Addressing the safety of anakinra in patients with rheumatoid arthritis

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Anakinra (Kineret®; Amgen Inc., Thousand Oaks, CA) is the first and only recombinant human interleukin-1 receptor antagonist available for therapeutic use. It has been approved by the US Food and Drug Administration and the European Commission for the treatment of patients with rheumatoid arthritis (RA). Anakinra, as an anti-rheumatic therapy, has been assessed in five placebo-controlled clinical trials, either alone or in combination with methotrexate. These trials have shown anakinra to be efficacious and well tolerated by most patients, with the most frequently reported adverse events being mild-to-moderate injection-site reactions that generally resolved rapidly. One of these trials was a large, prospective safety study, which included typical RA patients with a wide variety of co-morbid conditions and receiving concomitant medications. This confirmed that anakinra is a well-tolerated treatment in an RA population representative of that seen by the practising rheumatologist.

KEY WORDS: Anakinra, Biological response modifier, DMARD, Interleukin-1 receptor antagonist, Rheumatoid arthritis, Safety, Tuberculosis.

Within the past 4 yr, biological response modifiers (BRMs) that target specifically the proinflammatory cytokines interleukin-1 (IL-1) or tumour necrosis factor alpha (TNFα) have been developed and introduced into clinical practice. These cytokines are thought to play an important role in mediating the pathogenesis of RA. In clinical trials, BRMs have been shown to be effective in controlling the signs and symptoms of RA and also in retarding joint destruction [12–19]. Anakinra (Kineret®; Amgen Inc., Thousand Oaks, CA) is a recombinant form of the naturally occurring human IL-1 receptor antagonist (IL-1Ra) that has been approved by the US Food and Drug Administration (FDA) and the European Commission for the treatment of RA. It is the first and only selective blocker of IL-1. This paper reviews the safety of this novel treatment and compares it with the safety of conventional DMARDs and other BRMs.

Safety of conventional DMARDs

Gold

Parenteral organic gold compounds have been used for the treatment of RA since the 1920s [20] with the benefits of therapy being well documented [21]. In a comparison of weekly administration of parenteral gold (50 mg) with
weekly administration of i.m. methotrexate (MTX; 15 mg), a higher proportion of patients obtained remission from the symptoms of RA following treatment with gold; however, such treatment was also associated with increased relative toxicity [21]. Adverse events (AEs), which include mucocutaneous reactions, proteinuria and cytopenias, have thus limited the use of this therapy [22]. It has been estimated that, after 5 yr, only 15–20% of patients treated with parental gold remain on therapy; 60% of treatment discontinuation has been attributed to toxicity [23].

**Sulphasalazine**

Sulphasalazine has a wide range of toxic effects, which limits its clinical usefulness [24]. In an analysis of six placebo-controlled trials, AE-related withdrawals were 3-fold greater with sulphasalazine compared with placebo [25]; indeed, ~30% of patients discontinue sulphasalazine because of AEs [23]. These include nausea, vomiting, headache, malaise, rash, neutropenia, aplastic anaemia, agranulocytosis, haemolysis and yellowish discoloration of skin, urine and contact lenses, as well as reversible infertility in men [22, 24].

**Methotrexate**

Prospective long-term studies have shown that MTX is better tolerated and more efficacious than older DMARDs such as gold salts, parenteral gold, penicillamine, azathioprine and hydroxychloroquine. Furthermore, a far higher percentage of patients remain on MTX for longer periods of time when compared to these older DMARDs [2, 26, 27]. Side effects of MTX include stomatitis, gastrointestinal intolerance (occurring in as many as 60% of patients) and bone marrow suppression (which are all responsive to folic acid supplementation), as well as idiosyncratic drug hypersensitivity reactions resulting in lung injury and liver damage [10, 28–31]. MTX is also an abortifacient and causes birth defects; conception should, therefore, be avoided while on this medication and both men and women should employ appropriate contraceptive measures [30].

**Leflunomide**

Leflunomide is an anti-proliferative isoxazole compound that has been shown to have comparable efficacy to MTX in a 52-week randomized, placebo-controlled trial in patients with active RA [32]. Two further trials have shown a significant clinical improvement with the combination of leflunomide and MTX [11, 33]. Common side-effects of leflunomide, including diarrhoea, dyspepsia, abdominal pain, hypertension, rash, reversible alopecia and headaches, were seen across all three clinical trials. Furthermore, in each of these trials, a significant number of leflunomide-treated patients had an elevation in transaminases during treatment. These findings have been extended in post-marketing reports: 296 hepatic reactions have been reported across an estimated 104 000 patient yr of leflunomide exposure, 129 of which were considered to be serious [34]. Many of the cases were associated with confounding factors such as concomitant hepatotoxic medications, history of alcohol abuse and existing liver function disturbance. Because of this, the European summary of product characteristics for leflunomide recommends that liver enzyme levels are monitored monthly for the first 6 months of treatment and every 8 weeks thereafter [35]. In addition, it is recommended that alcohol consumption be avoided during leflunomide therapy. Haematological reactions have also been observed with leflunomide in post-marketing analyses; therefore, it is advised that a complete cell count be performed prior to treatment initiation, every 2 weeks during the first 6 months of therapy and every 8 weeks thereafter [35].

**Safety of BRMs**

**Etanercept**

Etanercept (Enbrel®, Amgen Inc.) is a soluble TNF-receptor fusion protein that binds to circulating TNF, blocking the cytokine’s interaction with cell-surface receptors. The only consistent safety concern raised during clinical trials of etanercept was injection-site reactions (ISRs), which were considered to be mild-to-moderate in severity and did not generally require discontinuation of treatment [36]. Since etanercept has been approved in the USA, however, some safety concerns over this drug have emerged, although the true incidence of serious adverse events (SAEs) and their relationship to etanercept therapy remains unclear. Seventeen cases of development of confusion and difficulty in walking while receiving etanercept had been reported to the FDA Adverse Events Reporting System as of December 2001 [37]. These neurological events were temporally related to etanercept and partially or completely resolved on discontinuation of therapy, although one patient developed further symptoms when rechallenged with etanercept. Caution is recommended when considering prescribing etanercept to patients with pre-existing or recent-onset demyelinating diseases [36].

Serious infections, including tuberculosis and sepsis, have also been reported following the introduction of etanercept. Many of these serious infections have occurred in patients receiving concomitant immunosuppressive therapy. As of August 2001, the reporting rate for tuberculosis was 20 patients, 15 of whom were from the USA, out of 114 000 patients exposed to etanercept (E. Keystone, personal communication, Update on Biologics, EULAR 2002, Stockholm, Sweden). There has been no temporal association observed between the introduction of etanercept and the onset of clinical tuberculosis [38]. Furthermore, 20 patients with a known history of tuberculosis and nine patients with a history of a positive tuberculin test have been enrolled in etanercept clinical trials; none of these patients has developed evidence of reactivation of tuberculosis [38]. When the rate of infection was assessed in the same population, it
was found to be consistent with that observed in the pre-TNF antagonist literature [39]. The US package insert for etanercept has been updated to include warnings about the use of the drug in patients with active infections, a history of recurring infections, or underlying co-morbidities, such as advanced or poorly controlled diabetes, that may increase the risk of infections [36].

Infliximab

Infliximab (Remicade®; Centocor Inc., Malvern, PA) is a chimeric monoclonal antibody that binds specifically to human TNFα, thus inhibiting the cytokine’s interaction with its receptors.

The most common AEs in clinical trials of infliximab were infusion-related reactions, occurring in 20% of infliximab recipients compared with 9% of placebo recipients [40]. In a phase II trial of infliximab in patients with congestive heart failure (CHF), there was a higher rate of mortality or hospitalization due to worsening heart failure in infliximab-treated patients compared with placebo-treated patients [40]. This effect was not seen in trials with etanercept (D. Mann, personal communication, European Society of Cardiology Heart Failure Update, Oslo, Norway, 11 June 2002). Following the approval of infliximab in the USA, reactivation of latent tuberculosis, histoplasmosis, Pneumocystis carinii, candidiasis, listeriosis, coccidioidomycosis and herpes virus infections have been reported with the drug [41, 42]. Some of the infections have proved fatal. As of May 2001, there were 70 reported cases of tuberculosis following infliximab therapy, 64 of which were from countries with a low incidence of the disease [42]. The median time from initiation of infliximab to development of tuberculosis was 12 weeks (range 1–52 weeks). Forty of the patients (56%) had extrapulmonary disease and 17 patients (24%) had disseminated disease, forms of tuberculosis associated with significant immunosuppression. As of 23 February 2002, 181 cases of tuberculosis had been reported in the ~271 000 patients who had received infliximab world-wide (E. Keystone, personal communication, Update on Biologics, EULAR 2002, Stockholm, Sweden). The US package insert for infliximab has been updated to warn that patients should be evaluated for latent tuberculosis infection before commencing therapy with infliximab [40].

Safety of anakinra

The overall safety analysis of anakinra has focused on data from five randomized, placebo-controlled trials involving a total of 2932 patients. Two of these trials compared the use of anakinra as monotherapy vs placebo, one explored dosages of anakinra up to 150 mg/day [12] and the other dosages up to 30 mg/day [43]. Two further trials have investigated the use of anakinra in combination with MTX, one testing dosages of anakinra up to 2 mg/kg/day [13], with the other assessing anakinra at 100 mg/day [44]. The fifth trial was a large prospective safety study of anakinra 100 mg/day undertaken to characterize further the safety profile of anakinra in a patient population with diverse disease activity and co-morbid conditions [45].

Large, prospective safety study

The safety study included a large number of patients (n = 1399) to ensure that AEs that occurred at a low incidence would be detectable [45]. This was the first randomized, placebo-controlled trial of a BRM that included a patient population representative of typical RA patients seen in clinical practice, with a variety of co-morbid conditions, including a history of asthma, diabetes, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), CHF, or prior pneumonia. For the first 6 months of the study, patients were randomized to receive anakinra 100 mg/day or placebo, in a double-blind manner, at a ratio of 4:1, respectively. Those completing the first phase of the trial were able to continue in an open-label extension for an additional 30 months. Patients were required to have presented with clinical features of RA for at least 3 months prior to study entry, with evidence of active disease defined as a minimum of three swollen joints and at least three tender or painful joints, or morning stiffness of at least 45 min duration. This trial was designed to represent the actual RA population in that patients were allowed to receive non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and DMARDs, either alone or in any combination, and were also permitted to change these medications during the course of the study if clinically indicated.

Patient demographics across the five placebo-controlled trials

The baseline demographics of patients included in these five studies are shown in Table 1. In all five studies, patients were predominately Caucasian and female, with a mean age ranging from 52 to 56 yr and active RA. The patients in the monotherapy studies had a shorter duration of disease compared with those who received anakinra in combination with MTX, or those who participated in the wide-ranging safety study [43].

Details of the concomitant medications received by patients in these studies are shown in Table 2. Patients in all five trials could be treated with stable doses of NSAIDs or corticosteroids. Concomitant use of DMARDs or other BRMs was not allowed in the monotherapy studies; in the combination therapy studies, all patients received MTX, but no other DMARDs or BRMs [43]. In the large safety study, patients were allowed to receive any combination of NSAIDs, corticosteroids and DMARDs, although they were excluded from the use of other BRMs. At baseline, 31% of patients received concomitant MTX alone, 22% were treated with MTX in addition to other DMARDs and 21% received no DMARD therapy. Almost half of the patients were treated with a combination of cortico-
steroids and DMARDs, while 10% did not receive any DMARDs or corticosteroids [45].

The completion rates across the five studies ranged from 73 to 88%, with some patients receiving anakinra for as long as 5 yr in trial extensions [43]. Of the 1399 patients in the safety study who received at least one dose of the study drug, 79.0% (n = 1105) completed 6 months of treatment: 78.4% (875/1116) anakinra recipients and 81.3% (230/283) placebo recipients [45].

Anakinra overall safety profile

Across the five placebo-controlled trials, there were no significant differences between anakinra ≤100 mg/day and placebo with respect to the development of AEs (88–92% vs 85%), SAEs (7.1–8.4 vs 6.5%), death (0.2–0.3% vs 0.1%) or withdrawal due to AEs (9.5–13.6 vs 11.6%). There was a slightly higher rate of occurrence in all these categories at doses of anakinra >100 mg/day. ISRs were the most common cause for withdrawal with any dose of anakinra—7.3% of patients receiving anakinra 100 mg/day and 7.1% of patients receiving anakinra at doses >100 mg/day withdrew due to ISRs, compared with 1.3% of patients receiving placebo. Not unexpectedly, the most common reason for withdrawal in the placebo group was worsening of RA, which occurred in 6.2% of patients compared with 1.8% in the anakinra 100 mg/day group [43].

During the anakinra clinical trials, patients were required to self-administer the study drug via s.c. injection. Although there was initial concern regarding patients’ compliance with this regimen, it was found that subjects missed very few injections, with approximately half of the patients in the safety study missing no injections at all and another 35% missing less than seven injections in a 6 month period [45]. An ISR developed in 27% of placebo-treated patients compared with 71% of patients receiving anakinra 100 mg/day. The majority (95%) of such reactions were considered to be mild-to-moderate in severity. ISRs were characterized by erythema, pruritus, rash, pain, or ecchymosis and almost all responded to topical applications. They generally occurred early in the course of treatment and were unlikely to arise at a subsequent stage if they did not develop within the first 4 weeks of therapy [43].

Serious adverse events

‘SAE’ is a regulatory term that includes events that are: (i) fatal, (ii) life threatening, (iii) result in or prolong hospitalization, (iv) persistent and result in significant
disability or incapacity, or (v) cause a congenital abnormality. The overall incidence of SAEs was not markedly different between anakinra 100 mg/day (7.1%) compared with placebo (6.5%). SAEs in the placebo groups were notable only for worsening of RA (1.6%). In the anakinra 100 mg/day group, SAEs that occurred in >0.2% of patients included worsening of RA (0.7%), pneumonia (0.9%), abdominal pain (0.3%), abdominal hernia (0.2%) and dyspnoea (0.3%) [43].

**Infections**

Infectious episodes occurred in 36.2% of placebo-treated patients and 39.8% of patients receiving anakinra 100 mg/day. Of these infections, 0.7% of those in the placebo group and 1.8% in the anakinra 100 mg/day group were considered to be serious [43]. In all five studies, the rate of serious infection following anakinra treatment did not appear to be considerably higher than that seen in the placebo group or that previously reported in the general population [46].

Across the five studies, the most common serious infection experienced by patients receiving anakinra was pneumonia (Table 3) [43, 47]. Of the 14 anakinra-treated patients who developed pneumonia, 13 had a history of COPD, asthma, CAD, CHF, or prior pneumonia, or were concomitantly treated with corticosteroids or other DMARDs [43, 47]. Details of the patients who developed pneumonia are shown in Table 4. History of asthma or prior pneumonia, and use of corticosteroids appeared to be risk factors for the development of this infection when the characteristics of pneumonia patients were compared with patients who did not develop pneumonia. There are three additional important points to consider with respect to the pneumonias experienced by anakinra-treated patients. The first is that the pneumonias were typical of patients with RA, were treated with usual antibiotics and none were fatal. The second point is that of the 14 patients, nine continued treatment and completed the study without further problems due to pneumonia. Thirdly, there were many other patients in these studies with the same risk factors as those who developed pneumonia but who did not develop the condition.

**Other safety issues with anakinra**

Unusual or opportunistic infections such as tuberculosis, histoplasmosis, listeriosis and aspergillosis, which have been reported more frequently in post-marketing studies of patients using anti-TNF antibodies, were not observed in any of the anakinra placebo-controlled studies [43]. In

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**Table 3. Serious infectious episodes reported in anakinra trials [47]**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Placebo (n = 759)</th>
<th>Anakinra &lt;100 mg/day (n = 610)</th>
<th>Anakinra 100 mg/day (n = 1367)</th>
<th>Anakinra &gt;100 mg/day (n = 196)</th>
<th>All anakinra (n = 2173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious event</td>
<td>5 (0.7)</td>
<td>7 (1.1)</td>
<td>25 (1.8)</td>
<td>4 (2.0)</td>
<td>36 (1.7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0 (0.0)</td>
<td>2 (0.3)</td>
<td>12 (0.9)</td>
<td>0 (0.0)</td>
<td>14 (0.6)</td>
</tr>
<tr>
<td>Cellulitis/abscess</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>7 (0.5)</td>
<td>1 (0.5)</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>Other respiratory infection</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
<td>3 (0.2)</td>
<td>1 (0.5)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>GI infection</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>3 (0.2)</td>
<td>0 (0.0)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Bursitis</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
<td>1 (0.5)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Pelvic inflammation°</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)°</td>
<td>1 (0.1)°</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
<td>1 (0.0)</td>
</tr>
</tbody>
</table>

°Reproductive AE rates are gender specific.

**Table 4. Medical histories and concomitant medications received by anakinra-treated patients who developed pneumonia [47]**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Pneumonia type</th>
<th>Relevant co-morbidities</th>
<th>Concomitant medication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>F</td>
<td>Pneumonia</td>
<td>None</td>
<td>DMARD, steroid</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>Right mid lobe</td>
<td>COPD, asthma</td>
<td>DMARD</td>
<td>Continued</td>
</tr>
<tr>
<td>77</td>
<td>M</td>
<td>Interstitial</td>
<td>None</td>
<td>DMARD, steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>64</td>
<td>M</td>
<td>Pneumonia</td>
<td>COPD, asthma</td>
<td>DMARD, steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>62</td>
<td>M</td>
<td>Right low lobe</td>
<td>CAD, CHF, coronary artery bypass graft</td>
<td>None</td>
<td>Continued</td>
</tr>
<tr>
<td>66</td>
<td>M</td>
<td>Left low lobe</td>
<td>Atopy, pneumonia, asthma, CHF</td>
<td>DMARD, steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>59</td>
<td>F</td>
<td>Right lung, pleurisy, effusion, empyma</td>
<td>Dyspnoea, atopy, asthma, pneumonia</td>
<td>Steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>46</td>
<td>M</td>
<td>Left lung</td>
<td>Pneumonia, COPD, bronchiectasis</td>
<td>DMARD, steroid</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>51</td>
<td>F</td>
<td>Pneumonia</td>
<td>None</td>
<td>DMARD, steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>Bronchopneumonia</td>
<td>Asthma</td>
<td>DMARD, steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>Streptococcal pneumonia</td>
<td>Dyspnoea, COPD, pulmonary fibrosis</td>
<td>DMARD, steroid</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>Left low lobe</td>
<td>None</td>
<td>None</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>Pneumonia, CHF</td>
<td>CAD, COPD</td>
<td>DMARD, steroid</td>
<td>Continued</td>
</tr>
<tr>
<td>66</td>
<td>F</td>
<td>Legionella pneumonia</td>
<td>None</td>
<td>DMARD, steroid</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>
addition, malignancies occurred in the anakinra-treated patients at the same rate as would be expected in an age- and sex-matched control group [based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) programme] [48]. The types of malignancies reported in anakinra recipients were also similar to those included in this database.

Anakinra has a short half-life compared with other BRMs, particularly infliximab. This may explain the lack of occurrence of some of these AEs with anakinra as duration of the IL-1 receptor blockade is short and, thus, the role of IL-1 in host defence against infection is not compromised. Furthermore, animal studies indicate that TNF may have a much greater role in host defensive mechanisms than IL-1 [49], thus blockade of TNF may leave patients more vulnerable to opportunistic infections. This potential benefit of anakinra will not be elucidated fully, however, until there has been a large post-marketing experience with the drug.

**Safety of anakinra in combination with etanercept**

The combination of anakinra and etanercept has been investigated in a 24 week open-label safety study in which patients who were receiving treatment with etanercept were initiated on anakinra 1 mg/kg/day via s.c. injection [50]. A total of 58 subjects who had active disease despite receiving treatment with etanercept 25 mg twice weekly for an average of 14.4 months were enrolled. The patients were predominately female, with a mean age of 48.9 yr and a mean disease duration of 11.9 yr. There were no deaths during the study and seven SAEs (12.1%), including a case of accidental electrocution, one of opiate/barbiturate withdrawal syndrome and one gastric ulcer haemorrhage. The other four SAEs (7%) were infections and included two cases of pneumonia and two cases of cellulitis. All patients who experienced an SAE recovered. No cases of tuberculosis or opportunistic infection were reported. The safety of combination therapy with anakinra and etanercept has also been investigated further in a large, double blind, placebo-controlled trial. Combination therapy was associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared with etanercept alone. Accordingly, the concurrent administration of anakinra and etanercept is not recommended.

**Summary**

Anakinra is a novel molecule with a unique mechanism of action and a short half-life. The extensive safety analysis of anakinra in patients with RA has demonstrated that the agent is well tolerated, even in those with co-morbidities or receiving concomitant medications. Furthermore, the short half-life of anakinra (4–6 h) provides flexible control of therapy and may therefore have significant benefits with respect to the prevention and treatment of SAEs. Discontinuation of anakinra when an AE appears may allow for a more rapid response to appropriate therapy, as opposed to other BRMs, which have longer half-lives. Greater post-marketing experience with anakinra will help to answer some of these important questions.

**References**