Preliminary results of early clinical trials with the fully human anti-TNFα monoclonal antibody D2E7

Joachim Kempeni

Current pharmacological treatments for rheumatoid arthritis (RA), including non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), and corticosteroids, have been moderately successful in alleviating the discomforts associated with swollen, painful joints. However, conventional medical approaches to treatment have had little or no impact on the disease course of RA. Innovative strategies, particularly those based on new concepts in the immunobiology of RA, are being developed to target cellular inflammatory mechanisms and potentially prevent disease progression. The more promising of these treatments seem to be those that block the effects of tumour necrosis factor (TNF) α, because this proinflammatory cytokine seems to play a central part in the immunopathogenesis of RA.

Anti-TNF treatments

Biological agents such as antibodies and soluble TNF receptors that bind TNF α with high specificity neutralise its activity and have been developed for use as therapeutic agents. Several are currently being evaluated in patients with RA (table 1). Infliximab, cA2, is a chimeric monoclonal antibody (mAb) that consists of the variable region of a murine anti-TNF mAb coupled to the constant region of human IgG1. The resulting construct is approximately two thirds human. CDP571 is a humanised mAb consisting of the complementarity determining regions of a murine anti-TNF mAb grafted into a human immunoglobulin (IgG4). This mAb is approximately 95% human. Etanercept is a fusion protein consisting of two recombinant p75 TNF receptors attached to the Fc portion of a human IgG1. Although this construct is approximately 95% human, Etanercept is a fusion protein consisting of two recombinant p75 TNF receptors attached to the Fc portion of a human IgG1. Although this construct consists of two independent elements, which themselves contain 100% human peptide sequences, they are arranged in an unnatural configuration. The duration of the therapeutic efficacy of these TNF antagonists may be limited by an immune response to their non-human elements or artificially fused human sequences.

The development of antibodies to these biological agents could reduce their half life, thereby decreasing efficacy. In addition, an immune response could result in adverse events from the formation of immune complexes or the development of hypersensitivity. For these reasons, an antibody that is fully human may have greater therapeutic potential.

Development of a fully human anti-TNF antibody

BASF Pharma set out to develop a fully human, anti-TNF mAb structurally identical to naturally occurring human antibodies and therefore less likely to engender an immune response in the recipient. The generation of a fully human anti-TNF mAb required bioengineering techniques that mimic immune selection in humans and contrast with existing means of "humanising" murine monoclonal antibodies in that the antibodies derived are completely human. The result of this effort is D2E7, a new class of anti-TNF mAb, which may have advantages in minimising antigenicity in humans.

Preclinical pharmacology

The efficacy and safety of D2E7 were evaluated in a number of experimental systems. The ability of D2E7 to neutralise TNF bioactivity was demonstrated in three different in vitro cell systems. Additionally, the effectiveness of D2E7 in preventing polyarthritis was shown in a transgenic mouse model that mimics the clinical and histopathological progression of RA in humans. D2E7 treated mice showed no clinical signs of arthritis during the 11 week study period. Microscopical examinations of the ankle joints of the animals showed no histopathological changes. In contrast, control mice developed severe arthritis with cartilage destruction and bone erosion.

Preliminary clinical data

There are important similarities in the designs of the early clinical trials assessing D2E7 in RA. All studies enrolled patients with an established diagnosis of RA who also had active disease, as evidenced by having a combination of swollen and tender joints, increased concentrations of acute phase reactants, and prolonged early morning stiffness. In addition, all trials involved RA patients with long disease duration and a history of failure of several DMARDs. During the trials, patients were allowed to continue stable doses of NSAIDs and corticosteroids. Efficacy was assessed...
Clinical trials with the fully human anti-TNFα monoclonal antibody D2E7

Table 2 Early trials of D2E7 in rheumatoid arthritis

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Patients</th>
<th>D2E7 dosing schedule</th>
<th>Concurrent DMARD</th>
<th>Maximum ACR 20 response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, double blind, placebo controlled</td>
<td>n=120; 83% RF; mean disease duration=12 years; mean DMARDs failed=3.6</td>
<td>Single and multiple iv injections, ascending doses ranging from 0.5 to 10 mg/kg</td>
<td>No</td>
<td>78%</td>
</tr>
<tr>
<td>Randomised, double blind, placebo controlled</td>
<td>n=24; mean disease duration=10 years; mean DMARDs failed=3.4</td>
<td>Weekly 0.5 mg/kg sc injections</td>
<td>No</td>
<td>70%</td>
</tr>
<tr>
<td>Randomised, double blind, placebo controlled</td>
<td>n=54; 87% RF; mean disease duration=11 years; mean DMARDs failed (including MTX)=3.6</td>
<td>Single iv or sc injection of 1 mg/kg</td>
<td>MTX</td>
<td>67%*</td>
</tr>
</tbody>
</table>

RF=rheumatoid factor positive; DMARD=disease modifying anti-rheumatic drug; MTX= methotrexate; iv=intravenous; sc=subcutaneous. *With subcutaneous administration.
out period of three weeks, patients were treated with subcutaneous D2E7 or placebo for three months. The dose of D2E7 was increased to 1 mg/kg subcutaneously weekly for non-responders or those losing their responder status. Blood samples were collected to determine D2E7 plasma concentrations. All responding patients continued in an open label extension of this study. Based on preliminary data, plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration. Up to 78% of patients achieved a DAS/ACR 20 response after three months of treatment with subcutaneous D2E7. With the exception of mild and transient injection site reactions, adverse events occurred with the same frequency and distribution in the D2E7 and placebo groups. The investigators concluded that D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery.

Monotherapy is often inadequate to control arthritic symptoms and rapid progression of RA. D2E7 (1 mg/kg as a single subcutaneous or intravenous injection) was evaluated in a randomised, double blind, placebo controlled trial in patients whose stable dose of methotrexate was insufficient to control symptoms. An ACR 20 response was seen in 67% and 72% of patients receiving D2E7 by subcutaneous and intravenous injection, respectively. The safety profile of single dose D2E7 administration was comparable to that of placebo.

Collectively, these early data suggest that the fully human anti-TNFα mAb D2E7 is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections. Additional studies are underway to further define optimal use of this novel treatment.

Preliminary results of early clinical trials with the fully human anti-TNF α monoclonal antibody D2E7

Joachim Kempeni

Ann Rheum Dis 1999 58: I70-I72
doi: 10.1136/ard.58.2008.i70

Updated information and services can be found at:
http://ard.bmj.com/content/58/suppl_1/I70

Email alerting service

These include:

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/