Efficacy and Safety of Tocilizumab in the Treatment of Rheumatoid Arthritis and Juvenile Idiopathic Arthritis

New Evidence reports on presentations given at EULAR 2010
Report on EULAR 2010 presentations

- Efficacy of tocilizumab in RA patients who had never been exposed to or never failed methotrexate: a long-term extension study (Jones G, et al. EULAR 2010: Abstract FRI0213)

- Pooled analysis of the safety of tocilizumab after a median of 3.1 years of treatment in patients with rheumatoid arthritis (Van Vollenhoven RF, et al. EULAR 2010: Abstract SAT0172)

- Tocilizumab in rheumatoid arthritis patients with an inadequate response to DMARDs and/or TNF inhibitor therapy: ACT-SURE preliminary results (Bykerk V, et al. EULAR 2010: Abstract FRI0193)

- Effectiveness and safety of tocilizumab in patients with active rheumatoid arthritis: final results from the TAMARA study (Rubbert-Roth A, et al. EULAR 2010: Abstract SAT0170/SAT0171)

DMARD = disease-modifying anti-rheumatic drug  
RA = rheumatoid arthritis; TNF = tumour necrosis factor

Synovitis and osteitis in RA patients treated with tocilizumab: results from a multi-site low-field MRI study (Troum O, et al. EULAR 2010: Abstract OP0135)

Radiographic progression, physical function, and efficacy after treatment with tocilizumab: LITHE year 2 data (Fleischmann R, et al. EULAR 2010: Abstract FRI0205)

Efficacy and safety of tocilizumab in patients with systemic juvenile idiopathic arthritis: twelve-week data from the TENDER trial (De Benedetti F, et al. EULAR 2010: Abstract OP0273)

MRI = magnetic resonance imaging
RA = rheumatoid arthritis
Efficacy of tocilizumab in RA patients who had never been exposed to or never failed methotrexate: a long-term extension study

Background

- The AMBITION study demonstrated the efficacy and safety of tocilizumab as monotherapy in patients with active RA who had never been exposed to or had never failed MTX.\(^1\)

- Using data from the ongoing LTE of the AMBITION study, Jones and colleagues analyzed the longer-term efficacy of tocilizumab as monotherapy or combined with DMARDs/MTX.

- The LTE analysis from the AMBITION study was presented at EULAR 2010.\(^2\)

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DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
LTE = long-term extension; MTX = methotrexate
RA = rheumatoid arthritis
Patients included in the analysis received ≥1 dose of tocilizumab (8 mg/kg) every 4 weeks in AMBITION or LTE.

Patients receiving tocilizumab with <50% reduction from baseline in TJC and SJC during AMBITION could receive MTX or other permitted DMARDs during LTE.

A subgroup of patients who received tocilizumab (8 mg/kg) monotherapy for the duration of their treatment was evaluated separately.

Efficacy parameters were assessed every 12 weeks from initial tocilizumab exposure.

Results included patients who had assessments at each visit.
Key findings

- A total of 618 patients received at least one dose of tocilizumab (8 mg/kg), either as monotherapy or with MTX/DMARDs in AMBITION, its transition phase, or in LTE (GROWTH96).
  - A subgroup of 234 patients (38%) received tocilizumab (8 mg/kg) monotherapy for the duration of their treatment.
  - 239 patients were randomly assigned to MTX in AMBITION and were later exposed to tocilizumab therapy; none are included in the monotherapy subgroup.
    - 171 patients transitioned to tocilizumab (8 mg/kg) monotherapy.
    - 68 patients received tocilizumab (8 mg/kg) in addition to MTX (combination therapy).

DMARD = disease-modifying anti-rheumatic drug
LTE = long-term extension
MTX = methotrexate; RA = rheumatoid arthritis
Key findings (cont’d)

- A total of 533 patients (86%) completed 48 weeks of treatment at the time of the analysis.
- Mean treatment duration was approximately 2.4 years.
- Overall, 2.4% of patients withdrew because of insufficient therapeutic response.
- ACR20/50/70 response rates increased continuously over time.
Key findings (cont’d)

- Proportions and absolute numbers of patients who achieved an LDAS, defined as DAS28 ≤3.2, and/or DAS28 remission (DAS28 ≤2.6) were sustained through week 60; these proportions of patients were maintained through week 156.

- By week 96, 25% of patients had no TJC, 40% had no SJC, and 23% achieved HAQ-DI scores of zero.

- Efficacy of tocilizumab monotherapy was demonstrated by sustained improvements in ACR20/50/70 and DAS28 remission rates.

ACR = American College of Rheumatology
DAS28 = 28-joint disease activity score
HAQ-DI = health assessment questionnaire-disability index
LDAS = low disease activity score
SJC = swollen joint count; TJC = tender joint count

## Table 1. Efficacy for up to 3 years of tocilizumab treatment in RA patients never exposed to/never failed MTX

<table>
<thead>
<tr>
<th>Week</th>
<th>Analysis population (n = 618)</th>
<th></th>
<th>Monotherapy subpopulation (n = 234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACR20/50/70 (%)</td>
<td>n</td>
<td>LDA (%)</td>
</tr>
<tr>
<td>36</td>
<td>66/44/27</td>
<td>525</td>
<td>514</td>
</tr>
<tr>
<td>60</td>
<td>71/48/32</td>
<td>494</td>
<td>481</td>
</tr>
<tr>
<td>84</td>
<td>73/55/35</td>
<td>466</td>
<td>449</td>
</tr>
<tr>
<td>108</td>
<td>78/62/38</td>
<td>386</td>
<td>372</td>
</tr>
<tr>
<td>132</td>
<td>82/65/45</td>
<td>229</td>
<td>214</td>
</tr>
<tr>
<td>156</td>
<td>83/66/43</td>
<td>77</td>
<td>68</td>
</tr>
</tbody>
</table>

*ACR = American College of Rheumatology (score); DAS28 = 28-joint disease activity score; LDA = low disease activity; MTX = methotrexate*
Figure 1. Proportions of patients achieving ACR20, ACR50, and ACR70 responses in (A) the long-term AMBITION population and (B) the monotherapy subgroup.

Key conclusions

- Response rates to tocilizumab alone or in combination with DMARDs were maintained for up to three years of treatment.

- Results of this analysis show that the benefits of tocilizumab treatment for these RA patients who had never been exposed to or had never failed methotrexate continued beyond 24 weeks.

Pooled analysis of the safety of tocilizumab after a median of 3.1 years of treatment in patients with rheumatoid arthritis

Van Vollenhoven RF, et al. EULAR 2010: Abstract SAT0172
Background

- The safety of tocilizumab as monotherapy or combined with DMARDs has been demonstrated in patients with RA in phase III clinical trials and long-term extension studies.¹⁻⁶

- At EULAR 2010, van Vollenhoven and colleagues presented results from their analysis of the longer-term safety of tocilizumab in RA patients using pooled data from ongoing long-term extension studies.

- Data were reported for a median of 3.1 years of treatment.⁷

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DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
RA = rheumatoid arthritis
Study design

- Patients included in the analysis received ≥1 dose of tocilizumab in four 24-week, phase III clinical trials (OPTION, AMBITION, RADIATE, TOWARD), in a two-year phase III clinical trial (LITHE), in a phase I study, or in the ongoing, open-label extension studies (GROWTH95, GROWTH96).

- Safety data (all-exposed population) were pooled and analyzed from the time of initial tocilizumab exposure to the cutoff date of August 28, 2009.

Key findings

- Tocilizumab was administered to 4,009 patients.
- Median treatment duration was 3.1 years (mean 2.7 years).
- Total exposure to tocilizumab was 10,011 patient-years, and total duration of observation was 10,994 patient-years.
- Rate of withdrawals because of adverse events was 5.4/100 patient-years.
- Mean total cholesterol, LDL, HDL, and TG levels increased from baseline to week 6 and did not increase further over time.

HDL = high-density lipoprotein
LDL = low-density lipoprotein
TG = triglyceride
Key findings (cont’d)

- During treatment with tocilizumab, 313 patients (7.8%) initiated lipid-lowering therapy and generally responded to treatment without complications.
- Incidence of ALT or AST elevation >3 times the upper limit of normal was 7.8% during the first 12 months of treatment; the rate did not increase over time.
- Transaminase elevations were managed with dose reductions and/or interruptions and were not associated with clinically apparent hepatitis or hepatic dysfunction.
**Table 1. Safety of tocilizumab in RA patients after a median of 3.1 years of treatment**

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate/100 patient-years</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>14.6</td>
<td>13.9–15.4</td>
</tr>
<tr>
<td>Serious infections</td>
<td>4.5</td>
<td>4.1–4.9</td>
</tr>
<tr>
<td>Malignancies (including non-melanoma skin cancers)</td>
<td>1.1</td>
<td>n/a</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.27</td>
<td>0.18–0.39</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.16</td>
<td>0.10–0.26</td>
</tr>
</tbody>
</table>

*CI = confidence interval; n/a = not available*
Key conclusions

- Results demonstrate that no new safety signals have emerged with prolonged exposure to tocilizumab.

- During longer-term treatment with tocilizumab (median duration 3.1 years), AE and SAE rates were stable over time.

- Transaminase elevations could be effectively managed in this setting, and no clinically significant sequelae were detected.

- Data show a favourable benefit/risk ratio for tocilizumab use in patients with moderate-to-severe RA.

AE = adverse event; SAE = serious adverse event
RA = rheumatoid arthritis

Tocilizumab in rheumatoid arthritis patients with an inadequate response to DMARDs and/or TNF inhibitor therapy: ACT-SURE preliminary results

Bykerk V, et al. EULAR 2010: Abstract FRI0193
Background

- At EULAR 2010, Bykerk and colleagues presented preliminary results from the ACT-SURE study.

- ACT-SURE is an ongoing phase IIIb, open-label, single-arm, multinational, 24-week study of tocilizumab, either alone or in combination with DMARDs, in the treatment of RA patients.

- Patients included in the study had demonstrated an inadequate response to DMARDs and/or to TNFIs.

- ACT-SURE was designed to confirm the safety and efficacy of tocilizumab in a setting that is close to real-life clinical practice, including no wash-out period requirement for switching to tocilizumab from either non-biologic DMARDs or TNFI therapy.

DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
RA = rheumatoid arthritis
TNFI = tumour necrosis factor inhibitor
Study design

- Patients with active RA received tocilizumab (8 mg/kg) either as monotherapy or in combination with DMARDs for a total of 24 weeks.

- For analysis, patients were grouped by prior TNFI use into three groups:
  - naïve (DMARD-IR; never used TNFI);
  - previous use (>2 months since TNFI washout);
  - recent use (received TNFIs ≤2 months before baseline with no washout).

- Safety endpoints included AEs and SAEs; efficacy endpoints included ACR and DAS28 responses.

ACR = American College of Rheumatology; AE = adverse event
DAS28 = 28-joint disease activity score
DMARD = disease-modifying anti-rheumatic drug
IR = inadequate response; RA = rheumatoid arthritis
SAE = serious adverse event; TNFI = tumour necrosis factor inhibitor
A total of 1,681 patients were enrolled in the three patient groups: 976 naïve, 298 previous use, and 407 recent use.

Mean age was 54 years; 81% of the patients were women.

Mean RA duration was 8.2 years in naïve patients, 11.2 years in previous use patients, and 11.7 years in recent use patients.

Baseline DAS28 was similar among groups (5.9–6.2).

Most patients (86%) received background DMARD therapy.

Fewer patients withdrew for safety reasons (4.8%) than for non-safety reasons (8.0%); only 1.1% of patients withdrew from treatment because of infections.
Table 1. Adverse events after treatment with tocilizumab in RA patients with an inadequate response to DMARDs and/or TNFIs

<table>
<thead>
<tr>
<th>Event</th>
<th>Naïve (n = 976)</th>
<th>Previous use (n = 298)</th>
<th>Recent use (n = 407)</th>
<th>All patients (n = 1681)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pt-ys</td>
<td>452.1</td>
<td>132.4</td>
<td>183.3</td>
<td>767.7</td>
</tr>
<tr>
<td>Adverse events (rate/100 pt-ys)</td>
<td>551.1</td>
<td>654.4</td>
<td>652.6</td>
<td>593.1</td>
</tr>
<tr>
<td>Serious adverse events (rate/100 pt-ys)</td>
<td>18.6</td>
<td>28.7</td>
<td>18.0</td>
<td>20.2</td>
</tr>
<tr>
<td>Serious infections (rate/100 pt-ys)</td>
<td>4.2</td>
<td>7.6</td>
<td>6.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Infusion reactions* n (%)</td>
<td>66 (6.8)</td>
<td>22 (7.4)</td>
<td>25 (6.1)</td>
<td>113 (6.7)</td>
</tr>
<tr>
<td>ALT shift from baseline &gt;3 x ULN n (%)</td>
<td>23 (2.4)</td>
<td>9 (3.0)</td>
<td>3 (0.7)</td>
<td>35 (2.1)</td>
</tr>
</tbody>
</table>

*Defined as any adverse event that occurred during infusion — not limited to hypersensitivity reactions.
ALT = alanine aminotransferase; DMARD = disease-modifying anti-rheumatic drug; pt-ys = patient-years; TNFI = tumour necrosis factor inhibitor; ULN = upper limit of normal.
Key findings (cont’d)

- ALT shifts from normal at baseline to >3 times the ULN occurred in 2.1% of patients.
- Four deaths were reported in the study, one of which was due to *Streptococcus* infection.
- More than 25% of patients across all three groups achieved remission by week 8, showing an increase in efficacy; no plateau was reached throughout the study.
- Clinical response at week 24 tended to be higher in the naïve group of patients, with little difference between recent and previous TNFI users.

ALT = alanine transaminase  
TNFI = tumour necrosis factor inhibitor  
ULN = upper limit of normal

Figure 1. Clinical response at week 24 of tocilizumab treatment in RA patients with an inadequate response to DMARDs and/or TNFIs

*DAS28 < 2.6
ACR = American College of Rheumatology (score); DAS28 = 28-joint disease activity score; DMARD = disease-modifying anti-rheumatic drug; TNFI = tumour necrosis factor inhibitor

Key conclusions

- ACT-SURE preliminary results confirm the safety and efficacy of tocilizumab (with or without DMARDs) in a setting resembling day-to-day clinical practice when used as a first-line biologic in patients intolerant of, or with inadequate response to, conventional DMARDs and in patients with an inadequate response to TNFIs.

- The pattern of response in this study was characterised by a rapid onset of action and by increasing efficacy over time, confirming the phase III trial results for tocilizumab.

- Results suggest that the safety profile of tocilizumab in patients who do observe, or in those who do not observe, the 3–5 half-life washout period from TNFI therapy is not different from that established in earlier studies.

DMARD = disease-modifying anti-rheumatic drug
TNF-I = tumour necrosis factor inhibitor

Effectiveness and safety of tocilizumab in patients with active rheumatoid arthritis: final results from the TAMARA study

Rubbert-Roth A, et al. EULAR 2010: Abstracts SAT0170/SAT0171
Background

- The clinical efficacy and safety of tocilizumab have been evaluated in five randomized, double-blind, multicentre phase III trials that enrolled more than 4,200 patients.\(^1\)\(^–\)\(^5\)

- At EULAR 2010, Rubbert-Roth and colleagues presented final results from the TAMARA (Tocilizumab and DMARDs: Achievements in Rheumatoid Arthritis) study.\(^6\),\(^7\)

- TAMARA was a German multicentre, open-label, non-controlled phase IIIb study designed to confirm the effectiveness and safety of tocilizumab in a setting close to real-life medical care.


DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
Study design

- Adult patients with moderate-to-severe RA, despite treatment with conventional and/or biologic DMARDs, were enrolled at 70 sites from September 2008 to July 2009.

- Eligibility criteria included:
  - DAS28 > 3.2;
  - ESR ≥ 28 mm/h or CRP ≥ 1 mg/dL;
  - previous treatment with at least one DMARD (stable for at least 8 weeks prior to entry) to be continued during the study; wash-out for biologics was required.

- Patients received treatment with tocilizumab (8 mg/kg) given intravenously over 4 weeks for 24 weeks.
Study design (cont’d)

- Nonsteroidal anti-inflammatory drugs and systemic steroids (equivalent to ≤10 mg/day prednisone) at stable doses were permitted.

- Primary endpoint was the proportion of patients achieving a DAS28 LDAS, defined as DAS28 ≤3.2, at week 24.

- Secondary endpoints included ACR and EULAR responses, as well as a decrease in the CDAI score and acute phase reactants.

- PROs were examined, including the HAQ-DI, the SF-36, the FACIT-F, the TSQM, and a patient diary documenting fatigue, pain, and morning stiffness on a daily basis for 28 days.

- Adverse events of special interest were documented throughout the study.

ACR = American College of Rheumatology; CDAI = clinical disease activity index
DAS28 = 28-joint disease activity score
EULAR = European League Against Rheumatism
FACIT-F = functional assessment of chronic illness therapy-fatigue
HAQ-DI = health assessment questionnaire-disability index
LDAS = low disease activity state; PRO = patient-reported outcome
SF-36 = short form (36-item) health survey
TSQM = treatment satisfaction questionnaire for medication

Key findings

- A total 239 patients (71.6%) completed the study, with a drop-out rate due to insufficient therapeutic response of 3%.

- Mean age was 54.9 ± 12.2 years (range 18.0–84.0), mean disease duration was 8.1 ± 7.3 years (range 0.11–37.0), and baseline DAS28 was 6.0 ± 1.0 (range 2.8–8.1).

- Previous RA therapy in the ITT population was as follows:
  - patients treated with any DMARDs (n = 285);
  - patients treated with biologic DMARDs (n = 122);
  - patients treated with conventional DMARDs only (n = 163);
  - patients treated with TNFIs (range: 1–3) (n = 119).

- Treatment with a traditional DMARD was continued concomitantly with tocilizumab in 277 patients.

**Rubbert-Roth A, et al. EULAR 2010: Abstract SAT0170/SAT0171.**
Key findings

- A good or moderate EULAR response at week 24 was achieved by 54.9% or 20.3% of patients, respectively, with a 75.2% EULAR response in total.

- A total of 23.1% and 47.6% of patients achieved a DAS <2.6 by weeks 4 and 24, respectively.
  - 41.2% of the 119 patients who had received previous therapy with TNFIs achieved DAS remission by week 24 (95% CI: 32.2–50.6).
  - 53.4% of patients who had received previous treatment with conventional DMARDs achieved DAS remission by week 24 (95% CI: 45.4–61.2).
  - 48.2% of the 56 patients previously treated with leflunomide achieved DAS remission by week 24 (95% CI: 34.7–62.0).
Figure 1. DAS28 response after 4 and 24 weeks of tocilizumab (8 mg/kg) treatment in patients with moderate-to-severe RA

<table>
<thead>
<tr>
<th>Week 4</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS delta ≥1.2*</td>
<td>DAS ≤3.2 (LDAS)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>75.2 (n = 215)</td>
<td>74.5 (n = 213)</td>
</tr>
<tr>
<td>40.9 (n = 117)</td>
<td>23.1 (n = 66)</td>
</tr>
</tbody>
</table>

*Clinically significant reduction
Data as observed. Missing data were evaluated as no response.

DAS = disease activity score
LDAS = low disease activity state
Key findings (cont’d)

- ACR20/50/70 response rates were 50.0%, 25.5%, and 12.2%, respectively, at week 4; and 65.0%, 50.7%, and 33.9%, respectively, at week 24.

- The relative change in CDAI from baseline (34.7 ± 12.5) to week 24 (9.9 ± 10.6) was a reduction by 70.9% ± 29.3%.

- The mean CRP level was normalized one week after first administration of tocilizumab.

- An early and sustained increase in hemoglobin was observed; leukocytes dropped immediately at initiation of treatment and reached a plateau afterwards.

- Improvements in many outcomes were achieved by week 4; these were sustained or improved by week 24.


ACR = American College of Rheumatology
CDAI = clinical disease activity index
CRP = C-reactive protein
Figure 2. ACR response rates after 4 and 24 weeks of tocilizumab (8 mg/kg) treatment in patients with moderate-to-severe RA

Data as observed. Missing data were evaluated as no response.
ACR = American College of Rheumatology (score)
Key findings (cont’d)

- Up to week 4, patients’ pain decreased by about 30%, duration of morning stiffness by about 40%, and fatigue by about 20% on average.
- Mean HAQ-DI decreased from 1.48 ± 0.65 to 1.00 ± 0.75 after 24 weeks; the mean absolute improvement of 0.48 score points exceeded the minimal clinically important difference of >0.22.
- PROs in the SF-36, FACIT-F, and take-home form (diary for pain, morning stiffness, and fatigue) confirmed DAS28 results.
- Patients’ overall TSQM results were 74.7% ± 25.9%.
- Early onset of effectiveness was noted in the patients’ global self-reported outcomes within the first 4 weeks of treatment.
- The clinical benefits of tocilizumab were reflected in an improvement of quality of life in terms of physical and mental functioning after 24 weeks of treatment.


DAS28 = 28-joint disease activity score
FACIT-F = functional assessment of chronic illness therapy-fatigue
HAQ-DI = health assessment questionnaire-disability index
PRO = patient-reported outcome; SF-36 = short form (36-item) health survey
TSQM = treatment satisfaction questionnaire for medication
Figure 3. Mean changes from baseline in HAQ-DI over 24 weeks of tocilizumab (8 mg/kg) treatment in patients with moderate-to-severe RA

Error bars show standard deviation.
HAQ-DI = health assessment questionnaire-disability index
Figure 4. SF-36 scores at baseline and week 24 after tocilizumab (8 mg/kg) treatment in patients with moderate-to-severe RA
Table 1. Adverse events after 24 weeks of tocilizumab (8 mg/kg) treatment in moderate-to-severe RA patients

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients</th>
<th>Percentage (%) (n = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events (AEs)</td>
<td>240</td>
<td>83.9</td>
</tr>
<tr>
<td>Adverse drug reactions</td>
<td>189</td>
<td>66.1</td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>31</td>
<td>10.8</td>
</tr>
<tr>
<td>Serious adverse drug reactions</td>
<td>15</td>
<td>5.2</td>
</tr>
<tr>
<td>AEs leading to discontinuation of study drug</td>
<td>16</td>
<td>5.6</td>
</tr>
<tr>
<td>AEs of special interest*</td>
<td>156</td>
<td>54.5</td>
</tr>
<tr>
<td>Serious infections</td>
<td>9</td>
<td>3.1</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Infections requiring treatment with drugs available on prescription only.

ASAT or ALAT ≥3 x ULN; neutrophils <1000/mm³; LDL >160 mg/dL.

LDL = low-density lipoprotein; ULN = upper limit of normal
Key conclusions

- This study confirmed the known favourable safety profile of tocilizumab in a setting close to routine clinical conditions.

- Final results of the TAMARA trial are consistent with the favourable results of the interim analyses, as well as with the pivotal phase III trials from the clinical development program in a diversified population.

- Treatment with tocilizumab is likely to bring immediate and sustained relief to patients with RA.

Rubbert-Roth A, et al. EULAR 2010: Abstract SAT0170/SAT0171. RA = rheumatoid arthritis
Efficacy of tocilizumab in patients with moderate-to-severe active RA: the ROSE study

Yazici Y, et al. EULAR 2010: Abstract SAT0181
Background

- At EULAR 2010, Yazici and colleagues presented data from the randomized, double-blind ROSE (Rapid Onset and Systemic Efficacy) study.
- The study was designed to assess the efficacy of tocilizumab versus placebo in combination with DMARDs in reducing the signs and symptoms of moderate-to-severe RA.
- Tocilizumab was given over 24 weeks to patients who had an inadequate clinical response to DMARDs.


EULAR = European League Against Rheumatism
DMARD = disease-modifying anti-rheumatic drug
RA = rheumatoid arthritis
Study design

- A total of 619 patients were randomized to two study arms:
  - tocilizumab (8 mg/kg) plus DMARDs (n = 412);
  - placebo plus DMARDs (n = 207).
- Primary efficacy endpoint was ACR50 response at week 24.
- Disease activity was also assessed at week 1 for a subset of 62 patients.

ACR = American College of Rheumatology
DMARD = disease-modifying anti-rheumatic drug
Key findings

- Most patients were female (81%) and Caucasian (81%); mean age was 55 years, mean disease duration was 8.5 years, mean number of previous DMARDs was 1.2, and mean DAS28 was 6.5.

- Statistically significant differences between treatment groups were demonstrated for ACR20 and ACR50 response rates, beginning at week 4 and measured every 4 weeks through week 24.

- Statistically significant differences between treatment groups were also demonstrated for ACR70 response rates, beginning at week 8 (6.8% vs. 0.5%; \( p = 0.0002 \)) and measured every 4 weeks through week 24.

ACR = American College of Rheumatology
DAS28 = 28-joint disease activity score
DMARD = disease-modifying anti-rheumatic drug

Key findings (cont’d)

- Similar results were obtained for DAS28 and RAPID3 scores, with tocilizumab resulting in significantly higher reductions from baseline compared to control at each visit, starting as early as 4 weeks.

- In the subset, more patients achieved DAS28 remission (DAS28 <2.6) with tocilizumab than with control.
  - DAS28 responses were significantly improved ($p = 0.007$) one week after treatment, as were pain and patient and physician global assessment scores.

- SAE rates/100 patient-years were 23 (95% CI: 17–31) and 18 (95% CI: 10–30) for tocilizumab and control groups, respectively.


DAS28 = 28-joint disease activity score
RAPID = routine assessment of patient index data
SAE = serious adverse event
Figure 1. ACR response in patients with moderate-to-severe RA treated with tocilizumab (8 mg/kg) or placebo

*Two-sided Fisher’s exact test was used to determine p-values. ACR = American College of Rheumatology (score); DMARD = disease-modifying anti-rheumatic drug
Table 1. Change in DAS28, RAPID3 scores, and DAS remission in patients with moderate-to-severe RA treated with tocilizumab (8 mg/kg) or placebo

<table>
<thead>
<tr>
<th>Data measurement timepoint</th>
<th>Change in DAS28 (adjusted mean)</th>
<th>Change in RAPID3 (adjusted mean)</th>
<th>Remission (DAS &lt;2.6) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tocilizumab</td>
<td>Placebo</td>
<td>p-value*</td>
</tr>
<tr>
<td>Week 4</td>
<td>-1.77 (n = 391)</td>
<td>-0.45 (n = 194)</td>
<td>*p &lt;0.0001</td>
</tr>
<tr>
<td>Week 24</td>
<td>-3.18 (n = 264)</td>
<td>-1.24 (n = 116)</td>
<td>*p &lt;0.0001</td>
</tr>
</tbody>
</table>

* ANCOVA model with baseline as covariate and treatment group as a factor was used to determine p-values.
† Two-sided Fisher’s exact test was used to determine p-values.

DAS28 = 28-joint disease activity score; RAPID = routine assessment of patient index data.
Key conclusions

- The ROSE study showed that treatment with tocilizumab led to significant improvement in ACR responses and RAPID3 scores as early as week 4 and in DAS28 scores as early as week 1.
- Improved responses persisted through week 24.
- Tocilizumab, with its early and sustained efficacy, is a new biologic option for rheumatoid arthritis patients who have failed DMARDs.
Synovitis and osteitis in RA patients treated with tocilizumab: results from a multi-site low-field MRI study

Troum O, et al. EULAR 2010: Abstract OP0135
Background

- At EULAR 2010, Troum and colleagues presented results from a multi-site, low-field MRI sub-study of the randomized, double-blind, phase IIIb ACT-RAY trial.

- The sub-study was designed to examine early effects of tocilizumab on synovitis and osteitis in patients with erosive rheumatoid arthritis who were inadequate responders to methotrexate.

Study design

- As part the ACT-RAY study, which added tocilizumab to MTX versus switching to tocilizumab monotherapy, 63 RA patients on stable MTX were randomized to continue stable MTX or to receive a placebo.
- Both study arms also received tocilizumab (8 mg/kg) intravenously every 4 weeks.
- In this MRI sub-study, 0.2T extremity MRI of one hand (MCP 1–5) and wrist was acquired at baseline and at weeks 2 and 12.
- MRI images underwent quality control and were scored by two radiologists using a rheumatoid arthritis RAMRIS method blinded to visit order.
- Blinded data from both tocilizumab arms were pooled and analyzed.


MCP = metacarpophalangeal joints
MRI = magnetic resonance imaging
MTX = methotrexate; RA = rheumatoid arthritis
RAMRIS = magnetic resonance image score
Key findings

- At week 2, 44% of patients had improved synovitis scores, and 7% of patients had improved scores ≥SDC.
- At week 12, 65% of patients had improved synovitis scores, and 32% of patients had improved ≥SDC (1.7).
- By week 12, median osteitis score had improved from baseline, and 28% of patients had improved ≥SDC (3.0).
- Osteitis developed in two normal joints with persistent synovitis, but no new erosions or synovitis developed in normal joints.
- Median erosion score did not change at either time point, but 10 patients showed erosion score change ≥SDC (2.2) (7 regressed, 3 progressed) at week 12.


SDC = smallest detectable change
Figure 1. Improvement in RAMRIS score ≥SDC* at week 12 after treatment with tocilizumab (8 mg/kg)

*SDC: 1.7 synovitis; 3.0 osteitis; 2.2 erosion
RAMRIS = rheumatoid arthritis magnetic resonance image score; SDC = smallest detectable change
Table 1. Median RAMRIS scores with changes from baseline after treatment with tocilizumab (8 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 2</th>
<th>ΔWeek 2 (95% CI)</th>
<th>Week 12</th>
<th>ΔWeek 12 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis</td>
<td>7.0</td>
<td>6.5</td>
<td>0.0 (-0.5, 0.0)</td>
<td>5.5</td>
<td>-0.5 (-1.5, -0.5)</td>
</tr>
<tr>
<td>Osteitis</td>
<td>4.0</td>
<td>4.0</td>
<td>0.0 (0.0, 0.0)</td>
<td>2.0</td>
<td>-0.5 (-1.0, 0.0)</td>
</tr>
<tr>
<td>Erosion</td>
<td>16.5</td>
<td>17.0</td>
<td>0.0 (0.0, 0.0)</td>
<td>14.5</td>
<td>0.0 (0.0, 0.5)</td>
</tr>
</tbody>
</table>

CI = confidence interval; RAMRIS = rheumatoid arthritis magnetic resonance image score
Key conclusions

- Tocilizumab reduced synovitis in only 2 weeks and pre-erosive osteitis within 12 weeks of treatment initiation.

- Early MRI evidence of improvement with tocilizumab is consistent with inhibition of X-ray joint damage at 1 year.


MRI = magnetic resonance imaging
Radiographic progression, physical function, and efficacy after treatment with tocilizumab: LITHE two-year data

Fleischmann R, et al. EULAR 2010: Abstract FRI0205
Background

- The LITHE study is a phase III study of tocilizumab plus MTX in patients with moderate-to-severe RA who had a previous inadequate response to MTX.

- Preliminary results of the LITHE study demonstrated that RA patients treated for one year with tocilizumab (8 mg/kg or 4 mg/kg) in combination with MTX experienced significant inhibition in progression of joint damage and improvement in RA signs and symptoms compared to MTX alone.\(^1\)

- At EULAR 2010, Fleischmann and colleagues presented data (mostly open-label) for year 2 of the LITHE study.\(^2\)

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EULAR = European League Against Rheumatism
MTX = methotrexate; RA = rheumatoid arthritis
Study design

- Patients were randomly assigned to receive tocilizumab (4 or 8 mg/kg) or placebo every 4 weeks plus MTX.
- From week 16, stepwise blinded rescue therapy was allowed if patients had <20% improvement in SJC and TJC.
- At 52 weeks, all patients (including rescue patients) with <70% improvement in SJC and TJC initiated OL tocilizumab (8 mg/kg).
- Patients with ≥70% improvement could also initiate OL tocilizumab (8 mg/kg); decision was made by the investigator and the patient.
- Primary endpoints were change from baseline to year 2 in GmTSS and physical function (AUC change from baseline to year 2 in the HAQ-DI).

AUC = area under the curve
GmTSS = Genant-modified total Sharp score
HAQ-DI = health assessment questionnaire-disability index
MTX = methotrexate; OL = open label
SJC = swollen joint count; TJC = tender joint count

Fleischmann R, et al. EULAR 2010; Abstract FRI0205.
Key findings

- The ITT population included 1,190 patients: 393 control, 399 tocilizumab (4 mg/kg), and 398 tocilizumab (8 mg/kg).
- Radiographic progression was inhibited by 81% and 70% in the original tocilizumab (8 mg/kg) and tocilizumab (4 mg/kg) groups, compared to the original control group.
- Patients in DAS28 remission on tocilizumab (8 mg/kg) increased during year 2 from 48% (132/275) at year 1 to 65% (156/241) at year 2.
- In patients starting tocilizumab (8 mg/kg) at baseline, the absolute number achieving DAS28 remission continuously increased until week 72 and was stable thereafter.

Fleischmann R, et al. EULAR 2010; Abstract FRI0205.

DAS28 = 28-joint disease activity score
ITT = intent-to-treat
Table 1. Patient disposition after 2 years of treatment with tocilizumab (4 or 8 mg/kg) plus MTX or placebo plus MTX

<table>
<thead>
<tr>
<th>Status</th>
<th>Placebo + MTX (n = 392)</th>
<th>Tocilizumab (4 mg/kg) + MTX (n = 399)</th>
<th>Tocilizumab (8 mg/kg) + MTX (n = 399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawals, n (%)</td>
<td>104 (27)</td>
<td>89 (22)</td>
<td>88 (22)</td>
</tr>
<tr>
<td>Completed, n (%)</td>
<td>288 (73)</td>
<td>310 (78)</td>
<td>311 (78)</td>
</tr>
<tr>
<td>Rescue, n (%)</td>
<td>196 (50)</td>
<td>97 (24)</td>
<td>60 (15)</td>
</tr>
<tr>
<td>Initiated open-label tocilizumab (8 mg/kg) at week 52, n (%)</td>
<td>266 (68)</td>
<td>253 (63)</td>
<td>248 (62)</td>
</tr>
<tr>
<td>Completed 104 weeks on initial therapy, n (%)*</td>
<td>21 (5)</td>
<td>37 (9)</td>
<td>48 (12)</td>
</tr>
</tbody>
</table>

*Patients who had a ≥70% improvement in SJC and TJC could remain on initial therapy.

MTX = methotrexate; SJC = swollen joint count; TJC = tender joint count

Fleischmann R, et al. EULAR 2010; Abstract FRI0205.
**Table 2. Radiographic progression, HAQ-DI, ACR70, and DAS28 remission after 2 years of treatment with tocilizumab (4 or 8 mg/kg) plus MTX or placebo plus MTX**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Initial randomized therapy</th>
<th>Placebo + MTX (n = 393)</th>
<th>Tocilizumab (4 mg/kg) + MTX (n = 399)</th>
<th>Tocilizumab (8 mg/kg) + MTX (n = 399)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GmTSS change from baseline, (n ± SD)</td>
<td>1.96 (294 ± 5.96)</td>
<td>0.58 (343 ± 2.36)*\dagger</td>
<td>0.37 (353 ± 1.55)*\‡</td>
<td></td>
</tr>
<tr>
<td>No GmTSS progression, % (n/n)</td>
<td>66 (195/294)</td>
<td>75 (256/343)\sa</td>
<td>83 (292/353)\sa</td>
<td></td>
</tr>
<tr>
<td>Adjusted mean AUC of HAQ-DI change from baseline, (n)</td>
<td>-139.4 (366)</td>
<td>-287.5 (376)\sb</td>
<td>-320.8 (374)\sb</td>
<td></td>
</tr>
<tr>
<td>ACR70, % (n/n)</td>
<td>12 (48/393)</td>
<td>24 (97/399)</td>
<td>22 (89/398)</td>
<td></td>
</tr>
<tr>
<td>DAS28 remission, % (n/n)</td>
<td>53 (72/136)</td>
<td>55 (124/224)</td>
<td>65 (156/241)</td>
<td></td>
</tr>
</tbody>
</table>

\*p calculated by Van Elteren test stratified by region; \dagger p < 0.0025 vs. placebo plus MTX; \sa p < 0.0001 vs. placebo plus MTX; \sb p = 0.0239; \‡p calculated by logistic regression analysis adjusted for region; Analyzed with ANOVA adjusted for region

\n
n/n = patients with response/evaluable patients. If ACR70 could not be calculated because of missing data, patient was deemed a nonresponder at that time point. Analysis of DAS remission was “as observed.”

ACR = American College of Rheumatology (score); AUC = area under the curve; DAS28 = 28-joint disease activity score; GmTSS = Genant-modified total Sharp score; HAQ-DI = health assessment questionnaire-disability index; ITT = intent to treat; MTX = methotrexate; SD = standard deviation
Key conclusion

- Treatment with tocilizumab plus methotrexate over two years resulted in inhibition of joint damage progression and improvement in physical function, as well as continuous reduction in signs and symptoms of rheumatoid arthritis.

Fleischmann R, et al. EULAR 2010; Abstract FRI0205.
Efficacy and safety of tocilizumab in patients with systemic juvenile idiopathic arthritis: twelve-week data from the TENDER trial

Background

- SJIA, a subtype of JIA, is associated with significant morbidity and mortality, and has limited treatment options.

- A vast body of evidence points to a pivotal role of IL-6 in the pathogenesis of SJIA.\(^1\)

- Tocilizumab, a humanized antibody to the IL-6 receptor, has been shown to be efficacious in a Japanese, phase III, placebo-controlled withdrawal design trial in SJIA patients refractory to conventional treatment.\(^2\)

- At EULAR 2010, De Benedetti and colleagues reported findings from their evaluation of the efficacy and safety of tocilizumab in the 12-week double-blind, placebo-controlled, parallel-group part of the 3-part, 5-year, global, multicentre phase III TENDER trial in patients with active SJIA.\(^3\)

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Study design

- Patients aged 2 to 17 years with active SJIA, a disease duration ≥6 months, and an inadequate response to NSAIDs and corticosteroids were enrolled in the study.

- Patients were randomized (2:1) to receive either tocilizumab every 2 weeks (8 mg/kg for patients ≥30 kg body weight; 12 mg/kg for patients <30 kg) or placebo.

- Stable doses of NSAIDs and MTX were continued.

- Tapering of corticosteroids was allowed starting at week 6.

- Patients who met rescue criteria received standard of care, were offered open-label tocilizumab, and were considered non-responders.

- Primary endpoint was the proportion of patients with JIA ACR30 response plus absence of fever at week 12 for tocilizumab patients vs. control (ITT analysis).

ACR = American College of Rheumatology
ITT = intent-to-treat; MTX = methotrexate
NSAIDs = nonsteroidal anti-inflammatory drugs

Key findings

- A total of 112 patients with a mean age of 9.6 years were enrolled in the study: 75 in the tocilizumab arm and 37 in the placebo arm.
- By week 12, one control patient (3%) and two tocilizumab patients (3%) withdrew from the study.
- More control vs. tocilizumab patients required rescue therapy (54% vs. 1%).
- Significantly more tocilizumab vs. control patients achieved the primary endpoint of JIA ACR30 response plus absence of fever at week 12 (85% vs. 24%, $p < 0.0001$).
- No control patients and three tocilizumab patients (4%) experienced SAEs: angioedema and urticaria in one patient, varicella, and bacterial arthritis, all of which resolved without sequelae.

### Table 1. Baseline characteristics of SJIA patients in the ITT population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group (n = 37)</th>
<th>Tocilizumab group (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median disease duration, years (SD)</td>
<td>4.0 (4.4)</td>
<td>4.0 (4.0)</td>
</tr>
<tr>
<td>Active joint count, mean (SD)</td>
<td>16.9 (12.9)</td>
<td>21.3 (15.9)</td>
</tr>
<tr>
<td>Fever past 7 days, n (%)</td>
<td>20 (54)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Concomitant MTX use, n (%)</td>
<td>26 (70)</td>
<td>52 (69)</td>
</tr>
</tbody>
</table>

*ITT = intent to treat; MTX = methotrexate; SD = standard deviation; SJIA = systemic juvenile idiopathic arthritis*
Figure 1. JIA ACR responses at week 12 in the ITT population

*Analysis adjusted for randomization stratification factors (body weight, disease duration, corticosteroid use, methotrexate use)
ACR = American College of Rheumatology (score); ITT = intent to treat; JIA = juvenile idiopathic arthritis
Key conclusion

- The findings of this first global phase III study demonstrated that tocilizumab has superior efficacy when compared with placebo in the short-term (twelve-week) treatment of patients with systemic juvenile idiopathic arthritis.