New Evidence reports on presentations given at EULAR 2012

Tocilizumab for the Treatment of Rheumatoid Arthritis
Tocilizumab monotherapy is superior to adalimumab monotherapy in reducing disease activity (Gabay C, et al. EULAR 2012: Abstract LB0003)

Clinical effects of a tocilizumab-based treatment strategy with or without methotrexate in RA (Dougados M, et al. EULAR 2012: Abstract THU0093)

Comparison of tocilizumab monotherapy or in combination with non-biological DMARDs in RA and an inadequate response to TNF agents (Östör A, et al. EULAR 2012: Abstract FRI0179)

DMARDs = disease-modifying anti-rheumatic drugs; RA = rheumatoid arthritis; TNF = tumour necrosis factor
Tocilizumab monotherapy is superior to adalimumab monotherapy in reducing disease activity

Background

- Approximately one-third of patients with RA who are on biologics receive them as monotherapy.\(^1\)
- Tocilizumab, an inhibitor of IL-6 receptor signalling, has been studied as monotherapy in three clinical trials but direct comparison with a TNF-I agent such as adalimumab has not previously been performed.
- The objective of this study was to compare the efficacy and safety of tocilizumab vs. adalimumab monotherapy in patients with RA.
- Results were presented at EULAR 2012.

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ADACTA was a multicentre, randomized, double-blind, 24-week study.

Study designed to test the superiority of either tocilizumab or adalimumab in patients who had RA for six months or longer and who were methotrexate intolerant, or for whom continued treatment with methotrexate was inappropriate.

Patients were randomly assigned (1:1) to:
- Tocilizumab 8 mg/kg iv every four weeks (plus placebo);
- Adalimumab 40 mg sc every two weeks (plus placebo) for 24 weeks.

Study design (cont’d)

- Escape to weekly adalimumab/placebo sc was permitted at week 16; 10 patients in the adalimumab arm and seven in the tocilizumab arm escaped.

- Primary endpoint: Mean change from baseline in DAS28 at 24 weeks.
ADACTA study design

Superiority trial design

Randomized Drug Treatment

TCZ 8 mg/kg iv Q4 weeks
+ sc placebo Q2 Weeks

ADA 40 mg sc Q2 weeks
+ iv placebo Q4 weeks

1:1 randomization

Week 16+: Escape*

24 weeks; primary endpoint: Δ DAS28

8 Weeks Safety Follow-up

* Criteria for escape: <20% improvement from baseline in SJC and TJC at week 16 or after
Escape therapy: Weekly sc (ADA/placebo) injections; study medication remained blinded

ADA = adalimumab; DAS28 = 28-joint disease activity score; iv = intravenous; Q2 = every two weeks; Q4 = every four weeks; sc = subcutaneous;
SJC = swollen joint count; TCZ = Tocilizumab; TJC = tender joint count
Key findings

- The mean change in DAS28 from baseline to week 24 was significantly greater with tocilizumab than with adalimumab:
  - $-3.3$ vs. $-1.8$; $p < 0.0001$.

- A numerical difference between the two arms in SJC, TJC, ESR, and PGA in favour of tocilizumab, was different from week 8 onwards.

- Statistical significance was also achieved in favour of tocilizumab for DAS28 remission, LDA, and ACR20, ACR50, and ACR70 responses.

ACR = American College of Rheumatology; DAS28 = 28-joint disease activity score; ESR = erythrocyte sedimentation rate; LDA = low disease activity; PGA = patient global assessment; SJC = swollen joint count; TJC = tender joint count.
Patients achieving remission and a LDA index (≤0 to ≥10) was greater for the tocilizumab group than the adalimumab group:

- 47.9% vs. 29.0%; \( p = 0.0003 \).

Incidence AEs was similar between the groups.

Serious AEs and SIs were also similar:

- Tocilizumab: 11.7%, 3.1%;
- Adalimumab: 9.9%, 3.1%.

Transaminase and LDL elevations, and neutrophil reductions occurred in both arms; however, the proportion of patients with abnormal values was numerically higher in the tocilizumab arm.

AEs = adverse events; LDA = low disease activity; LDL = low-density lipoprotein; SIs = serious infections
DAS28 over time

- ADA 40 mg + placebo (iv) (N = 162)
- TCZ 8 mg/kg + placebo (sc) (N = 163)

LOC = last observation carried forward; ESR = erythrocyte sedimentation rate; iv = intravenous; sc = subcutaneous; SE = standard error; TCZ = tocilizumab; VAS = visual analogue scale.
Secondary endpoints (proportions of patients with DAS28 remission/low disease activity at week 24)


*P < 0.0001 (vs. ADA); significance was determined using a logistic regression analysis (covariates included treatment, region, and duration of RA).

LOCF was used for missing TJC and SJC; no imputation was used for ESR and Patient’s Global VAS.

Non-responder imputation was used for missing data. If ESR = 0 then ESR = 1 was substituted into the DAS28 calculation to enable a non-missing DAS28.

ADA = adalimumab; DAS28 = 28-joint disease activity score; ESR = erythrocyte sedimentation rate; LOCF = last observation carried forward; SJC = swollen joint count; TCZ = tocilizumab; TJC = tender joint count; VAS = visual analogue scales
Secondary endpoints (proportions of patients with ACR20/50/70 response at week 24)

Key conclusions

- Tocilizumab monotherapy was superior to adalimumab monotherapy in reducing the signs and symptoms of RA.
- The overall AE profile was comparable between the two treatment arms.
- The safety observed in the tocilizumab arm was consistent with the known safety profile of tocilizumab, and no new or unexpected AEs were observed.

AE = adverse event; RA = rheumatoid arthritis

Clinical effects of a tocilizumab-based treatment strategy with or without methotrexate in RA

Dougados M, et al. EULAR 2012: Abstract THU0093
Methotrexate is a cornerstone in the treatment of RA. Although approximately 40% of patients are well controlled on methotrexate alone, many patients experience an IR to methotrexate. Tocilizumab is a humanized monoclonal antibody that inhibits the binding of IL-6 to its receptors and is effective as both monotherapy and in combination with methotrexate. The objective of the study was to assess the efficacy and safety of adding tocilizumab to methotrexate vs. switching to tocilizumab monotherapy in patients experiencing an IR to prior methotrexate therapy. Results were presented at EULAR 2012.
ACT-RAY is a multicentre, randomized (1:1), double-blind, placebo-controlled, parallel-group, phase IIIb clinical trial.

Patients were randomized to either the:
- Add-on group (tocilizumab plus methotrexate);
- Switch group (tocilizumab plus placebo).

Group blinding was continued from week 24 to week 52.

In both groups, treatment was adapted based on disease activity while maintaining blinding.
At week 24, if DAS28 was >3.2, an open-label conventional DMARD (sulfasalazine, leflunomide, chloroquine, hydroxychloroquine, parenteral gold, or azathioprine) was added.

At week 36, if DAS28 was >3.2 with an added open-label conventional DMARD, the patient was moved to the maintenance regimen arm (tocilizumab 8 mg/kg plus blinded methotrexate/placebo plus open label conventional DMARD, plus the option to add a third conventional DMARD at the investigator’s discretion).

Study design (cont’d)

Dougados M, et al. EULAR 2012: Abstract THU0093

DAS28 = 28-joint disease activity score; DMARD = disease-modifying anti-rheumatic drug
ACT-RAY study design — year 1

Oral MTX is blinded throughout the whole three-year study. TCZ and open-label conventional DMARDs are unblinded.

**Baseline**

- Add-on: TCZ + MTX
- Switch: TCZ + PBO

**Week 0-24**

- TCZ + MTX
- Add-on: DAS28 ≤3.2
- Switch: Yes → Continue treatment

**Week 24**

- Continue treatment and add conventional DMARD

**Week 24-36**

- DAS28 ≤3.2
- Yes → Continue treatment
- No → Continue treatment and add conventional DMARD

**Week 36**

- DAS28 ≤3.2
- Yes → Continue treatment
- No → No → Continue treatment and add conventional DMARD

**Week 36-52**

- Continue treatment

*The goal of the maintenance regimen is to maintain treatment effects without further pursuing the treat-to-target concept. Patients continue on TCZ plus blinded MTX/PBO and have the option of adding additional open-label conventional DMARDs.*

**Abbreviations:**

ACT-RAY = ACTemra (tocilizumab); 28-Joint Disease Activity Score (DAS28); MTX = methotrexate; PBO = placebo; TCZ = tocilizumab.

Dougados M, et al. EULAR 2012: Abstract THU0093
Key findings

- Similar proportions of patients in each group received open-label conventional DMARDs.

- Rates of improvements in the signs and symptoms of RA at week 24 were maintained or further improved at week 52 in both the add-on therapy group (tocilizumab plus methotrexate) and the switch group (tocilizumab plus placebo).

- Radiographic progression was observed in a small proportion of patients in both arms with a statistically significant difference in favour of the add-on strategy:
  - 7.6% vs. 14.5%; \( p = 0.007 \).

DMARD = disease-modifying anti-rheumatic drug; RA = rheumatoid arthritis
Key findings (cont’d)

- There was no difference in the mean change of the GSS between the add-on and switch groups at week 24 (0.24 vs. 0.4; \( p = 0.26 \)) and at week 52 (0.35 vs. 0.63; \( p = 0.36 \)).

- Safety outcomes were consistent between the two study groups.

- Preliminary immunogenicity analysis showed that the rate of overall and neutralizing anti-drug antibodies was similar in both groups.
Proportion of patients receiving open-label conventional DMARDs in addition to the study drug(s) before week 52

Dougados M, et al. EULAR 2012: Abstract THU0093
Percentage of patients achieving DAS28 remission or LDAS over time

- Add-on (N = 277)
- Switch (N = 276)

p-value is for a logistic regression model including region and baseline DAS28 (≤5.5 and >5.5).

BL = baseline; DAS28 = 28-joint disease activity score; DMARDs = disease-modifying anti-rheumatic drugs; LDAS = low disease activity state.

Dougados M, et al. EULAR 2012: Abstract THU0093
Percentage of patients achieving ACR20, 50, 70, or 90

- Add-on (N = 277)
- Switch (N = 276)

A CR20
Week 52: $p = 0.62$

ACR50
Week 52: $p = 0.22$

ACR70
Week 52: $p = 0.99$

ACR90
Week 52: $p = 0.65$

*p-value is for a Cochran-Mantel-Haenszel chi-square test, with strata defined by region and baseline DAS28 ($<5.5$ and $>5.5$)

ACR = American College of Rheumatology; BL = baseline; DAS28 = 28-joint disease activity score

Dougados M, et al. EULAR 2012: Abstract THU0093
Patients without radiographic progression

Dougados M, et al. EULAR 2012: Abstract THU0093
Mean change from baseline in total GSS at week 24 and week 52

Add-on  Switch

Calculated baseline annualized progression rate

p = 0.26

n = 265  n = 258

p = 0.36

n = 269  n = 264

Error Bars = Standard error of the mean
Baseline annualized progression rate = GSS/RA duration
Estimates and p values adjusted for baseline DAS28 and baseline GSS

DAS28 = 28-joint disease activity score; GSS = Genant-modified sharp score; RA = rheumatoid arthritis

Dougados M, et al. EULAR 2012: Abstract THU0093
### Overview of AE, SAE, SI, and deaths

<table>
<thead>
<tr>
<th></th>
<th>Add-on N = 277</th>
<th>Switch N = 276</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total TCZ exposure, PY</strong></td>
<td>247.1</td>
<td>237.5</td>
</tr>
<tr>
<td><strong>Adverse Events (AE)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients with ≥1 AE, % (n)</td>
<td>81.9% (227)</td>
<td>82.6% (228)</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>1,061</td>
<td>969</td>
</tr>
<tr>
<td>Rate of AEs (per 100 PY)</td>
<td>429.3</td>
<td>407.9</td>
</tr>
<tr>
<td><strong>Serious Adverse Events (SAEs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients with ≥1 SAE, % (n)</td>
<td>8.7% (24)</td>
<td>9.4% (26)</td>
</tr>
<tr>
<td>Total number of SAEs</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>Rates of SAEs (per 100 PY)</td>
<td>14.2</td>
<td>17.7</td>
</tr>
<tr>
<td><strong>Serious Infections (SIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients with ≥1 SI, % (n)</td>
<td>3.6% (10)</td>
<td>3.3% (9)</td>
</tr>
<tr>
<td>Total number of SIs</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Rate of SIs (per 100 PY)</td>
<td>4.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Total number of deaths</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

*Similar rates of adverse events, serious adverse events, and serious infections occurred between the groups.*

_PY = person-years; TCZ = tocilizumab_
<table>
<thead>
<tr>
<th></th>
<th>Add-on</th>
<th>Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of anti-drug</td>
<td>4.7% (10)</td>
<td>5.4% (11)</td>
</tr>
<tr>
<td>antibodies, % (n)</td>
<td>N = 215</td>
<td>N = 214</td>
</tr>
<tr>
<td>Detection of neutralizing</td>
<td>3.7% (8)</td>
<td>4.4% (8)</td>
</tr>
<tr>
<td>anti-drug antibodies,</td>
<td></td>
<td></td>
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<tr>
<td>% (n)</td>
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</tbody>
</table>
Key conclusion

- Despite some signals in favour of the add-on strategy, this analysis suggests that tocilizumab monotherapy might be an acceptable therapeutic strategy in patients with a contraindication for, or intolerance to, methotrexate.
Comparison of tocilizumab monotherapy or in combination with non-biological DMARDs in RA and an IR to TNF agents

Östör A, et al. EULAR 2012: Abstract FRI0179

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

- Monotherapy with a biologic can offer an alternative treatment approach for patients with RA for whom therapy with the conventional DMARD methotrexate is considered inappropriate.¹

- The objective of this post-hoc analysis was to examine the safety and efficacy of tocilizumab as monotherapy or with add-on DMARDs in patients with moderate-to-severe RA who had a DMARD-IR and/or TNF-IR in a setting that closely resembled real-life clinical practice.

- Results were presented at EULAR 2012.


DMARD = disease-modifying anti-rheumatic drug; IR = inadequate response; RA = rheumatoid arthritis; TNF = tumour necrosis factor
Study design

- ACT-SURE was a phase IIIb, open-label single-arm, non-randomized, 24-week study that included patients from 25 countries and 264 centres (not including the U.S.).
- Patients received tocilizumab 8 mg/kg iv every four weeks for 24 weeks.

Östör A, et al. EULAR 2012: Abstract FRI0179
Key findings

- Of 1,681 patients evaluable in the ACT-SURE study, 705 patients (42%) had an IR to TNFs.
  - Number of patients who received tocilizumab monotherapy: n = 173/705 (25%);
  - Number of patients who received tocilizumab in combination with DMARD(s): n = 532/705 (75%).

- The mean age, duration of RA, and baseline disease activity scores were slightly higher in patients who received tocilizumab monotherapy.
Key findings (cont’d)

- The proportion of patients who reported AEs, SAEs, and AEs leading to withdrawal were similar in the tocilizumab monotherapy and the tocilizumab plus DMARD(s) groups.

- Serious infections, infusions reactions, and major adverse cardiac events occurred at similar rates in both groups.

- At week 24, the proportions of patients achieving ACR20, ACR50, ACR70, and ACR90 responses were similar in the tocilizumab monotherapy and the tocilizumab plus DMARD(s) groups.

Östör A, et al. EULAR 2012: Abstract FRI0179

ACR = American College of Rheumatology; AEs = adverse events; DMARD = disease-modifying anti-rheumatic drug; SAEs = serious adverse events;
In both patient groups, EULAR good and moderate responses were observed as early as week 4, and the proportions of patients who achieved good or moderate responses were maintained through week 24.

The proportions of patients achieving DAS28-ESR <2.6 increased steadily from baseline through week 20 for the tocilizumab monotherapy group and through week 24 for the tocilizumab plus DMARD(s) group.

At week 24, similar proportions of patients in the tocilizumab plus DMARD(s) group achieved CDAI and SDAI remission, and LDA status.

CDAI = clinical disease activity index; DAS28-ESR = 28-joint disease activity score-erythrocyte sedimentation rate; DMARD = disease-modifying anti-rheumatic drug; EULAR = European League Against Rheumatism; LDA = low disease activity; SDAI = simplified disease activity index
All ACR core parameters improved from baseline to week 24; the degree of improvement was similar in the tocilizumab monotherapy and tocilizumab plus DMARD(s) groups.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>TCZ Monotherapy n = 173</th>
<th>TCZ + DMARD(s) n = 532</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PY</td>
<td>76.5</td>
<td>239.1</td>
</tr>
<tr>
<td>AE, % (95% CI)</td>
<td>82.1 (75.5, 87.5)</td>
<td>81.4 (77.8, 84.6)</td>
</tr>
<tr>
<td>AE/100 PY (95% CI*)</td>
<td>596.1 (542.6, 653.3)</td>
<td>671.2 (638.8, 704.9)</td>
</tr>
<tr>
<td>SAE, % (95% CI)</td>
<td>9.8 (5.8, 15.3)</td>
<td>8.5 (6.2, 11.2)</td>
</tr>
<tr>
<td>SAE/100 PY (95% CI*)</td>
<td>23.5 (13.9, 37.2)</td>
<td>21.8 (16.2, 28.5)</td>
</tr>
<tr>
<td>AEs leading to withdrawal, % (95% CI)</td>
<td>6.9 (3.6, 11.8)</td>
<td>5.6 (3.8, 8.0)</td>
</tr>
<tr>
<td>Infections, % (95% CI)</td>
<td>38.7 (31.4, 46.4)</td>
<td>40.4 (36.2, 44.7)</td>
</tr>
<tr>
<td>Infections/100 PY (95% CI*)</td>
<td>138.6 (113.4, 167.6)</td>
<td>147.6 (132.6, 163.9)</td>
</tr>
<tr>
<td>Serious Infections, % (95% CI)</td>
<td>2.9 (0.9, 6.6)</td>
<td>2.4 (1.3, 4.1)</td>
</tr>
<tr>
<td>Serious infections/100 PY (95% CI*)</td>
<td>6.5 (2.1, 15.3)</td>
<td>6.3 (3.5, 10.3)</td>
</tr>
<tr>
<td>Infusion reaction, % (95% CI)</td>
<td>19.7 (14.0, 26.4)</td>
<td>21.1 (17.7, 24.8)</td>
</tr>
<tr>
<td>Drug Infusion</td>
<td>6.4 (3.2, 11.1)</td>
<td>6.8 (4.8, 9.2)</td>
</tr>
<tr>
<td>Within 24 hours of infusion</td>
<td>14.5 (9.6, 20.6)</td>
<td>16.9 (13.8, 20.4)</td>
</tr>
<tr>
<td>Major adverse cardiac event, % (95% CI)</td>
<td>0.6 (0.0, 3.2)</td>
<td>0.4 (0.0, 1.4)</td>
</tr>
<tr>
<td>Grade 3 neutropenia at ≥1 time point, %</td>
<td>1.2</td>
<td>4.2</td>
</tr>
<tr>
<td>ALT/AST &gt;1.5 x ULN at any time point, %</td>
<td>10.7/1.8</td>
<td>14.6/5.9</td>
</tr>
<tr>
<td>ALT/AST &gt;3 x ULN at any time point, %</td>
<td>1.8/0</td>
<td>3.2/1.0</td>
</tr>
</tbody>
</table>

95% CI are based on the Clopper-Pearson method unless otherwise indicated
* 95% Poisson CI; † No grade 4 neutropenia cases were reported
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase;
CI = confidence interval; PY = patient-year; SAE = serious adverse event;
TCZ = tocilizumab; ULN = upper limit of normal

Östör A, et al. EULAR 2012: Abstract FRI0179
ACR20/50/70/90 response rates at week 24

ACR = American College of Rheumatology; DMARD = disease-modifying anti-rheumatic drug; TCZ = tocilizumab

Östör A, et al. EULAR 2012: Abstract FRI0179
Proportions of patients achieving DAS28 (ESR) over time

DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; TCZ = tocilizumab

Östör A, et al. EULAR 2012: Abstract FRI0179
Proportions of patients achieving predefined CDAI and SDAI disease activity status at week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CDAI (Remission ≤ 2.8)</th>
<th>SDAI (Remission ≤ 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCZ monotherapy</td>
<td>47.3% (18.5%)</td>
<td>56.5% (16.0%)</td>
</tr>
<tr>
<td>TCZ + DMARD(s)</td>
<td>53.2% (14.2%)</td>
<td>51.4% (20.4%)</td>
</tr>
</tbody>
</table>

Remission: CDAI ≤ 2.8, SDAI ≤ 3.3
LDA: CDAI > 2.8 to ≤ 10, SDAI > 3.3 to ≤ 11

CDAI = clinical disease activity index; DMARD = disease-modifying anti-rheumatic drug; LDA = low disease activity; SDAI = simplified disease activity index; TCZ = tocilizumab

Östör A, et al. EULAR 2012: Abstract FRI0179
Key conclusions

- Overall, the safety profiles of tocilizumab and tocilizumab plus DMARD(s) in patients who were TNF-IR were comparable.

- In a refractory TNF-IR patient population, in a setting resembling real-life clinical practice, the efficacy of tocilizumab monotherapy was clinically meaningful and not statistically significantly different from that of tocilizumab plus DMARD(s).

- These findings suggest that tocilizumab monotherapy confers clinical benefit in patients who are TNF-IR and who cannot tolerate methotrexate or for whom methotrexate treatment is inappropriate.