Interleukin-6 Inhibition and Clinical Efficacy in Rheumatoid Arthritis Treatment: Data from Randomized Clinical Trials

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Abstract
Interleukin 6 (IL-6), a pleiotropic cytokine with numerous and varied effects on the inflammatory cascade and immune response, appears to be an attractive target for novel immunomodulatory therapy for systemic inflammatory autoimmune diseases. Proof of principle for this approach has come from studies of the anti-IL-6 receptor monoclonal antibody, tocilizumab. Tocilizumab has been assessed in a number of studies in recent years, mainly in patients with rheumatoid arthritis (RA). Data from randomized controlled clinical trials demonstrate the efficacy of tocilizumab in improving the signs and symptoms of RA. In addition, it appears that such inhibition of IL-6 can have positive effects on functional status, an important outcome for RA patients. Finally, data suggest that treatment with this agent may also inhibit the progression of disease as assessed radiographically. Data from studies currently underway will help refine the ultimate use of this novel approach to treatment, and help clinicians optimize therapy using this approach.

Among the most important advances in rheumatology, in recent years, has been the introduction of biologic agents. The dramatic clinical efficacy achieved with these agents, in particular, inhibitors of the proinflammatory cytokine tumor necrosis factor (TNF), has raised the goals of therapy for patients with RA and other autoimmune diseases. This, in turn, has fueled further basic research and clinical development. Several additional components of the dysregulated immune response that might prove to be relevant targets for novel immunomodulatory therapies have been identified, and studies testing various other approaches are well underway.

Among the most promising new targets for immunomodulatory antirheumatic therapy is the pleiotropic cytokine interleukin 6 (IL-6). IL-6 has numerous and varied effects on the inflammatory cascade and immune responses and appears to play a role in several autoimmune conditions. To date, almost all of the experience targeting IL-6 has been with the monoclonal antibody (mAb) tocilizumab. Previously referred to as MRA (myeloma receptor antibody), tocilizumab is a humanized IgG1 mAb that binds with high affinity to soluble and membrane bound forms of the 80 kDa component of the IL-6 receptor (IL-6R). Treatment with this mAb effectively inhibits IL-6 mediated interactions on cells constitutively expressing the IL-6R. In addition, because soluble forms of the IL-6R can productively interact with the 130 kDa signal transducing component gp130, which is expressed on a wide of cell types, treatment with tocilizumab effectively inhibits a broad array of IL-6 driven processes.

The diverse activities of IL-6, its potential roles in various models of arthritis, and the rationale for its choice as a target in RA are well reviewed elsewhere. In addition, the effects of IL-6 inhibition with tocilizumab on systemic manifestations of RA, as well as its safety profile, are assessed in detail in other publications. In this paper, we will examine the clinical efficacy data related to IL-6 inhibition in patients with RA, focusing on data from randomized clinical trials. Key implications from this data as regards additional clinical study and the clinical use of this therapeutic approach are also discussed.

Clinical Efficacy Data
As is common in development programs, the earliest clinical experience with tocilizumab was in small open studies. While such studies do not definitely establish clinical effi-
cacy, they can provide a “signal” regarding the potential utility of the approach. Moreover, these studies help delineate key characteristics of the agent under evaluation, such as the pharmacokinetics and appropriate dosing. Such early, open studies of tocilizumab provided the foundation for the design and conduct of more rigorous controlled clinical trials. In these studies, clinical efficacy was observed at several doses of tocilizumab, and a terminal half-life of approximately 240 hours was observed.\textsuperscript{6,7} It is worth noting that, in distinction to some other antirheumatic therapies, tocilizumab has had development programs conducted in Japan and also in Europe and North America. Because the standard of care for the treatment of RA can vary somewhat across the globe, aspects of study design will also differ, which readily can be seen in the individual trials of tocilizumab. Nevertheless, each study provides relevant clinical information that has contributed to the current fund of knowledge concerning this drug.

An early double-blind, placebo-controlled, randomized clinical trial (DBPCRCT) evaluated escalating dosages of tocilizumab that were given as a single intravenous infusion in 45 patients with active RA in Europe.\textsuperscript{8} Doses received were 0.1, 1, 5, or 10 mg/kg or placebo; no concomitant disease modifying antirheumatic drugs (DMARDs) were permitted during the study. The primary outcome was an ACR20 response at 2 weeks, and patients were followed through 8 weeks. At week 2, five of nine (56%) patients receiving tocilizumab 5 mg/kg achieved an ACR20 response, compared with two of 11 (18%) patients receiving placebo. Interestingly, at 2 weeks, no response was seen at any of the other doses assessed. However, at 8 weeks, there were statistically significant ACR20 responses seen in the 10 mg/kg group (approximately 40%) as well as the 5 mg/kg group (approximately 55%). Substantial decreases in measures of the acute phase response, including the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) concentration, were seen in the higher dosage groups (5 and 10 mg/kg) as early as 1 week and were largely sustained through week 4. This study established proof of principal for targeting of IL-6 and provided information regarding doing that was used in the design of further studies.

A larger phase II study tested tocilizumab in 164 Japanese RA patients.\textsuperscript{9} This DBPCRCT assessed tocilizumab at doses of 4 or 8 mg/kg or placebo, administered intravenously every 4 weeks over 3 months. No concomitant DMARDs were used. The primary end point of the study was the ACR20 response at week 12, with LOCF (last observation carried forward) methodology. Disease Activity Scores (DAS28) were also assessed. Patients had relatively refractory disease, with a mean duration of approximately 8 years and a mean of five prior DMARD failures. Disease was also fairly active at the time of enrollment, with a mean tender joint count of 18 of 49 examined, a mean swollen joint count 14 out of 47 examined, and a mean ESR of approximately 70 mm/hour. In this study, a dose dependent clinical response was noted with treatment (Table 1).

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Placebo</th>
<th>4 mg/kg</th>
<th>8 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>11.3%</td>
<td>57.4%</td>
<td>78.2%</td>
</tr>
<tr>
<td>ACR50</td>
<td>1.9%</td>
<td>25.9%</td>
<td>40%</td>
</tr>
<tr>
<td>ACR70</td>
<td>0</td>
<td>20.4%</td>
<td>16.4%</td>
</tr>
<tr>
<td>EULAR Good responses</td>
<td>0</td>
<td>5.6%</td>
<td>18.2%</td>
</tr>
<tr>
<td>EULAR Good or moderate responses</td>
<td>18.9%</td>
<td>72.2%</td>
<td>90.9%</td>
</tr>
</tbody>
</table>

Most individual measures of arthritis activity had already improved to a statistically significant level by the 4-week evaluation time point although the extent of response continued to improve through 12 weeks. Among the various measures, the acute phase reactants (ESR, CRP) demonstrated the clearest dose dependency in improvement. Of note, longer term data from patients originally in this study who elected to continue to receive therapy with tocilizumab in long-term open label follow-up were recently reported.\textsuperscript{10} Of the 164 patient in the original study, 143 (87%) chose to continue open label treatment with tocilizumab given at a dose of 8 mg/kg intravenously every 4 weeks. Importantly, 89 patients (54% of the original cohort, 62% of those entering the open label study) had received therapy for 5 years or more at the time of this report.\textsuperscript{10} Sustained clinical responses appeared to have been maintained over time, an important attribute as regards treatment of such a chronic condition as RA. Moreover, higher levels of treatment response appeared to be maintained for a considerable number of patients (e.g., ACR50, 68.4%; ACR70, 44.7%) over 5 years of follow-up.

Whereas the studies reviewed above established the potential efficacy of tocilizumab given as monotherapy, the utility of combination therapy with methotrexate (MTX) was examined in a European study known as CHARISMA (Chugai Humanized Anti-human Recombinant Interleukin-6 Monoclonal Antibody).\textsuperscript{11} In this study, 359 RA patients with active disease, despite the concomitant use of MTX, were enrolled into one of seven treatment arms: tocilizumab 2, 4, or 8 mg/kg, as monotherapy, or tocilizumab at the same doses in combination with MTX; the seventh arm consisted of MTX with placebo. Tocilizumab was given intravenously every 4 weeks. The primary outcome measure was the ACR20 response at week 16, and additional measures included the DAS28 score. At entry, the groups were well balanced as regards important disease characteristics, and patients had fairly active disease, with a mean DAS28 score
of approximately 6.5. Clinical responses are shown in Figure 1. With tocilizumab monotherapy, doses of 4 mg/kg and 8 mg/kg were superior to MTX alone, whereas the lower dose of 2 mg/kg was not. However, among patients remaining on concomitant MTX, all three dosing groups achieved statistically significant improvement compared with MTX alone. While ACR20 results were comparable across treatment groups, more patients achieved higher levels of response (e.g., ACR70, DAS28 remission) with the higher doses. For example, DAS28 remission was achieved by 34% of patients receiving tocilizumab 8 mg/kg plus MTX, 17% of those receiving the same dose of tocilizumab as monotherapy, and 8% of those on MTX monotherapy.

In summary, this study reaffirmed the clinical efficacy of tocilizumab. It also suggested the potential for additive benefit with combination therapy using MTX. This is, of course, of great relevance to clinicians, who desire the highest level of response for patients, and because MTX is frequently the ‘anchor’ drug upon which additional antirheumatic therapies are added.

In addition to its effect on clinical signs and symptoms, the ability of treatment with tocilizumab to alter the progression of joint damage was assessed in a study called SAMURAI (Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 inhibitor). This study enrolled 306 Japanese patients with relatively early RA (required disease duration more than 6 months and less than 5 years; mean disease duration observed among enrolled patients, 2.3 years; required DMARD failure, at least 1; mean number of prior DMARDs failed among enrolled patients, 2.75). Patients also had active disease, with a mean DAS28 score at entry of 6.5. Patients were randomized to treatment with tocilizumab monotherapy, 8 mg/kg intravenously every 4 weeks, or to conventional DMARD therapy. Although the study was open, radiographs were scored by readers who were blinded as to treatment and order. Radiographs of the hands and feet were taken at baseline, 28 weeks, and 52 weeks, and were scored using a modified Sharp score with a range of 0 to 448. At baseline, patients had a mean total Sharp score (TSS) of about 29, yielding an estimated yearly progression rate of 13 units/year. In the conventional DMARD group, changes in dose and medication were at the treating physicians’ discretion. MTX was the most common DMARD used, alone or in combination with other DMARDs. The average MTX dose was 8 mg/week, which is in keeping with standard practice in Japan. As was seen in earlier studies, treatment with tocilizumab was effective in improving the signs and symptoms of disease. Thus, at week 52, ACR20, 50, and 70 response rates were 78%, 64%, and 44% with tocilizumab, respectively, compared with 34%, 13%, and 6%, respectively, for conventional DMARD therapy. Remission, quantified by DAS28 scores less than 2.6, was achieved by 59% of tocilizumab patients, compared to 3% of controls. Moreover, improvement in functional status, assessed by significant changes in HAQ (Health Assessment Questionnaire) scores, were achieved by 68% of tocilizumab treated patients, compared to 40% of those on conventional DMARDs. In this study, therapy with the anti-IL-6R mAb was also shown to have a beneficial effect on the progression of radiographic joint damage. Mean changes in TSS were less in the tocilizumab group, and at week 52, 56% of tocilizumab treated patients had no discernible radiographic progression (defined as a change in TSS to equal or less than 0.5 units), as compared to 39% of those on conventional DMARDs (p < 0.01). This study confirms the previously suggested beneficial effect of tocilizumab on the signs and symptoms of disease and also on functional status and as well establishes an effect on the structural integrity of the joints.

A number of additional studies that will shed further light on the utility of tocilizumab in RA are underway. Some have recently been completed, and preliminary data has become available. A 6 month study known as OPTION (tOcilizumab Pivotal Trial in methotrexate ImaDequate respOnDers) was conducted across several continents. This study enrolled 623 patients with active RA despite concomitant MTX. Patients remained on MTX and were randomized to placebo or to tocilizumab at doses of 4 mg/kg or 8 mg/kg, given intravenously every 4 weeks. The primary endpoint, an ACR20 response at 24 weeks, was achieved by significantly
more patients in the tocilizumab groups (4 mg/kg, 47.9%; 8 mg/kg, 58.5%) than in the placebo group (26.5%). In addition, higher levels of response, including ACR50 and 70 as well as EULAR good responses, were seen more commonly with active treatment. Importantly, treatment was also associated with significant improvement in quality of life (measured by the SF-36 score), as well as in physical function (measured by HAQ) and fatigue (measured by the FACIT-fatigue [Functional Assessment of Chronic Illness Therapy-Fatigue] score). Changes in these latter parameters have a very significant effect on ultimate outcome and are of great importance to patients with RA.

**Future Directions**

There are several key questions that will impact the ultimate utility of tocilizumab in the clinic (Table 2). Of note, many of these are being addressed by studies that are presently being conducted, and answers may be forthcoming in the near future.

Because of the extensive worldwide experience with TNF inhibitors, given the broad and impressive clinical efficacy as well as the good tolerability of these agents, they have largely become the biologic agent of choice for patients with RA. However, not all patients achieve the desired results with TNF inhibitors. Indeed, the notable success of the TNF inhibitors has been one of the key driving forces that has “raised the bar” as regards the goals of treatment for RA and for other autoimmune conditions. Therefore, it has become increasingly important for newer biologic agents to be assessed in patients who have failed prior treatment with TNF inhibitors. These studies are underway for tocilizumab, and the results will be very relevant to clinicians. From a theoretical standpoint, because TNF is a key driver of IL-6, it may be hypothesized that blockade of IL-6 might not be as efficacious among patients who had not responded to inhibition of TNF. However, one point that has clearly been learned with the development of novel immunomodulatory agents is that the complexity of the immune system and the inflammatory response belies such simplistic considerations. This is particularly the case for cytokines, which interact in chaotic cascades. Moreover, recent data highlighting the role of IL-6 in stimulating so-called IL-17 lineage T cells provides a potential mechanism for IL-6 blockade that may be independent of TNF.

As reviewed above, several dosages of the IL-6 inhibitor tocilizumab have been assessed in clinical studies. However, with broader use, it is possible that alternative regimens may prove to be useful. Likewise, because not all RA patients can take MTX, the potential combination of tocilizumab with other DMARDs may provide an additional option for clinicians. This too is under study at present. When considering combination therapy, a topic that has bedeviled rheumatologists in recent years is the issue of combination biologic therapy. Such an approach has considerable theoretic appeal in terms of synergistic efficacy and has been proven in animal models of arthritis. In patients with RA, however, two negative approaches (combination TNF inhibitor plus IL-1 inhibitor and combination TNF inhibitor plus T cell costimulatory molecule inhibitor) were abject failures, with no synergistic or even additive efficacy, yet clearly with additive toxicity. Because this concept still has theoretic appeal, it may be worth testing with newer biologic agents, including IL-6 inhibitors.

Despite the notable radiographic data as described above, greater information concerning the ability of IL-6 inhibition to inhibit structural damage in RA is eagerly awaited. These studies, which have the advantage of being DBPCRCT, are in progress. Although patients with relatively early RA have been studied, additional testing in this population would be of interest. Likewise, the utility of IL-6 inhibition in other systemic inflammatory autoimmune conditions would be of interest. In Japan, tocilizumab is already approved for Castleman’s disease, a rare condition, the expression of which is largely IL-6 driven. Based on the myriad effects of IL-6, it could readily be hypothesized that inhibition of IL-6 may find utility in a number of other diseases.

In the future, it is possible that additional inhibitors of IL-6 may be developed. Because of the ability of the IL-6R to interact with gp130 present on numerous cell types, antibodies or other therapeutic agents that target IL-6 may have distinct efficacy or safety profiles compared to those targeting IL-6R. This may therefore differ from data observed with other cytokines, such as IL-1 and TNF, where it appears relatively comparable results may be achieved by inhibiting the cytokine or its receptor. There are also other methods that may be of use in inhibiting IL-6, including inhibition of the signaling molecules that drive its production or are downstream from its receptor ligation. In the case of TNF, a variety of such strategies, using small molecule inhibitors of relevant kinases, for example, are under study. This would be possible in the case of IL-6 as well.

Finally, although this review focuses on efficacy, it goes without saying that a key item for further research and study centers around longer-term safety data on larger numbers of patients treated with IL-6 inhibition.

**Conclusions**

From an efficacy standpoint, there is compelling data regarding the beneficial effect of tocilizumab in improving the signs

**Table 2** Research Agenda for IL-6 Inhibitors

- Efficacy and tolerability among TNF-Inhibitor failures
- Potential utility of alternate dosages
- Utility with DMARDs other than MTX
- Potential use in combination biologic therapy
- Additional data on radiographic outcomes
- Utility in patients with early RA
- Utility in other autoimmune conditions
- Alternate methods to inhibit IL-6
- Additional long term safety data

**Research Agenda for IL-6 Inhibitors**
and symptoms of RA. In addition, it appears that such inhibition of IL-6 can have positive effects on functional status and may also inhibit the progression of disease as assessed radiographically. Data from studies currently underway will help refine the ultimate use of this novel approach to treatment and assist clinicians in optimizing therapy.

References

Disclosure Statement
Arthur Kavanaugh, M.D., has served as a Consultant for Roche Laboratories, Inc.