight control of CRP or ESR is not easy and not yet satisfactory; at best, most second line drugs provide a median improvement in CRP of 50%, if treatment with a single agent can be maintained for one year. Available agents also have considerable toxicity, and 30–40% of patients discontinue treatment in the first year as a result of side effects.14 However, with closely supervised care, 73% of patients can be maintained on sequential second line drugs over a 10 year period, and in this group an improvement in ESR showed less radiographic progression.15 In view of these limitations, the analogy is better extended from diabetes to hypertension, for which single and combined treatments impinging on different pathophysiological pathways regulating blood pressure are used. Such an approach in manipulating the various arms of the immune response may be more within our grasp,
rather than searching for a single curative agent or defining a rigorous order to the use of second line drugs.

Tenidap
Tenidap is an oxindole \([Z]-5\)-chloro-2,3-dihydro-3-[hydroxy-2-thienylmethylene]-2-oxo-1H-indole-1-carboxamide, sodium salt\) anti-inflammatory that was further developed because it inhibited both cyclo-oxygenase and 5-lipooxygenase in vitro. Lipooxygenase inhibition, however, was not observed in vivo because it is highly protein bound. In phase two clinical studies, in addition to cyclo-oxygenase inhibition, a decrease in CRP and ESR was noticed, differentiating it from NSAIDs. Subsequent in vitro studies showed that the macrophage derived cytokines, interleukin-1, interleukin-6, and tumour necrosis factor \(\alpha\) are inhibited by tenidap to a greater extent than with NSAIDs. At a molecular level, one proposed mechanism of action is inhibition of anion leading to changes in intracellular ion homeostasis and subsequent effects on cell function.

COMPARISON WITH NSAIId
There are two key double blind, prospective, randomised trials comparing tenidap with NSAIDs alone; table 1 summarises the results of both studies.

The first, a dose escalation study, compared tenidap 40-120 mg daily in 326 RA patients with naproxen 1 g daily in a further 160 RA patients. Patients receiving stable second line treatment, and those taking prednisolone 10 mg were included. In the tenidap group, 43% were taking oral corticosteroids, compared with 35% in the naproxen group. The majority of patients entering the study were classed as having mild to moderate disease (tenidap 62%, naproxen 73%), but there was no prior definition of severity. The mean dose for the tenidap group at one year was 101 mg/day. All results were analysed on an intention to treat basis. At one year, a significant improvement from baseline was observed in the tenidap group, in number of swollen joints, pain score (visual analogue scale (VAS)), and global assessments by patient and physician. CRP decreased by a mean of 47% from baseline. Fewer patients discontinued treatment because of inefficacy in the tenidap group (tenidap 19%, naproxen 28%; p = 0.0045). This trial is part of a five year study, the final clinical evaluations of which are not yet completed.

The second study included 384 RA patients who received either tenidap 120 mg or diclofenac 150 mg per day. Second line treatment was an exclusion criterion, but approximately 50% of patients in both groups were receiving a stable dose of prednisolone. Disease activity was judged as mild in 8-9% of patients, moderate in 55-3%, and severe in 35-8%. Sixteen percent of patients discontinued treatment because of inefficacy in the tenidap group, compared with 10% of those receiving diclofenac. At one year there was a significant improvement in swollen and painful joint counts, VAS pain, and global assessment, in addition to a decrease in ESR and CRP from baseline in the tenidap group.

COMPARISON WITH SECOND LINE DRUGS
Two separate double blind randomised studies have compared tenidap with hydroxychloroquine and auranofin. The choices of comparative second line drugs are surprising, particularly as auranofin has a greater incidence of side effects, and both are considered less effective than intramuscular gold, sulphasalazine, penicillamine, or methotrexate. (A comparative study with sulphasalazine is in progress.)

The first was a two year study that compared hydroxychloroquine 400 mg a day plus piroxicam 20 mg a day, piroxicam 20 mg a day, and tenidap 120 mg daily in 367 patients with RA. The average disease duration was four years, and prior use of second line treatment was an exclusion criterion, except that prednisolone, up to 10 mg daily, was allowed and used by approximately 20% of patients. Disease severity was mild in 13% and moderate or severe in 87%. Table 2 shows the changes in efficacy from baseline to 24 weeks for the hydroxychloroquine plus piroxicam and tenidap groups. The tenidap versus piroxicam alone data are not shown but, like the NSAID alone trials, a significant beneficial effect of tenidap over piroxicam was demonstrated in clinical and laboratory parameters. There was an improvement in all parameters within both the hydroxychloroquine plus piroxicam and the tenidap groups, with no difference in the extent of response in the two groups. Patients in the tenidap group had a 26% greater decrease in CRP than those in the hydroxychloroquine group. The rate of discontinuation for lack of efficacy was similar within the hydroxychloroquine plus piroxicam and the tenidap group, at 12%.

The second trial was also a two year study and compared tenidap with auranofin 6 mg daily plus diclofenac 150 mg per day, in 374 patients with early RA (disease duration less than three years). Prior or concomitant second line treatment were exclusion criteria and prednisolone use was not allowed. Improvement in all clinical and laboratory parameters within both groups was seen at nine months. Tenidap produced a faster reduction in CRP than auranofin, but at nine months there was no difference. The rate of withdrawal because of inefficacy was similar (18-20%) in both groups. Blinding in this study is questionable because of the invariable occurrence of diarrhoea with auranofin.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial 1 (mean % change)</th>
<th>Trial 2 (mean % change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful joints</td>
<td>-45</td>
<td>-51</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>-36</td>
<td>-46*</td>
</tr>
<tr>
<td>Pain by VAS</td>
<td>-30</td>
<td>-38*</td>
</tr>
</tbody>
</table>

*VAS = visual analogue scale; CRP = C reactive protein; ESR = erythrocyte sedimentation rate.
*p < 0.05.

Table 2 Tenidap compared with hydroxychloroquine plus piroxicam over 6 months (Trial 3) and with auranofin plus diclofenac over 9 months (Trial 4) in early rheumatoid arthritis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial 3</th>
<th>Trial 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCQ (mean % change)</td>
<td>Tenidap (mean % change)</td>
<td>Auranofin (mean % change)</td>
</tr>
<tr>
<td>Painful joints</td>
<td>-40</td>
<td>-30</td>
</tr>
<tr>
<td>Swollen joints</td>
<td>-38</td>
<td>-35</td>
</tr>
<tr>
<td>Pain by VAS</td>
<td>-33</td>
<td>-26</td>
</tr>
<tr>
<td>Assessment of disease activity</td>
<td>-18</td>
<td>-18</td>
</tr>
</tbody>
</table>

*HCQ = Hydroxychloroquine; VAS = visual analogue scale; CRP = C reactive protein; ESR = erythrocyte sedimentation rate.
*p < 0.05.
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In both second line studies, a planned interim analysis of radiographic progression on an intention to treat basis has been undertaken. Initial results showed progression of erosions in the tenidap group that was less than that observed with hydroxychloroquine plus piroxicam alone, but similar to that reported for the auranofin plus diclofenac group.27

Quality of life using the arthritis impact measurement scales has also been assessed.26 Scores were better with tenidap than with NSAID monotherapy, but equivalent in the second line plus NSAID combinations.

ADVERSE REACTIONS

Of the 617 RA patients treated with tenidap in double blind placebo controlled studies, 327 (53%) reported a side effect or developed an abnormality detected in laboratory testing after a mean duration of seven months.6 The drug was discontinued in 49 patients (8%). Of the 430 receiving an NSAID alone, 211 (49%) developed a side effect or laboratory abnormality, and 43 of those (10%) discontinued treatment. In the second line plus NSAID groups, 261 of 422 patients (62%) (auranofin 298; hydroxychloroquine 124) developed a side effect and 59 (13%) discontinued treatment. There was a statistically greater incidence of side effects in the latter group, attributed primarily to auranofin induced diarrhoea.

Eighty seven percent of adverse events with tenidap were gastrointestinal symptoms, of which dyspepsia and abdominal pain were the most common (26%). The incidence of upper gastrointestinal perforation and bleeding was similar in all groups, but the number of treated patients was small and included only those suitable for admission to clinical trials. Skin rashes, alopecia, peripheral oedema and headache occurred in a similar frequency in all three groups. There has been only one recorded death in a patient receiving tenidap. This was a Japanese patient who developed liver failure; the relationship to drug treatment has yet to be established. Increased concentrations of transaminases have been observed, but no more frequently than with diclofenac, and the concentrations returned towards normal values with drug discontinuation.

Proteinuria has occurred in 40% of a 617 patient cohort, at levels of >250 mg/1 on dipstick testing. The occurrence of proteinuria appears to be independent of the duration of treatment. A progressive increase is not invariable, but should values exceed 1-5 g daily, the drug should be discontinued. The mean ratio of urinary albumin to β2-microglobulin in 85 tenidap patients studied was low, suggesting that tubular protein loss, rather than glomerular loss, is responsible for the proteinuria.28 No change in the glomerular filtration rate (GFR) has been reported in those developing proteinuria, but a decrease in serum uric acid, phosphate, calcium, and bicarbonate relative to baseline concentrations, though maintained within the normal range, also occurs, indicating that tubular function is affected. On discontinuation of tenidap, proteinuria invariably resolves within six months. In those patients in whom proteinuria had persisted for one year, a concomitant disorder was identified. In 300 patients in whom the drug had been continued for up to three years, despite proteinuria (<1-5 g/day) no deterioration in GFR or urinary sediment has occurred.29

Conclusions

Tenidap appears to fit the description of drugs with a second line activity. The second line effect is equivalent to that obtained with hydroxychloroquine and auranofin when these are used with an NSAID. Comparative studies with other second line drugs are required to define its extent of benefit. From a practical approach in treating patients with an inflammatory arthritis, there are many benefits to using a single agent that has anti-inflammatory and second line effects. The convenience of monotherapy will improve compliance during the initial crucial years that erosive disease is establishing itself. In those patients in whom CRP is not controlled, another second line drug could be added; this approach, however, requires to be tested rigorously before being implemented, to exclude deleterious effects, and the extent of combined benefit must be defined before tenidap is universally embraced as the initial monotherapy. It also offers the advantage of having no more side effects than NSAIDs in the short term, and a toxicity that is no greater than that of either auranofin or hydroxychloroquine. If phase four pharmacovigilance studies confirm its safety profile, we will indeed be stretching the pyramid.

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23 Data on file. Central Research Division, Pfizer Inc, Groton, CT, USA.
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