Introduction

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The 2007 European League Against Rheumatism (EULAR) meeting held on 13–16 June 2007 in Barcelona, Spain, whetted the intellectual appetite of rheumatologists from around the world due to the diversity of investigators, analyses, topics, sessions, and abstracts. The entire meeting was capped on both ends by the State-of-The-Art sessions that were representative “book-ends” for this engaging view of modern rheumatology. The Open Plenary Session focused on genetics, the importance of epidemiology in driving treatments for rheumatic disorders and the crossroads of imaging, pathology, and novel therapeutics in the study of the spondyloarthropathies. If one had to write a headline for this year’s EULAR meeting, it would be: “Explosion in new, effective, and safe biologic disease modifiers for the rheumatic diseases”. Another one might be: “Much improved treatment of rheumatologic disorders and measuring of therapy outcomes”. At the end of the sessions on Saturday, Jean-Michel Dayer delivered the mesmerizing and extraordinarily stimulating Fred Wyss EULAR Lecture entitled “Cytokines – lessons from the past to a brighter future in therapeutics”. The message of this presentation pervaded the entire meeting, which was one of rapid progress in cytokine research during recent years resulting in novel medications that work like a scalpel rather than an immunological club. In a further session, we were served with an abundance of exciting new information on issues varying from the innate to the adaptive immune system, novel biologic drugs (eg, the pegylated tumor necrosis factor [TNF] antagonist certizumab and the monoclonal antibody tocilizumab, which is directed at interleukin-6) for rheumatoid arthritis (RA), and data analysis of TNF antagonists in respect to safety and efficacy in the long-term treatment of RA, ankylosing spondylitis, and psoriatic arthritis. Topics of further interest covered the spondyloarthropathies, systemic lupus erythematosus, scleroderma, and myositis, as well as the biochemical aspects of cartilage, genomics, biomarkers, back pain, epidemiology, and autoantibodies to name just a few.

In this the second issue of the Abstracts in Rheumatology newsletter, abstracts were selected from the congress with the goal of choosing the abstracts that will be particularly valuable to clinicians caring for patients with inflammatory arthritides. While there were many presentations and abstracts that were viewed by the >12,000 attendees at the meeting, a few have been chosen that perhaps best reflect the current investigative work. These were picked from numerous posters and presentations as a representative sampling. As you will see, I have attempted to highlight some of the more interesting and innovative aspects of advances in rheumatology, particularly those relating to the revolutionary new biologic therapies that have transformed the care of patients with musculoskeletal disorders.

I hope that you will find the newsletter of selected abstracts and analysis both informative and useful.
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Shift from new drugs to new strategies

Eric M Ruderman, MD, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Although rheumatologists have come to expect that the treatment of rheumatoid arthritis (RA), and inflammatory arthritis in general, will improve each year, it seems that the nature of these improvements has begun to shift. Whereas the past 10 years have been marked by the approval and availability of a host of new compounds for treating RA, recent emphasis has been placed on studies designed to determine how to use these medications most effectively. With new compounds continuing to be developed, there are now sufficient options available (barring issues of cost and reimbursement) for treating patients, and relatively few patients whose disease cannot be controlled with one combination or another of existing alternatives. Instead of asking simply, “what can I do to control this patient’s disease?”, the questions now being raised have become more complex: “how fully do I want/need to control their disease? Which of the available options is most likely to work? When is it time to switch to a new treatment?” And, “which treatment should be selected next?”

One of the more important studies to address some of these questions, the BeSt trial (Dutch acronym for Behandel-Strategieën “treatment strategies”), data from which have now been reported in several publications, followed a different approach than many previous studies by researching several strategies for managing early RA rather than studying individual drugs [1,2]. The results of the BeSt trial showed quite clearly that early combination therapy leads to better outcomes than adding further agents to ineffective monotherapy. More recently published data from this trial support the potential for tumor necrosis factor (TNF) antagonists, in this case infliximab, to be used as induction therapy in RA. These data also suggest that patients failing to respond to initial therapy with methotrexate are unlikely to respond later to other conventional disease-modifying anti-rheumatic drugs (DMARDs), and will almost certainly require biologic therapy [3,4].

The next step for the BeSt and future trials will be to determine which patients are best suited for particular strategies. Clearly, some RA patients will have an adequate response to initial methotrexate therapy. Identifying those patients at the outset could save the additional expense of a biologic when it is not necessary and avoid an unnecessary delay in disease control in those patients who will ultimately require a biologic agent. While early evidence suggests that genetic markers may be helpful in this regard [5], it seems likely that a combination of genetic and clinical markers will provide the best guidance on the risk of progression and the likelihood of response to a given therapy. As more biologic therapies become available, it may be that these, or similar, markers will guide rheumatologists on the next choice of therapy after methotrexate, ie, are there patients who are more appropriately suited to being treated with abatacept or rituximab before being treated with a TNF antagonist?

Another important observation from several recent studies is the apparent disconnect between clinical and structural disease in patients treated with biologic therapies. Historically, it has been presumed that patients with persistent clinical disease on methotrexate are at greatest risk for progression of joint damage, and that only those with complete resolution of clinical disease activity are believed to be protected from this outcome. While this continues to be the finding in some of the more recent trials of methotrexate administered alone or in combination with a TNF antagonist, it has also become apparent that the latter agents prevent joint damage independently of their clinical effects, so that radiographic progression may be halted even in the presence of persistent clinical disease [6].

The significance of all of this in clinical practice is that the bar for success has been raised even higher. Clinicians strive to use the available agents as effectively as possible to eliminate clinical, functional, and structural evidence of disease activity. This has prompted increasing concern over how best to measure this activity. While this question has not been resolved, and it may be that there is no single measurement that can provide an ideal assessment of treatment success, the simple answer is that any measurement is better than no measurement. Studies like the BeSt and the Tight Control for Rheumatoid Arthritis (TICORA) trials have demonstrated quite clearly that treating a specific target, and changing therapies when the agent fails short of that target, leads to better outcomes.

In the past year, new data have shed some light on how to choose the most appropriate therapies at each point in the disease course. When practical, early use of combination DMARD therapy can lead to a higher success rate and better outcomes. As noted, TNF antagonists may perform better than methotrexate at preventing structural damage when residual disease activity remains. The long-term outcome of this may be improved maintenance of function and reduced disability. However, data will be necessary to confirm this, and to show that modest differences in Sharp scores in the short run do, indeed, translate into less disability over the long term.

For patients with more established disease, there are now several different options for patients who have had an inadequate response to TNF antagonists. Published data for abatacept and rituximab show that both drugs may be effective in this situation [7,8]. Larger, prospective studies have confirmed the anecdotal evidence that switching to an alternate TNF antagonist may also be an appropriate option [9,10]. The development of additional TNF antagonist agents, along with the first published European trial using the interleukin-6 antagonist, tocilizumab, suggests that the list of options will continue to grow [11]. The first comparative study of biologics, investigating abatacept and infliximab, was presented in the past year. More studies of this nature should help clinicians to better navigate the biologic waters.

In addition to the trials examining efficacy, more data have become available recently about the safety of existing biologic agents for RA. One thought-provoking meta-analysis of the adalimumab and infliximab clinical trials suggested that these agents are associated with a higher risk of infection and malignancy [12]. However, data from registries and other
sources of post-marketing information have suggested that the risk of malignancy, and lymphoma in particular, may not be increased [13–16]. Analysis of infection data, on the other hand, appears to confirm that there is an increased risk with TNF antagonist use, and that this risk is highest during the initial months of therapy [17–20]. This type of information is invaluable to the clinician seeking to advise and monitor his or her patients.

Finally, recently presented data have hinted at what may be next in the field of rheumatologic therapeutics. Results of the first controlled trial with a Janus kinase-3 inhibitor suggest that this type of agent may finally be the first successful oral, small-molecule therapy for RA. Data from a large trial of belimumab in systemic lupus erythematosus (SLE), an antibody to B lymphocyte stimulator, while not entirely positive, suggest that the biologic era has arrived for SLE as it has for RA. Given the potential for improved safety with this type of targeted approach, this development can only be seen as positive for an illness in which much of the associated morbidity stems not from the disease but from its therapy. This has been an exciting year in the field of rheumatologic therapeutics, and abstracts from the 2007 European League Against Rheumatism meeting, highlighted for review and discussion in this publication, provide a glimpse of the advances that are yet to come.

References

Abstract AB0180

Correlations between serum matrix metalloproteinases (MMP-1, MMP-3, MMP-9, MMP-13) and tissue inhibitors of metalloproteinases (TIMP-1, TIMP-2) concentrations and markers of the disease activity in early rheumatoid arthritis

Fiedorczyk M, Klimiuk PA, Sierakowski S, et al.

Background
Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are thought to play an important role in the destruction and remodeling of articular tissues in patients with rheumatoid arthritis (RA).

Type of study
Cross-sectional study

Objectives
To analyze the correlations between serum concentrations of MMPs and TIMPs and clinical markers of disease activity in the early stages of RA.

Results
Positive correlations were revealed between MMPs and TIMPs, and clinical markers of disease activity (e.g., number of swollen joints or erythrocyte sedimentation rate).

Conclusion
The studied MMPs and TIMPs might be useful clinical markers of disease activity in the early stages of RA.

Editor’s comments
We continue to look for biomarkers that can be used as sensitive indicators of disease activity in systemic inflammatory diseases such as RA. Our interest has grown out of expanding knowledge about the disease’s pathogenesis. Just as vascular endothelial growth factor is a marker for disease activity and potential joint damage, this study demonstrated that MMPs and TIMPs may play a role in disease activity in early RA. It should be noted, however, that this was a small study, and thus we cannot be assured that these serum concentrations are ready to be used in a greater laboratory assessment of RA.

Abstract AB0201

Anti-cyclic citrullinated peptide antibodies and high IL-15 serum levels predict better than rheumatoid factor the requirement of intensive treatment in early arthritis patients


Background
Intensive treatment of rheumatoid arthritis (RA) achieves better long-term functional and radiologic outcomes than conservative treatment, but can confer some risks. Therefore, identifying markers that can predict an aggressive course, especially at disease onset, could help in the selection of optimum candidates for more intensive therapy.

Type of study
Analysis study of markers in patients with early RA treated with disease-modifying anti-rheumatic drugs (DMARDs)

Objectives
To analyze the correlation between different DMARDs in patients with early RA, and the presence of rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), and increased serum interleukin (IL)-15 levels.

Patient characteristics
120 patients prospectively enrolled in the early RA clinic who had completed 2 years of follow-up (72.5% female; median age 53.5 years [interquartile range 38.5–63.1 years] at disease onset; median 6.6 months [interquartile range 4.2–10 years] of disease duration at first visit).

Study design/methods
Serum concentrations of anti-CCP, RF, IL-15, and IL-6 were blinded for the investigators involved in therapeutic decisions. The time on each DMARD was calculated to measure the intensity of treatment, and a new variable, TDMARD, was defined as the cumulative number of days on treatment with each DMARD adjusted by the following correcting factors derived from the evidence-based efficacy of each drug:

1. Anti-CCP: ×1 for anti-TNF agents
2. Parenteral gold salts, sulfasalazine, cyclosporin A, leflunomide, or methotrexate: ×1.5 for antimalarials
3. Anti-tumor necrosis factor (anti-TNF) agents: ×2 for anti-TNF agents

Statistical analysis was performed using the chi-squared and Mann–Whitney tests.

Results
A summary of the percentage of patients with various marker attributes, broken down by DMARD, is shown in Table 1. Although TDMARD reached significantly higher values for patients with positive RF, anti-CCP, or increased serum IL-15 than their respective controls, data from
RF-positive patients showed a noticeably wider range than values from those positive for anti-CCP or with increased serum IL-15 levels.

**Conclusion**
The detection of anti-CCP and increased serum IL-15 levels in the first visit is a better predictor than the presence of RF for selecting which early RA patients are candidates for aggressive treatment in the first 2 years of follow-up.

**Disclosures**
Supported by grants FIS G03/0152 and 04/2009.

**Abstract THU0113**
Anti-CCP-status and radiographic progression: the 5-year experience from the FIN-RACO study

**Origin of study**
Finland

**Type of study**
Randomized, 5-year study

**Objective**
To evaluate the impact of anti-cyclic citrullinated peptide (anti-CCP) on radiographic progression in patients with early rheumatoid arthritis (RA) who were initially treated either with a combination of three disease-modifying anti-rheumatic drugs (DMARDs) or with a single DMARD

**Patient characteristics**
129 patients with early active RA

**Study design/methods**
Patients were initially randomized to be treated either with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone (COMBI) (n=69), or with a single DMARD (initially sulfasalazine), with or without prednisolone (SINGLE) (n=60). After 2 years, the DMARD and prednisolone treatments became unrestricted. Radiographic progression (Larsen score) was assessed in hands and feet at baseline and at 1, 2, 3, 4, and 5 years. Anti-CCP levels at baseline were determined using enzyme immunoassay.

**Results**
Anti-CCP was positive in 92 (71%) patients. Anti-CCP positive versus anti-CCP negative patients were more frequently rheumatoid factor (RF) positive and had erosive disease at baseline (83% versus 22% [P<0.001] and 54% versus 22% [P<0.001], respectively). The presence of anti-CCP predicted radiographic progression in the COMBI group even when the impact of RF was controlled; the radiographic progression was markedly slower in anti-CCP-negative than in anti-CCP-positive cases (RF-adjusted change over time between groups, P=0.034) (Figure 1). In the SINGLE group, radiographic progression was similar in both anti-CCP-negative and -positive patients (P-value between groups was not significant).

**Conclusion**
Anti-CCP in early RA is a strong predictor of radiographic progression. In patients treated with the SINGLE strategy during the first 2 years, erosion progressed both in anti-CCP-negative and anti-CCP-positive patients, while treatment with a combination of DMARDs markedly slowed the radiographic progression in anti-CCP-negative patients.

**Editor’s comments**
FIN-RACO was a landmark 2-year study that compared clinical and radiologic outcomes of early RA patients treated with either sulfasalazine alone or a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone. After 2 years, the DMARD and prednisolone treatments became unrestricted. This 5-year follow-up confirmed the correlation of anti-CCP with radiographic progression and, importantly, demonstrated that joint damage, as defined by the Larsen score, was significantly greater in those combination-treated patients who were anti-CCP positive rather than anti-CCP negative. Erosions progressed in the single-drug-regimen group regardless of CCP status. Thus, attempts to change outcome in RA patients depends not only on the choice of DMARDs, but also on the presence of anti-CCP status.

**Table 1. Summary of the percentage of patients with various marker attributes, broken down by DMARD.**

<table>
<thead>
<tr>
<th>Markers</th>
<th>AM</th>
<th>GS</th>
<th>SSZ</th>
<th>CyA</th>
<th>LF</th>
<th>MTX</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF Positive</td>
<td>24</td>
<td>7</td>
<td>16</td>
<td>1.6</td>
<td>33</td>
<td>75</td>
<td>7</td>
</tr>
<tr>
<td>RF Negative</td>
<td>43*</td>
<td>5</td>
<td>19</td>
<td>2.2</td>
<td>19</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Anti-CCP Positive</td>
<td>32</td>
<td>8</td>
<td>19</td>
<td>5</td>
<td>35</td>
<td>86</td>
<td>8</td>
</tr>
<tr>
<td>Anti-CCP Negative</td>
<td>38</td>
<td>4</td>
<td>18</td>
<td>0*</td>
<td>21</td>
<td>56**</td>
<td>6</td>
</tr>
<tr>
<td>sIL-15 Increased</td>
<td>36</td>
<td>9</td>
<td>9</td>
<td>4</td>
<td>41</td>
<td>82</td>
<td>23</td>
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<tr>
<td>sIL-15 Not increased</td>
<td>37</td>
<td>5</td>
<td>22</td>
<td>1</td>
<td>20*</td>
<td>61</td>
<td>3**</td>
</tr>
</tbody>
</table>

*P<0.5, **P<0.01. AM: antimalarials; Anti-CCP: anti-cyclic citrullinated peptide; anti-TNF: anti-tumor necrosis factor agents; CyA: cyclosporin A; DMARD: disease-modifying anti-rheumatic drug; GS: parenteral gold salts; LF: leflunomide; MTX: methotrexate; RF: rheumatoid factor; sIL-15: serum interleukin-15; SSZ: sulfasalazine.

IL-15 shares many activities exerted by IL-2 (including the stimulation and expansion of T cells, thymocytes, B cells, and natural killer cells), owing to the fact that the receptors for IL-2 and IL-15 share the same subunits. In an attempt to predict which early RA patients were candidates for aggressive treatment, the authors demonstrated that the presence of anti-CCP and increased concentrations of IL-15, a proinflammatory cytokine, provided a better predictor than RF. There are many biomarkers currently being studied, including, but not limited to, vascular endothelial growth factor, metalloproteinases, IL-15, and anti-CCP. Which will be part of the most sensitive profile for early RA remains to be seen.
Serum VEGF as a predictor of 2-year clinical outcome in early rheumatoid arthritis

Hetland ML, Johansen JS, Østergaard M, et al.

Objective
To investigate whether baseline serum VEGF in untreated early RA predicts treatment response after 2 years

Patient characteristics
152 patients with early RA (104 women, median age 53 years [range 20–75 years], a disease duration of <6 months, and a disease activity score [DAS28] of 5.5 [2.2–8.4])

Study design/methods
VEGF was measured in serum by enzyme-linked immunosorbent assay during treatment with intraarticular glucocorticoids, methotrexate, and cyclosporin A (CyA)/placebo-CyA (CIMESTRA study [Hetland, et al. 2006; Harslev-Petersen, et al. 2005]). At week 68, hydroxychloroquine was added, and CyA/placebo-CyA was tapered from week 76. VEGF was measured at weeks 0, 2, 4, 6, 8, 12, 24, 36, 52, 56, 80, and 104. The area-under-the-curve (AUC) for VEGF was calculated. The treatment response after 2 years was assessed by DAS28, European League Against Rheumatism (EULAR) response (good, moderate, none), American College of Rheumatology (ACR) 20/50/70 response, and ACR remission.

Results
At baseline, the median VEGF level was 564 pg/ml (interquartile range 292–1,143 pg/ml). A total of 54 patients had elevated VEGF (>90th percentile in healthy controls=782 pg/ml). Results at baseline and at any time point during follow-up were similar in both treatment groups, which were then pooled. At baseline, VEGF level was independent of age and gender, and correlated with DAS28 (R=0.44, P<0.01) and C-reactive protein (R=0.45, P<0.01). There was no difference in VEGF level between immunoglobulin M-rheumatoid factor or anti-cyclic citrullinated peptide-positive and -negative patients. After initiation of treatment, VEGF decreased by 31% to 396 pg/ml (median; interquartile range [IQR] 221–647 pg/ml, P<0.0001) and remained at this level throughout the study. VEGF level at baseline was higher in patients who achieved an ACR20 response at 104 weeks (median 626 pg/ml; IQR 352–629, P=0.004). The same tendency was seen for ACR50 (P=0.057) and ACR70 (P=0.055). VEGF level decreased significantly from baseline to year 2 in patients who achieved an ACR20 response (from 626 to 362 pg/ml, P<0.00001) in contrast to those who did not (from 352 to 321, P=0.13). Patients with a good EULAR response at 2 years had a significantly higher baseline VEGF level (564 pg/ml; IQR 309–1,155) than those with an inadequate response (352 pg/ml; IQR 233–629, P=0.004). The same tendency was seen for ACR50 (P=0.057) and ACR70 (P=0.055). VEGF level decreased significantly from baseline to year 2 in patients who achieved an ACR20 response (from 626 to 362 pg/ml, P<0.0001) in contrast to those who did not (from 352 to 321, P=0.13). Patients with a good EULAR response at 2 years had a significantly higher baseline VEGF level (564 pg/ml; IQR 309–1,155) than those with a poor response (279 pg/ml; IQR 215–491, P=0.005). The VEGF AUC did not add any significant information. There was no difference in baseline VEGF level between patients who were in ACR remission at 2 years and those who were not.

Conclusion
Serum VEGF level was increased in untreated, early RA patients compared with healthy controls, and decreased in response to therapy. High serum VEGF levels at baseline were associated with an improved treatment response at 2 years (ACR20 and EULAR responses), but not with ACR remission.

References
Abstract AB0339
Efficacy of etanercept including radiographic results in patients with early versus long-term rheumatoid arthritis

van der Heijde D, Klareskog L, Pedersen R, et al.

Background
Long-term clinical trials of the safety and efficacy of drugs used in the treatment of chronic diseases, such as rheumatoid arthritis (RA), provide critical therapeutic information. Further insight may be gained by subgroup analysis of the study population, based on demographic parameters such as disease duration.

Origin of study
The Netherlands, Sweden, USA

Type of study
Randomized 3-year trial

Objective
To analyze key clinical outcomes (American College of Rheumatology [ACR] response rate and disease activity score [DAS]) and radiographic results after 3 years of treatment in patients with early RA (duration ≤3 years) versus long-term RA (duration >3 years)

Patient characteristics
682 patients

Study design/methods
Patients received etanercept (ETN) 25 mg twice weekly, methotrexate (MTX) up to 20 mg weekly, or a combination. An analysis of covariance model (with the last observation carried forward) for discontinued patients was used for analyses of DAS, DAS28, and ranks of modified total Sharp scores (TSS). The chi-squared analysis was used for ACR20, ACR50, ACR70, DAS remission (<1.6), DAS28 remission (<2.6), and non-progression (TSS change ≤0.5). Additional covariate analyses using baseline disease characteristics supplemented the main analysis. Safety measurements, including adverse events (AEs) and infections, were based on AE reports, routine physical examinations, and laboratory determinations.

Results
• At baseline, patients with early and long-term RA had mean values for disease duration of 1.35 and 9.29 years; ages of 50.5 and 54.1 years; DAS of 5.37 and 5.70; and DAS28 of 6.66 and 6.85, respectively.
• The numbers of patients with early RA achieving ACR20, ACR50, and ACR70 were not significantly different from the equivalent numbers of patients with long-term RA in each of the three treatment groups.
• The numbers of patients achieving remission (DAS, DAS28) were not significantly different for the early RA and long-term RA cohorts in the combination and MTX monotherapy treatment groups (Table 2).
• Radiographic results at year 3 showed a decrease in mean TSS change for early RA and long-term RA patients receiving combination therapy. This was significantly different from the increase in mean TSS change for early RA and long-term RA patients in the ETN and MTX treatment groups (Table 2).
• The numbers of patients with no progression at 3 years in the early RA and long-term RA groups were similar for patients receiving the combination (90.4% and 84.4%, respectively, P = 0.2278), ETN only (73.3% and 73.3%, P = 1.000), and MTX only (59.1% and 62.3%, P = 0.657).
• The incidence of treatment-emergent AEs and serious AEs was similar across treatment groups in both the early RA and long-term RA cohorts.

Conclusion
Early RA and long-term RA patients showed similar results for clinical outcomes after 3 years of ETN combination therapy. Early RA patients treated with either combination or ETN monotherapy achieved similar levels of disease remission. Combination therapy halted radiographic damage regardless of disease duration.

Editor’s comments
This study, from distinguished clinical investigators, employed data from long-term trials and demonstrated that not only was VEGF elevated in untreated, early RA patients, but that optimal treatment was associated with a decrease in its concentration. The authors also demonstrated a correlation between VEGF concentration at baseline, and ACR20 and EULAR responses at 2 years. While these data are enticing, the authors did not routinely use VEGF concentrations to follow their patients because too many medical problems, including tumors, infections, and inflammation elsewhere, led to elevated concentrations. Despite this, VEGF blockers remain an interesting therapeutic option.

Editor’s comments
Cancers seem to respond to a combination of routine chemotherapeutic agents and VEGF blockers. This has resulted in an increased interest regarding the role of VEGF in RA, and the possibility that its blockade would help to ameliorate the disease. The current study demonstrated that not only was VEGF elevated in untreated, early RA patients, but that optimal treatment was associated with a decrease in its concentration. The authors also demonstrated a correlation between VEGF concentration at baseline, and ACR20 and EULAR responses at 2 years. While these data are enticing, the authors did not routinely use VEGF concentrations to follow their patients because too many medical problems, including tumors, infections, and inflammation elsewhere, led to elevated concentrations. Despite this, VEGF blockers remain an interesting therapeutic option.
Abstract THU0148
Certolizumab pegol monotherapy 400 mg every 4 weeks improves physical functioning and reduces pain in patients with rheumatoid arthritis who have previously failed DMARD therapy


Background
In a 24-week, Phase III, randomized, double-blind trial, monotherapy with subcutaneous certolizumab pegol 400 mg (a novel pegylated anti-tumor necrosis factor [anti-TNF] agent) demonstrated efficacy and tolerability in patients with rheumatoid arthritis (RA) who had previously failed at least one disease-modifying anti-rheumatic drug (DMARD).

Table 2. Clinical and radiographic results in early and long-term RA.

<table>
<thead>
<tr>
<th>RA group*</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETN + MTX</td>
</tr>
<tr>
<td>ACR20</td>
<td>Early</td>
</tr>
<tr>
<td>(% responders)</td>
<td>Long term</td>
</tr>
<tr>
<td>ACR50</td>
<td>Early</td>
</tr>
<tr>
<td>(% responders)</td>
<td>Long term</td>
</tr>
<tr>
<td>DAS28 (% in remission)</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td>Long term</td>
</tr>
<tr>
<td>DAS (% in remission)</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td>Long term</td>
</tr>
<tr>
<td>TSS change (mean [CI])</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td>Long term</td>
</tr>
</tbody>
</table>

*Responders: n=326 early RA, n=451 long-term RA; TSS: n=219 early RA, n=414 long-term RA; **P<0.05. ACR: American College of Rheumatology; CI: confidence interval; DAS: disease activity score; ETN: etanercept; MTX: methotrexate; RA: rheumatoid arthritis; TSS: total Sharp score.

ETN studies that strongly supported the position that whether a patient has RA for less than or more than 3 years, the capacity to attain good clinical responses and halt X-ray damage is equivalent. While we do believe that the earlier the disease is diagnosed and treated the better the outcome, there is still a reason for optimism for those who are treated later.

Origin of study
USA, Belgium

Type of study
Randomized, double-blind clinical trial

Objective
To assess the impact of monotherapy with subcutaneous certolizumab pegol 400 mg every 4 weeks on physical functioning and pain in patients with active, adult-onset RA

Patient characteristics
220 patients were randomized to receive certolizumab pegol 400 mg (n=111) or placebo (n=109) every 4 weeks (at baseline, and at weeks 4, 8, 12, 16, and 20)

Study design/methods
The patient-reported outcomes assessments included physical functioning using the health assessment questionnaire-disability index (HAQ-DI), and pain using the patient’s assessment of arthritis pain visual analog scale (VAS) and the modified brief pain inventory (mBPI). The HAQ-DI and VAS were assessed at baseline, and at weeks 1, 2, 4, 8, 12, 16, 20, and 24, while the mBPI was assessed at baseline, days 1–6, and week 1. The proportion of patients achieving a clinically meaningful improvement (a decrease in the HAQ-DI score from baseline of ≥0.22) (Wells, et al. 1993) was analyzed using a repeated-measures logistic regression. The mean score from baseline to all endpoints was analyzed using analysis of covariance with standardized score imputation.

Results
As early as the first week of treatment, certolizumab-pegol-treated patients reported improvements in physical functioning. These patients reported significant improvements in overall HAQ-DI score and for each of its eight domains (P<0.001) from week 1 through to week 24. Significantly more patients on certolizumab pegol than on placebo reported a clinically meaningful improvement in HAQ-DI score (P<0.001) from week 1 and throughout the entire study period. Compared with the placebo group, pain in the treatment group was significantly reduced by day 2 according to mBPI scores (P<0.05) and by week 1 according to VAS scores (P<0.001). Patients experienced sustained pain relief following treatment with certolizumab pegol as reported by VAS scores at each assessment from week 1 through to week 24 (P<0.001).

Conclusion
Monotherapy with subcutaneous certolizumab pegol 400 mg administered every 4 weeks provides a rapid, sustained, clinically meaningful improvement in physical functioning. As early as day 2, certolizumab-pegol-treated patients experience rapid and sustained pain relief.

Reference

Editor’s comments
Today’s rheumatologists feel comfortable with the effectiveness and safety profiles of anti-TNF biologic agents. However, it is clear that some RA patients do not respond to any of these agents. If or when to change to B- or T-cell therapies has not yet been completely established. Thus, the availability of another effective and safe anti-TNF agent such as certolizumab is an important event, especially since the drug is given every 4 weeks by the subcutaneous route and, because of its pegylation, seems to have a
Abstract THU0168

Inhibition of radiographic progression in patients with long-standing rheumatoid arthritis treated with adalimumab plus methotrexate for 5 years


**Background**
A previous 1-year, double-blind, randomized, placebo-controlled trial (DE019) in patients with long-standing rheumatoid arthritis (RA) who had inadequate response to MTX demonstrated that adalimumab (ADA) plus methotrexate (MTX) was superior to placebo plus MTX in inhibiting radiographic structural damage.

**Origin of study**
Canada, USA

**Type of study**
Open-label extension

**Objective**
To evaluate the radiographic disease progression, clinical efficacy, and safety of ADA plus MTX combination therapy after 5 years in patients with long-standing RA

**Patient characteristics**
553 patients who had completed DE019

**Study design/methods**
In DE019, patients received MTX plus either ADA 40 mg every second week, ADA 20 mg weekly, or placebo. In this open-label extension, patients were to receive MTX plus ADA 40 mg every second week. Two readers assessed radiographs taken at baseline (start of DE019), year 1 (end of DE019), year 3 (after 2 years in open-label extension), and year 5 (after 4 years in open-label extension). Radiographic assessments included total Sharp score (TSS), erosion scores, and joint space narrowing (JSN) scores, and were analyzed by original randomized treatment groups in DE019. With pooled observed data, clinical efficacy was assessed according to duration of ADA exposure. Safety was also assessed throughout the study.

**Results**
- Of 619 patients in DE019, 553 enrolled in the open-label extension, including 419 patients originally randomized to ADA and 134 patients originally randomized to placebo.
- At 5 years, 304 patients had completed the study and received ADA for a mean of 3.3 years (median 3.9 years). The other 249 patients withdrew from the study (95 for adverse events, 81 for consent withdrawal, 28 for lack of efficacy/disease progression, 7 due to death, 38 for other reasons).
- At year 5, 58% (66/113) of the remaining patients from the original ADA 40 mg group had no radiographic progression relative to their baseline visits, compared with 40% (34/86) initially receiving placebo plus MTX.
- The mean changes in radiographic scores in patients treated with ADA plus MTX demonstrated sustained inhibition of disease progression over 5 years (Table 3).
- Patients who were randomized to placebo in year 1 had an increase in TSS of 2.51 before starting ADA.
- Patients who received ADA 40 mg every second week had a mean change in TSS of –0.62; by 5 years, their mean change in TSS was 0.83.
- Substantial clinical responses were observed in patients who completed 5 years of treatment with ADA plus MTX (n=219), with American College of Rheumatology (ACR) 20/50/70 responses achieved by 75%/58%/35%, respectively, and a disease activity score 28 of <2.6 achieved by 45%.
- Health assessment questionnaire disability index scores improved by ≥0.22 in 77% of patients. The rates and types of adverse events reported were similar to those observed in the original, double-blind portion of DE019.

**Conclusion**
Among patients with long-standing RA and inadequate response to MTX who had remained in this study for 5 years, ADA 40 mg every second week plus MTX controlled radiographic progression and maintained clinical response and physical function.

**Editor’s comments**
Abstract THU0168 reported further good news regarding the long-term effect of ADA on the inhibition of radiographic progression in patients with RA. This study showed that among patients with long-standing RA and an inadequate response to MTX who had remained in this study for 5 years, ADA 40 mg every other week plus MTX controlled radiographic progression and maintained clinical response and physical function.

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**Table 3. Mean changes from baseline in radiographic progression in patients treated with ADA plus MTX.**

<table>
<thead>
<tr>
<th></th>
<th>Year 1 (n=120)</th>
<th>Year 3 (n=120)</th>
<th>Year 5 (n=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA + MTX TSS</td>
<td>–0.62</td>
<td>0.01</td>
<td>0.83</td>
</tr>
<tr>
<td>Erosion score</td>
<td>–0.27</td>
<td>–0.24</td>
<td>–0.08</td>
</tr>
<tr>
<td>JSN score</td>
<td>–0.36</td>
<td>0.25</td>
<td>0.91</td>
</tr>
<tr>
<td>Placebo + MTX TSS*</td>
<td>2.51</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Based on n=92. NA = not available, based on study design. ADA: adalimumab; JSN: joint space narrowing; MTX: methotrexate; TSS: total Sharp score.
Safety and efficacy of over 9 years of continuous etanercept therapy in patients with rheumatoid arthritis in North America and Europe

Klareskog L, Moreland LW, Cohen SB, et al.

Background
Patients with rheumatoid arthritis (RA) have been treated with etanercept (ETN) for >9 continuous years. Analysis of large global databases provides valuable insight into the long-term safety and efficacy of ETN in patients with RA.

Origin of study
North America, Europe

Type of study
Double-blind, controlled trial and open-label extensions

Objective
To assess the long-term safety and efficacy of ETN in a global RA population

Patient characteristics
2,054 patients with 9,212 patient-years of ETN exposure were included in this analysis

Study design/methods
European and North American patients with disease-modifying anti-rheumatic drug (DMARD)-refractory RA or North American patients with early RA (disease duration ≤3 years) were eligible to enroll. Safety was assessed in all patients receiving at least one dose of ETN. Safety assessments included the incidence of serious adverse events (SAEs), serious infectious events (SIEs), opportunistic infections (OIs), sepsis, malignancies, lymphomas, and deaths. Standard incidence ratios (SIRs) of malignancies and lymphomas were calculated using age- and sex-matched general population data from the surveillance, epidemiology, and end results database. The number of expected deaths was calculated according to Kochanek, et al. 2001. Efficacy was assessed in patients receiving ETN 25 mg twice weekly for up to 6 years in European DMARD-refractory patients (last observation carried forward analysis), 8 years in North American early RA patients (completers analysis), and 9 years in North American DMARD-refractory patients (completers analysis).

Results

- Kaplan–Meier analyses estimated that 62–71% of all patients continued to receive ETN at 3 years and 43–49% of patients continued at 8 years in the ongoing North American studies.
- The overall North American rates of SAEs for early RA patients (0.11/patient-year) and DMARD-refractory patients (0.17/patient-year) were similar to the rates in control groups (0.11–0.20/patient-year).
- The overall rates of SIEs for early RA patients (0.02/patient-year), North American DMARD-refractory patients (0.04/patient-year), and European DMARD-refractory patients (0.06/patient-year) were similar to the rates in control or placebo/methotrexate (MTX) patients in earlier trials (0.03–0.05/patient-year).
- Only one case of tuberculosis was reported. Reports of other OIs were rare. The SIR (observed/expected) for malignancies in the global database was 1.1 (84/78); the SIR for lymphoma was 4.3 (13 observed/3 expected). It is currently unknown whether the higher-than-expected rate of lymphoma is related to exposure to the anti-tumor necrosis factor (anti-TNF) agent, or whether it reflects the elevated risk of lymphoma in patients with RA (Askling, et al. 2005). A total of 57 deaths were reported; 95 were expected. The proportions of patients achieving American College of Rheumatology 20, 50, and 70 scores were 75–76%, 47–59%, and 28–34%, respectively, at the longest time points examined for each patient dataset.
- Improvements in disability (health assessment questionnaire scores), swollen joint counts, and C-reactive protein (CRP) levels were also sustained long term.

Conclusion
These global data suggest that the safety and efficacy profile of ETN therapy are maintained with long-term use for up to 9 years. Additional experience is required to understand the potential role of TNF inhibition in rare events such as lymphomas.

References

Abstract THU0181

Infliximab: better outcomes are seen in real-life with concomitant use of MTX in patients with RA

Maksymowych WP, Mitchell C.

Background
There are still limited data on the real-life effectiveness of combination infliximab (IFX) plus methotrexate (MTX) therapy versus IFX monotherapy over substantial time periods. Many rheumatologists and/or their patients discontinue treatment with MTX once a treatment response with IFX has been established.

Origin of study
Canada
Table 4. Outcome variables by MTX use for 12 and 24 months.

<table>
<thead>
<tr>
<th></th>
<th>Always on MTX</th>
<th>Never on MTX</th>
<th>P-value</th>
<th>Always on MTX</th>
<th>Never on MTX</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>71%</td>
<td>48%</td>
<td>0.04</td>
<td>83%</td>
<td>30%</td>
<td>0.001</td>
</tr>
<tr>
<td>ACR50</td>
<td>39%</td>
<td>24%</td>
<td>0.25</td>
<td>51%</td>
<td>20%</td>
<td>0.09</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.27</td>
<td>1.54</td>
<td>0.12</td>
<td>1.16</td>
<td>1.48</td>
<td>0.22</td>
</tr>
<tr>
<td>PAP</td>
<td>32</td>
<td>41</td>
<td>0.09</td>
<td>27</td>
<td>34</td>
<td>0.42</td>
</tr>
<tr>
<td>PGA</td>
<td>31</td>
<td>45</td>
<td>0.02</td>
<td>27</td>
<td>35</td>
<td>0.30</td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


Type of study
Multicenter, prospective

Objective
To investigate the real-life effectiveness of a combination of MTX plus IFX versus IFX alone in patients with rheumatoid arthritis (RA)

Patient characteristics
Patients were naïve to IFX and eligible for IFX therapy as per the Canadian Product Monograph

Study design/methods
A multicenter, prospective registry of RA patients is currently ongoing in Canada in which data on IFX treatment are collected at baseline, 2 months, and 6 months, and every 6 months thereafter. Data were collected for up to 24 months on painful joint count, swollen joint count (SJC), patient assessment of pain, patient assessment of global disease activity (PGA), physician assessment of global disease activity (Phy-GA), health assessment questionnaire (HAQ), and American College of Rheumatology (ACR)20 and ACR50 rates. The study population was divided into those who had never received MTX (no MTX from baseline to 24 months, n=284), and those always on MTX (continuous use of MTX from baseline to 24 months, n=96). Data were collected for up to 24 months on painful joint count, swollen joint count (SJC), patient assessment of pain, patient assessment of global disease activity (PGA), physician assessment of global disease activity (Phy-GA), health assessment questionnaire (HAQ), and American College of Rheumatology (ACR)20 and ACR50 rates. The study population was divided into those who had never received MTX (no MTX from baseline to 24 months, n=284), and those always on MTX (continuous use of MTX from baseline to 24 months, n=96)

Results
- Disease severity at baseline was similar between patients always on MTX and those never on MTX (P=non significant) for all outcome variables at baseline.
- Mixed-model analysis of variance showed an overall statistically significant improvement on all outcome variables from baseline to 12 months (P<0.001). Results at 12 months showed that concomitant use of MTX and IFX resulted in a better outcome, as measured by SJC (P=0.015), PGA (P=0.016), and Phy-GA (P=0.007).
- Results at 24 months for all outcome variables favored patients always on MTX (Table 4); however, there were no statistically significant differences between the two groups (n=82 for patients always on MTX and n=10 for patients never on MTX).
- ACR20 rates at 12 months showed that statistically more patients in the always-on MTX group achieved an ACR20 response to IFX therapy (71% for always on MTX versus 48% for never on MTX, P=0.04). This difference was even more pronounced at 24 months, with more patients achieving an ACR20 response rate to IFX therapy on combination treatment (83% for always on MTX versus 30% for never on MTX, P=0.001).
- ACR50 response rates at 12 months favored patients always on MTX (39%, n=119) versus patients never on MTX (24%, n=25). At 24 months, ACR50 response rates also favored patients always on MTX versus patients never on MTX (51% versus 20%). HAQ scores at 24 months showed a similar trend (1.16 versus 1.48, respectively, P=0.22).

Conclusion
Disease severity outcomes from this real-life registry favor patients receiving a combination of MTX plus IFX.

Editor's comments
IFX is approved for use against RA in conjunction with MTX. Without MTX, the drug’s efficacy would wane due to the neutralizing antibodies that naturally form against the mouse–human chimera. Often, patients with RA cannot tolerate immuno-suppressive drugs such as MTX or leflunomide due to side effects such as nausea, mouth sores, or liver function test abnormalities; hence, some people are treated solely with IFX. This study addresses whether patients need to be treated with the combination of IFX plus MTX to ensure an optimal clinical response. Clearly, the answer is yes. At 24 months of follow-up, ACR20 was achieved in 83% and 30% of patients, and ACR50 was achieved in 51% and 20% of patients on combination therapy versus IFX monotherapy, respectively.

Abstract THU0225
Safety profile, disease activity and physical function of patients with rheumatoid arthritis receiving ADA for up to 7 years

Origin of study
USA, Canada

Type of study
Extension study

Objective
To evaluate the long-term safety and efficacy of adalimumab (ADA) plus methotrexate (MTX) administered for up to 7 years in patients with long-standing rheumatoid arthritis (RA). Additionally, to determine the extent to which there were significant improvements in disease activity and physical function in patients who did not fulfill the American College of Rheumatology (ACR)20 response rate criteria.

Patient characteristics
Patients enrolled in the ARMADA, DE019, STAR, DE005, and DE037 randomized, controlled trials (RCTs)

Study design/methods
Patients received MTX and ADA 40 mg every second week subcutaneously or MTX. Efficacy
and safety were evaluated in all patients’ last visits for up to 7 years, including those who withdrew for any reason. The clinical characteristics of patients who did not achieve an ACR20 response (but either continued on long-term treatment or withdrew for any reason) were evaluated independently.

Results

- A total of 1,469 patients were treated with ADA plus MTX for at least 30 days and for up to 7 years (5,720 patient-years; mean ± SD exposure of 47 ± 26 months).
- A Kaplan–Meier survival analysis estimated that 58% of all patients will continue into year 7 of therapy.
- The rates and types of serious adverse events of all patients were consistent with results in the RCTs, including the rates for serious infections (3.2 events/100 patient-years).
- At their last visit, 65%, 43%, and 26% of all patients achieved ACR20, ACR50, and ACR70 responses, respectively.
- At their last visit, 35% of patients had a disease activity score (DAS28) using C-reactive protein (CRP) of <2.6; 24% of patients had had a tender joint count 68 of 0; 24% of patients had had a swollen joint count 66 of 0; and 20% of patients had had a health assessment questionnaire (HAQ) score of 0.
- Besides patients achieving ACR20 responses, those who did not achieve an ACR20 response but who continued on therapy also showed significant improvements in DAS28, the physician-reported ACR score components, and HAQ score. However, no changes were observed in patient global assessment (Table 5).

Conclusion

ADA plus MTX demonstrated a consistent safety profile over time, and induced sustained ACR20 responses in 65% and clinical remission in ≥20% of all treated patients for up to 7 years. While ACR20 responders showed at least 50% mean clinical improvement in all parameters, patients continuing on therapy despite a lack of ACR20 response had at least a 25% mean clinical improvement in joint counts, CRP levels, and physician global assessment scores.

Table 5. Improvements (%) from baseline values at last visit with adalimumab plus methotrexate.

<table>
<thead>
<tr>
<th>Patients n (%)</th>
<th>TJC68*</th>
<th>SJC66*</th>
<th>Patient global assessment*</th>
<th>Physician global assessment*</th>
<th>HAQ*</th>
<th>CRP* (mg/l)</th>
<th>DAS28*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline value</td>
<td>1,469 (100)</td>
<td>28</td>
<td>20</td>
<td>53</td>
<td>60</td>
<td>1.4</td>
<td>18</td>
</tr>
<tr>
<td>All patients</td>
<td>1,469 (100)</td>
<td>65%**</td>
<td>60%**</td>
<td>29%**</td>
<td>60%**</td>
<td>40%**</td>
<td>53%</td>
</tr>
<tr>
<td>ACR20 responders</td>
<td>953 (65)</td>
<td>84%**</td>
<td>81%**</td>
<td>55%**</td>
<td>75%**</td>
<td>57%**</td>
<td>65%</td>
</tr>
<tr>
<td>ACR20 non-responders on therapy</td>
<td>208 (14)</td>
<td>44%**</td>
<td>33%**</td>
<td>2%</td>
<td>46%**</td>
<td>14%**</td>
<td>44%</td>
</tr>
<tr>
<td>ACR20 non-responders who withdrew</td>
<td>308 (21)</td>
<td>20%**</td>
<td>12%</td>
<td>–33%***</td>
<td>21%**</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Mean values except C-reactive protein (median, no P-values), **P<0.001, ***P<0.01, versus baseline. The negative percentage indicates deterioration. ACR: American College of Rheumatology; CRP: C-reactive protein; DAS: disease activity score; HAQ: health assessment questionnaire; SJC: swollen joint count; TJC: tender joint count.

Editor’s comments

Abstract THU0225 addressed the long-term safety, disease activity, and physical function of RA patients receiving ADA for up to 7 years. ADA plus MTX demonstrated a consistent safety profile over time, and induced sustained ACR20 responses in 65% and clinical remission in ≥20% of all treated patients for up to 7 years. The rates and types of serious events were consistent with results from RCTs, including the rates for serious infections (3.2 events/100 patient-years). The combination of sustained clinical improvements together with a stable side-effect profile is heartening both for the rheumatologist and the RA patient.

Abstract THU0225

Tocilizumab, a novel monoclonal antibody targeting IL-6 signaling, significantly reduces disease activity in patients with rheumatoid arthritis


Origin of study

Austria, Canada, Germany, UK

Background

Interleukin (IL)-6 is a cytokine involved with the pathogenesis of rheumatoid arthritis (RA). Therefore, targeted blockade of IL-6 signaling may represent a novel and attractive approach to the treatment of RA.

Type of study

Large, Phase III, double-blind, randomized, controlled study

Objective

To investigate the efficacy and safety of tocilizumab (TOC), a new humanized anti-human IL-6 receptor monoclonal antibody, in patients with RA

Patient characteristics

623 patients with moderate to severe active RA, despite long-term treatment with methotrexate (MTX)

Study design/methods

Patients were randomly allocated to receive TOC 8 mg/kg, TOC 4 mg/kg, or placebo intravenously
every 4 weeks. All three groups received MTX (oral or parenteral) at their pre-study dose throughout the study (10–25 mg weekly), with all other disease-modifying anti-rheumatic drugs (DMARDs) discontinued at study entry.

Results

• An improvement in American College of Rheumatology (ACR)20 rates at 24 weeks (primary endpoint) was observed in a significantly higher proportion of patients receiving TOC 8 mg/kg (58.5%) and TOC 4 mg/kg (47.9%) compared with placebo (26.5%, P<0.0001). In the TOC 8 mg/kg group, significantly more patients achieved ACR50 (43.9%) and ACR70 (22.0%) responses compared with placebo (10.8% and 2.0%, respectively, P<0.0001).

• A reduction in disease activity score (DAS28) was observed from week 2 onwards in both TOC groups, with a significant change from baseline to week 24 for both TOC 8 mg/kg (~3.43) and 4 mg/kg (~2.68) versus placebo (~1.55, P<0.0001).

• A significantly higher proportion of patients achieved a good/moderate European League Against Rheumatism response at 24 weeks in both TOC groups compared with placebo (P<0.0001). A good/moderate response was seen in 79.5% of patients receiving TOC 8 mg/kg, 61.9% receiving TOC 4 mg/kg, and 34.8% receiving placebo.

• TOC was generally well tolerated, with an adverse event profile consistent with data reported in previous studies (Maini, et al. 2006).

• The overall frequency of adverse events was similar in all three groups, with serious infections reported by six patients in the TOC 8 mg/kg group, three patients in the TOC 4 mg/kg group, and two patients in the placebo group.

Conclusion

This study demonstrates that TOC, a novel monoclonal antibody targeting IL-6 signaling, is a highly effective therapy in patients with RA, and has a good safety and tolerability profile.

Reference


Table 6. ACR responses for secondary drugs with intent-to-treat analysis.

<table>
<thead>
<tr>
<th></th>
<th>MTX</th>
<th>LEF</th>
<th>CyA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>64</td>
<td>81</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>37</td>
<td>64</td>
<td>47</td>
<td>0.020*</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>14</td>
<td>35</td>
<td>21</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

*In favor of anakinra plus LEF versus anakinra plus MTX. ACR: American College of Rheumatology; CyA: cyclosporin A; LEF: leflunomide; MTX: methotrexate; NS: not significant.

Abstract SAT0010

Anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with conventional immunosuppressive DMARDs, for severe rheumatoid arthritis: final results of the GRASS (Greek anakinra assessment) study Karanikolas GN, Karras D, Lambropoulos A, et al.

Origin of study

Greece

Type of study

Open-label, three-armed, clinical study

Editor’s comments

IL-6 is a new immunologic target for patients who have failed to respond to MTX or other biologic agents. TOC is a novel, humanized, monoclonal antibody that inhibits IL-6 signal transduction, thereby blocking proinflammatory effects downstream. TOC has shown significant efficacy in a large, Phase III, randomized trial, equivalent to that seen in anti-tumor necrosis factor (anti-TNF) drug trials. However, the side-effect profile is an issue that needs monitoring. In this trial, serious infections occurred in six patients in the higher-dose group, three in the lower-dose group, and two in the MTX/control group. This is not unlike the two-fold increased risk for infections seen in anti-TNF drug trials. This presentation did not address the finding from other studies of elevated concentrations of transaminases and lipids. The latter is of particular potential significance as patients with RA already have a three-fold increased incidence of premature atherosclerosis and cardiovascular morbidity and mortality.

Objective

To evaluate the efficacy, safety, and tolerance of anakinra (ANK) administered in combination with either methotrexate (MTX), leflunomide (LEF), or cyclosporin A (CyA) in patients with active refractory rheumatoid arthritis (RA)

Patient characteristics

128 patients (89 female, mean age 47.4 years, mean disease duration 6.7 years, 25% early-stage disease, 79% rheumatoid factor positive, 87% anti-cyclic citrullinated peptide [anti-CCP] positive) with significant disease activity (a mean disease activity score [DAS]28 of 6.81)

Study design/methods

For at least 6 months, patients had received treatment with either MTX (group 1, n=48, mean DAS28 of 6.55, maximum dose 20 mg/week), LEF (group 2, n=42, mean DAS28 of 6.93, maximum dose 20 mg/day), or CyA (group 3, n=38, mean DAS28 of 6.97, maximum dose 3.5 mg/kg/day). ANK (100 mg/day) was added subcutaneously in groups at the indicated dose scheme. Concomitant administration of steroids (61% of patients) and/or nonsteroidal anti-inflammatory drugs (NSAIDs) (51% of patients) was continued as scheduled. All patients completed 12 months of follow-up. Clinical improvement was evaluated using the American College of Rheumatology (ACR) response criteria, while disease activity was measured using DAS28. The differences of values for variables from baseline were compared among the three treatment groups by means of the Kruskal–Wallis test. The Mann–Whitney test was used for pairwise comparisons.

Results

Fourteen patients discontinued treatment. This was due to inefficacy or disease worsening in
Evolution of active spondyloarthropathies treated with infliximab

Vicente EF, González I, Castañeda S, et al.

Background
Spondyloarthopathies (SpAs) have lacked remission inductive therapy for many years. Traditional disease-modifying anti-rheumatic drugs have not demonstrated adequate efficacy for controlling the inflammation of spinal joints that occurs in this disease group.

Origin of study
Spain

Type of study
Open-label study of patients with active SpAs

Objective
To evaluate the clinical and analytic evolution of patients with active SpAs treated continuously with infliximab (IFX)

Patient characteristics
52 active SpA (36.5% women) patients with spinal or both spinal and peripheral manifestations, with a mean period of treatment with IFX of 3.4 years (range: 0.2–7 years). The mean age was 51 ± 11 years and the evolution time was 13.5 years (2.5–43.8 years) [mean (p25–p75)]. Disease distribution was: 34 patients with ankylosing spondylitis, eight with psoriatic arthritis, five associated with inflammatory bowel disease (IBD), three with undifferentiated SpAs, and one with synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome.

Study design/methods
A Bath ankylosing spondylitis disease activity index (BASDAI) score of ≥4 and/or a score of ≥4 on a 0–10 numeric rating scale for spinal pain was the definition of disease activity. Functionality was measured using the Bath ankylosing spondylitis functional index (BASFI). Clinical and laboratory activity parameters were measured according to protocol. Statistical analysis was developed using the intent-to-treat principle.

Conclusion
The study suggests that the addition of ANK to traditional immunosuppressive disease-modifying anti-rheumatic drugs (DMARDs) results in a significant improvement in signs and symptoms as well as of functional disability in severe RA. The combination of ANK plus LEF showed the most beneficial outcome in terms of efficacy. Opportunistic infections, as well as ISRs, were of limited clinical importance. However, the possibility of severe infection or hematological abnormalities should not be underestimated.

Editor’s comments
Despite a reasonable showing in Phase III trials, ANK has not been embraced by rheumatologists worldwide because of its disappointing effect in practice and the need for daily dosing. Moreover, with the impressive effects of anti-tumor necrosis factor (anti-TNF) agents, use of ANK has been relegated to those RA patients who have failed on every other biologic and to febrile diseases such as systemic, juvenile-onset RA and autoinflammatory disorders, where its effect has been unexpected and remarkable. In this study, 128 RA patients who had failed on traditional DMARDs were treated with a combination of the previously used DMARD and ANK 100 mg/day subcutaneously. The ACR20/50/70 responses with all combinations were good and very similar to those of other trials assessing anti-TNF agents, with the MTX combination achieving 64%/37%/14%, respectively. The LEF group was even more impressive at 81%/64%/35%, respectively. Despite these seemingly stupendous results, ANK will probably remain at the bottom of the list of biologic DMARDs that rheumatologists use in patients with severe, active disease.
Comparisons between baseline and final studied variables were conducted using Student’s t-test for paired data.

**Results**

- Comparisons between baseline and final analyzed variables (expressed as mean ± standard deviation) are shown in Table 7.
- Results show significant improvements in all variables studied. At the final visit, the mean dose was 5 mg/kg (range: 2.5–10 mg/kg), and the mean period between infusions was 7.8 weeks (range: 4–12 weeks). The 10 mg/kg dose was used only in two patients with IBD due to poor control of digestive manifestations.
- At present, 76.4% of patients remain on active treatment.
- Therapy had to be withdrawn from 11 patients for the following reasons: inefficacy (n=8; 72.7%), toxicity (n=2; 18.2%), and cardiovascular risk (n=1; 9.1%).

**Conclusion**

The results confirm the efficacy of continuous therapy with IFX in SpAs. In some patients there is adequate control of disease activity with doses lower than 5 mg/kg and intervals between infusions longer than 6 weeks.

**Abstract AB0605**

The role of hereditary factors in patients suffering from psoriatic arthritis

Busquets-Pérez N, Gómez-Vaquero C, Rodríguez-Moreno J, et al.

**Background**

Psoriatic arthritis (PsA) as an entity has only been described quite recently. Although the first reports relating to “psoriatic” and “arthritis” are from the 19th century, it was not until 1973 that the current definition of the disease was assigned by Moll and Wright. The pathogenesis of psoriasis is not fully understood, but population and twin studies suggest that there is a large heritable component to the etiology.

**Objective**

To ascertain the prevalence of psoriasis and PsA among the relatives of patients suffering from PsA, the percentage of first-, second-, and third-degree relatives of patients with PsA, and the extent to which disease activity affects these data

**Patient characteristics**

155 patients with peripheral PsA

**Study design/methods**

Data including medical history, physical examination, laboratory findings, and disease management were collected in a standardized protocol. Disease activity was assessed by means of a modified health assessment questionnaire and disease activity score 28.

**Results**

- Among patients with PsA, 38% of first-degree relatives have psoriasis and 16.7% of first-degree relatives have PsA.
- 47.3% of patients with PsA had a relative with psoriasis; 18% of patients with PsA had a relative with PsA.
- There was a link between the proportion of first-degree relatives with PsA and the proportion of first-degree relatives with psoriasis (R=0.22).
- Women had a more prevalent family history of PsA than men.
- Patients with distal interphalangeal involvement tended to have a greater family history of psoriasis.
- There was a link between the age of onset of PsA and a family history of psoriasis.
- No relationship was observed between a family history of psoriasis or PsA and the physical disability of observed patients.

**Conclusion**

Psoriasis and PsA are prevalent among the relatives of patients suffering from PsA. A link exists between the age of onset of psoriasis and the presence of a family history of psoriasis. There is no link between a family history of psoriasis or PsA and the physical disability of observed patients.

**Editor’s comments**

The term “spondyloarthropathies” spans multiple disorders, including ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease-related arthritis, and SAPHO syndrome. This study demonstrated clinical efficacy of IFX for a mean of 3.4 years amongst all of these disorders. Lower than expected doses were adequate for disease control.

**Editor’s comments**

In all diseases, there appears to be an interplay between genetic predisposition and environmental triggers. The best examples of this include the connection between shared rheumatoid arthritis epitope, smoking, and anti-cyclic citrullinated peptide and HLA-B27 with reactive arthritis triggered by Chlamydia and enteric organisms. This study supports

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**Table 7. Clinical and analytical response variables.**

<table>
<thead>
<tr>
<th>Variables analyzed</th>
<th>Baseline</th>
<th>Final**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal pain (VAS 0–10 cm)</td>
<td>6.1 (2.3)</td>
<td>2.4 (2.3)</td>
</tr>
<tr>
<td>Patient global disease assessment (VAS 0–10 cm)</td>
<td>6.1 (2.2)</td>
<td>2.7 (2.5)</td>
</tr>
<tr>
<td>Morning stiffness (minutes)</td>
<td>60 (41.4)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>BASDAI</td>
<td>5.4 (2.5)</td>
<td>3.0 (2.2)</td>
</tr>
<tr>
<td>BASFI</td>
<td>5.4 (2.5)</td>
<td>3.6 (2.5)</td>
</tr>
<tr>
<td>ESR</td>
<td>37.9 (23.5)</td>
<td>23 (18.8)</td>
</tr>
<tr>
<td>CRP</td>
<td>2.6 (2.6)</td>
<td>0.8 (0.9)</td>
</tr>
</tbody>
</table>

*Results expressed as mean (standard deviation). **P<0.05. BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; VAS: visual analog scale.
Abstract OP0045

Effectiveness and safety of adalimumab (HUMIRA®) therapy after failure of prior TNF-antagonists in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS)

Burmester GR, Rudwaleit M, Smith V, et al.

Background
Some patients with active rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) do not respond optimally, or are intolerant to initial infliximab (IFX) or etanercept (ETN) therapy. Subsequent therapy with another anti-tumor necrosis factor (anti-TNF) agent has rarely been studied in large patient groups.

Objective
To investigate the effectiveness and safety of switching to adalimumab (ADA) in patients with RA, PsA, or AS who had failed on prior IFX or ETN therapy

Patient characteristics
Patients with active disease who had failed on prior IFX or ETN therapy could enroll provided IFX had been discontinued for \( \geq 2 \) months before enrollment in any study and ETN had been discontinued for \( \geq 3 \) weeks before enrollment in STEREO (PsA) or RHAPSODY (AS), or \( \geq 2 \) months before enrollment in the ReAct (RA) study.

Study design/methods
Patients who were enrolled into large, open-label studies designed to reflect normal clinical practice (the recently completed Phase IIIb studies ReAct or STEREO, or the ongoing RHAPSODY trial) had ADA 40 mg subcutaneously every second week for 12 weeks added to their current regimens. Reasons for discontinuing IFX/ETN were recorded. Adverse event (AE) reports were routinely collected.

Results
Prior anti-TNF therapy had been discontinued in 899 of 6,610 patients with RA (ReAct), 66 of 442 patients with PsA (STEREO) and, as of December 2006, 181 of 651 patients with AS (RHAPSODY). Patients reporting failure of ETN or IFX alone/together totaled 779/120 (RA), 52/14 (PsA), and 130/51 (AS), respectively. Discontinuation was attributed to loss of efficacy/intolerance in 195/327/190 (RA), 19/44/13 (PsA), and 62/99/47 (AS) patients, respectively. Overall, patients with a history of the long-held view that there is a strong familial/genetic association between psoriasis and PsA. In essence, the presence of a family member with psoriasis is supportive of PsA in a patient with a less than crystal-clear clinical picture.

Table 8. Baseline characteristics and ADA effectiveness observed at week 12.

<table>
<thead>
<tr>
<th>Time point</th>
<th>ReAct (RA)</th>
<th>STEREO (PsA)</th>
<th>Time point</th>
<th>RHAPSODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Anti-TNF history</td>
<td>Anti-TNF history</td>
<td>Parameter</td>
<td>Anti-TNF history</td>
</tr>
<tr>
<td></td>
<td>(n=5,711)</td>
<td>(n=899)</td>
<td>(n=376)</td>
<td>(n=66)</td>
</tr>
<tr>
<td>Baseline age* (years)</td>
<td>54</td>
<td>53</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Disease duration* (years)</td>
<td>11</td>
<td>12</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>DAS28*</td>
<td>6.0</td>
<td>6.3</td>
<td>4.9</td>
<td>5.1</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.60</td>
<td>1.85</td>
<td>1.22</td>
<td>1.39</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20 (%)</td>
<td>70</td>
<td>60</td>
<td>75</td>
<td>67</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>41</td>
<td>33</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>19</td>
<td>13</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>( \Delta )DAS28*</td>
<td>(-2.2)</td>
<td>(-1.9)</td>
<td>(-2.3)</td>
<td>(-2.1)</td>
</tr>
<tr>
<td>( \Delta )HAQ*</td>
<td>(-0.55)</td>
<td>(-0.48)</td>
<td>(-0.52)</td>
<td>(-0.48)</td>
</tr>
</tbody>
</table>

Spondyloarthropathies including psoriatic arthritis

previous anti-TNF use had greater disease activity at baseline compared with anti-TNF-naïve patients. ADA led to marked improvements across all three rheumatic diseases (Table 8). Through to week 12 of ADA therapy, safety data were comparable in patients with/without prior anti-TNF therapy, with 9.6%/5.3% of patients with RA, 3.0%/2.9% of patients with PsA, and 0%/1.7% of patients with AS, respectively, experiencing a serious AE. No changes in the known patterns of AEs were observed.

Conclusion
Switching from a failed anti-TNF therapy to ADA was effective and well-tolerated in patients with RA, PsA, or AS.

Table 9. Efficacy of adalimumab over time.

<table>
<thead>
<tr>
<th>Score</th>
<th>Baseline (n=442)</th>
<th>Week 2 (n=430)</th>
<th>Week 6 (n=426)</th>
<th>Week 12 (n=414)</th>
<th>Week 20 (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 (%)</td>
<td>–</td>
<td>41</td>
<td>65</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>ACR50 (%)</td>
<td>–</td>
<td>17</td>
<td>36</td>
<td>51</td>
<td>58</td>
</tr>
<tr>
<td>ACR70 (%)</td>
<td>–</td>
<td>5</td>
<td>15</td>
<td>32</td>
<td>41</td>
</tr>
<tr>
<td>TJC (0–78)*</td>
<td>20.1</td>
<td>13.9</td>
<td>9.9</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>SJC (0–76)*</td>
<td>10.3</td>
<td>5.6</td>
<td>3.5</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>HAQ*</td>
<td>1.24</td>
<td>0.93</td>
<td>0.80</td>
<td>0.71</td>
<td>0.66</td>
</tr>
<tr>
<td>DAS28*</td>
<td>4.9</td>
<td>3.5</td>
<td>3.0</td>
<td>2.7</td>
<td>2.4</td>
</tr>
<tr>
<td>PGA almost clear/clear (%)</td>
<td>34</td>
<td>38</td>
<td>52</td>
<td>68</td>
<td>74</td>
</tr>
<tr>
<td>DLQI (0–30)*</td>
<td>6.6</td>
<td>NA</td>
<td>NA</td>
<td>2.6</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Mean values. ACR: American College of Rheumatology; DAS: disease activity score; DLQI: dermatology life quality index; HAQ: health assessment questionnaire; NA: not available; PGA: physician’s global assessment; SJC: swollen joint count; TJC: tender joint count.

Type of study
Open-label, multicenter trial

Objective
In real-life clinical practice, the STEREO trial prospectively examined the safety and efficacy of adalimumab (ADA) in patients with active PsA and a history of poor response to prior therapies

Patient characteristics
442 (50% male) adults with active PsA and insufficient response to ≥1 disease-modifying anti-rheumatic drug (DMARD), enrolled at 85 sites

Study design/methods
Adults with active PsA and insufficient response to ≥1 DMARD received ADA 40 mg subcutaneously every second week for 12 weeks, and optionally to 20 weeks when ADA was not generally available. Joint and skin evaluations at weeks 2, 6, and 12 (optional at week 20) included American College of Rheumatology (ACR)20/50/70 responses, physician’s global assessment of psoriasis, and dermatology life quality index. Adverse event reports were routinely collected.

Results
In all, 94% of patients completed week 12 and 36% of patients completed week 20. Mean baseline characteristics included: age 48 years; psoriasis duration 19 years; PsA duration 11 years. Dactylitis was present in 30% of patients, 35% had enthesitis of the Achilles tendon and/or plantar-fascia, and 59% of patients exhibited PsA-related nail changes. Key outcomes are summarized in Table 9. Patients who had failed on prior etanercept and/or infliximab (n=66) therapy achieved comparable ACR20/50/70 scores of 67%/42%/ 25% at week 12, respectively. The serious infection rate was 3.2/100 patient-years. No malignancies, deaths, or new safety events were observed.

Conclusion
These data from the STEREO trial confirm that ADA is well tolerated by patients with PsA. Clinically important improvements are achieved both in the skin disease and in the arthropathy, including in patients with prior exposure to other biologic agents.

Editor’s comments
This abstract addresses the anti-TNF switching issue in patients with RA, PsA, or AS, and demonstrates well that a physician can feel comfortable switching from failed courses of ETN or IFX to ADA, with the likelihood of achieving both a good and safe clinical response. At present, because the longest and best data for good clinical and radiologic outcomes are drawn from anti-TNF trials and open-label, long-term follow-up of patients, rheumatologists feel most comfortable with these three medications, and will continue to use them until more experience and confidence is gained with the T- and B-cell-focused therapies.

Abstract OP0147
Adalimumab (HUMIRA®) is effective in treating patients with psoriatic arthritis (PsA) in real-life clinical practice: results of the STEREO trial

van den Bosch F, Manger B, Goupille P, et al.

Background
The safety and efficacy of anti-tumor necrosis factor (anti-TNF) agents have been confirmed in psoriatic arthritis (PsA) clinical trials. However, data were required for these agents in the real-life clinical practice scenario.

Origin of study
Belgium, Germany, France, UK, Norway, Denmark, Sweden, Finland, Ireland

Editor’s comments
The use of anti-TNF agents in PsA patients who have failed to achieve significant disease control with full-dose, weekly methotrexate has been another success story in rheumatology. Anti-TNF
Abstract FRI0383

Long-term efficacy and safety results and patient-reported outcomes in patients with ankylosing spondylitis treated with etanercept for 4 years

Dijkmans BAC, Sieper J, van der Linden S, et al.

Background
Ankylosing spondylitis (AS) is a spondyloarthropathy that starts early in life and has significant detrimental effects on quality of life due to pain and disability (Braun and Pincus 2002). Previous clinical trials have shown that treatment with etanercept (ETN) significantly improved AS signs and symptoms (Calin, et al. 2004; Davis, et al. 2005). We present the results of a multinational, open-label, Phase IV extension study after a total of approximately 4 years (200–212 weeks) of treatment, using clinical measures and patient-reported outcomes (PROs).

Origin of study
The Netherlands, Germany, Spain, Finland, USA

Type of study
12-week, randomized, double-blind, placebo-controlled trial and continuing in a 96-week, multinational, open-label, Phase IV extension study

Objective
To demonstrate sustained efficacy, PRO improvement, and long-term safety of ETN for the treatment of patients with AS over a 4-year period

Patient characteristics
84 patients with active AS

Study design/methods
A total of 84 patients with active AS were enrolled in a trial of ETN 25 mg subcutaneously twice weekly, of which 81 patients continued in a 96-week, open-label trial of ETN. A total of 59 patients (n=32 ETN; n=27 placebo) who completed the 96-week, open-label trial continued on open-label ETN 25 mg twice weekly for an additional 104 weeks: a total of 200 weeks for the original placebo group and 212 weeks for the ETN group. Clinical assessments included assessment in AS International Working Group criteria for improvement (ASAS)20, ASAS40, ASAS5/6, and measures of spinal mobility. Improvements in PROs were measured by patient global assessment, Bath AS disease activity index (BASDAI)50, morning stiffness, total back pain, and Bath AS functional index (BASFI). Last observation carried forward analysis was applied to the last 52 weeks for any missing values. Safety evaluations were based on spontaneous reports of adverse events.

Results
A total of 48 patients (81% in the current extension study) completed 200–212 weeks of ETN treatment. ASAS20 was achieved by 75% (n=44) of patients, ASAS40 by 64% (n=38), ASAS5/6 by 31% (n=18), and BASDAI50 by 64% (n=38) at week 212 of treatment. Modified Schober’s scores improved by 25.1%, occiput-to-wall by 27.6%, and chest expansion by 32.5%. ASAS responses, as well as individual components of ASAS criteria, were essentially unchanged from the start of the open-label extension, showing sustained efficacy through years 3 and 4 of treatment. Among PROs, mean BASDAI scores improved by 56.7% from the original baseline, morning stiffness by 57.6%, total back pain by 57.5%, BASFI by 45.4%, and patient global assessment by 60.1%. All PROs showed sustained efficacy over a total of 200–212 weeks of therapy, with similar results both in patients who were initially treated with placebo and in those initially treated with ETN. No cases of opportunistic infections or tuberculosis were reported.

Conclusion
In this study of patients with AS, ETN provided both sustained clinical efficacy and improvements in PRO measures over a 4-year period. There were no new safety signals during year 4 of treatment with ETN. Since AS is a chronic disease, treatment with therapeutic agents with long-term efficacy and safety is important.

References

Editor’s comments
AS is a systemic inflammatory disease that has finally found its rightful treatment – anti-TNF medications. Just as disease activity score 28, clinical disease activity index, or health assessment questionnaire scores are used to assess disease activity or function n RA, there are similar instruments that are employed for the assessment of AS. These include the BASDAI and BASFI scores. This study defines the long-term efficacy and safety and PROs in patients with AS who were treated in a Phase IV ETN extension study. The study demonstrated that ETN afforded AS patients sustained clinical efficacy and safety for 4 years. In the setting of chronic diseases, such as AS and RA, these studies are reassuring for both patients and their physicians.

Abstract FRI0440

Adalimumab treatment maintains efficacy and safety in patients with ankylosing spondylitis (AS) – 2-year results from ATLAS
van der Heijde D.

Origin of study
USA, Europe

Type of study
Randomized, placebo-controlled, double-blind, Phase III study

Spondyloarthropathies including psoriatic arthritis
**Objective**
The Adalimumab Trial Evaluating Long-term Efficacy and Safety (ATLAS) in ankylosing spondylitis (AS) assessed the ability of adalimumab (ADA), an anti-tumor necrosis factor (anti-TNF) agent, to maintain both reduction of signs and symptoms and induction of partial remission over 2 years.

**Patient characteristics**
ATLAS enrolled 315 patients with active AS who had an inadequate response to at least one nonsteroidal anti-inflammatory drug.

**Study design/methods**
Patients received either double-blind ADA 40 mg every second week or placebo for 24 weeks. Efficacy was measured by assessment in AS International Working Group criteria (ASAS20) response at week 12 (>20% improvement in three or more of four domains: patient’s global assessment (PGA), pain, function, and inflammation), the ASAS40 (40% improvement in three of four domains), and ASAS5/6 (20% improvement in five of six domains [which include the four ASAS domains, C-reactive protein, and spinal mobility]). The primary endpoint was ASAS20 at week 12. Starting at week 12, patients were eligible for early-escape therapy of open-label ADA 40 mg every second week. At week 24, all patients were switched to open-label ADA 40 mg every second week for an additional 80 weeks. This abstract presents 2-year data of ATLAS patients according to duration of exposure to ADA.

**Results**
- During the first 12 and 24 weeks of double-blind exposure, ADA patients showed a statistically significant reduction in signs and symptoms (ASAS20) compared with placebo. Some achieved partial remission.
- After conversion to open-label ADA, this improvement was sustained through 104 weeks of ADA treatment.
- ADA has a safety profile similar to that seen in rheumatoid arthritis (RA) and psoriatic arthritis (PA) trials.
- The following adverse event (AE) rates were observed per 100 patient-years in the double-blind versus 2 years of ADA exposure groups, respectively: serious AEs: 10.2, 10.5; serious infectious AEs: 0, 1.1; AEs leading to discontinuation: 3.8, 4.5; malignant AEs: 0, 0.9. At 2 years of exposure, AEs >5% included nasopharyngitis, upper respiratory tract infection, and headache. There were no cases of tuberculosis, lupus-like symptoms, demyelinating disease, or death.

**Conclusion**
ADA was efficacious in reducing signs and symptoms and inducing partial remission in AS patients, and this effect was maintained through 2 years of exposure. No new safety issues were observed during 2 years of exposure.

**Editor’s comments**
AS is a systemic, inflammatory disorder that can be as pernicious as RA and PsA in its life-altering capacity. With the introduction of anti-TNF drugs, disease-modifying medications for AS patients became available. Despite recent magnetic resonance imaging studies that have demonstrated the ability of anti-TNF agents to control inflammation, a radiologic, disease-modifying effect has not yet been defined. The science of AS today seems to support a partition between the inflammation of AS and the ossification that leads to X-ray abnormalities and dysfunction, and supports the possibility that anti-TNF agents work on the former, but not on the latter. This study demonstrates that ADA was efficacious and safe in reducing signs and symptoms of AS, and in inducing partial remission for 2 years. This gives AS patients a chance to improve both the survival and quality of life.
assessed anti-TNF agents and one assessed alefacept. Table 10 shows the results.

**Conclusion**
Gold, sulfasalazine, leflunomide, and anti-TNF agents are all effective treatments for PsA. The effect size of treatment was highest with gold and anti-TNF agents. Tolerability was worst with gold and leflunomide; more patients on active treatment had to be withdrawn from treatment due to side effects when compared with placebo. The NNT to NNH ratio was best with anti-TNF agents, followed by leflunomide, gold, and sulfasalazine.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy (effect size [95% CI])</th>
<th>Toxicity (effect size [95% CI])</th>
<th>NNT/NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td>0.25 [0.11, 0.53]</td>
<td>2.34 [1.10, 4.97]</td>
<td>0.79</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>0.45 [0.23, 0.89]</td>
<td>1.76 [0.98, 3.14]</td>
<td>0.93</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>0.25 [0.13, 0.48]</td>
<td>2.20 [0.82, 5.19]</td>
<td>0.25</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>0.44 [0.23, 0.83]</td>
<td>3.86 [1.20, 12.39]</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Anti-TNF: anti-tumor necrosis factor; CI: confidence interval; NNH: number needed to harm; NNT: number needed to treat.

**Editor’s comments**
This systemic review/meta-analysis for the period 1996–2006 evaluated the evidence for efficacy and toxicity of a group of DMARDs used to treat PsA, including gold (which is still used from time to time when all else has failed), sulfasalazine, anti-TNF agents, and leflunomide. While the authors found that all of the medications assessed were effective for treating PsA, the overall results favored the use of anti-TNF agents. However, this study does demonstrate that in those patients who do not have a favorable response to anti-TNF agents (and there are significant numbers of those), there are alternative treatments available.