Rituximab for the Treatment of Rheumatoid Arthritis
Report on EULAR 2012 presentations


- Analysis of infection risk in patients with limited return of peripheral B cells after a period of two years or more following any rituximab treatment course in RA clinical trials *(Mease P, et al. EULAR 2012. Abstract: FRI0201)*


RA = rheumatoid arthritis; TNF = tumour necrosis factor
Long-term safety of rituximab: 10-year follow-up in the RA global clinical trial program

van Vollenhoven RF, et al. EULAR 2012: Abstract THU0120

RA = rheumatoid arthritis
The long-term safety of rituximab treatment in patients with RA has not been established.¹

The objective of this study was to evaluate the long-term safety of rituximab in RA clinical trials.

Results were presented at EULAR 2012.

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

- This was a pooled observed case analysis of safety data in patients with moderate-to-severe active RA treated with rituximab plus methotrexate.

- A global clinical trial program, it comprised eight randomized clinical trials, two long-term open-label extensions, and one open-label prospective study.

- Each course of rituximab consisted of two courses of either 1,000 mg or 500 mg given iv two weeks apart.

- Prior to each rituximab infusion, all patients received methylprednisolone 100 mg iv; most patients also received paracetamol and an antihistamine.
Key findings

- As of September 2011, 3,595 patients had received up to 19 courses of rituximab over a period of 10 years.

- The number of patients available for analysis was:
  - Rituximab all-exposure: 3,595 (14,008 patient-years);
  - Long-term population: 1,145 (7,716 patient-years);
  - Pooled placebo group: 818 (1,107 patient-years).

- Rates of AEs and SAEs were similar in the all-exposure, five-year follow-up, and placebo populations.

- The overall rates of all infections and SIEs were similar across the analysis of the populations.

van Vollenhoven RF, et al. EULAR 2012: Abstract THU0120

AEs = adverse events; SAEs = serious adverse event; SIEs = serious infection events
Key findings (cont’d)

- The rate of all AEs over time was highest during the first six months after the first exposure to rituximab, in part due to IRRs, which predominantly occurred with the first infusion of the first course.
  - Thereafter, rates of AEs and SAEs remained stable, irrespective of the number of courses of treatment received.
- The rate of confirmed malignancies (excluding non-melanoma skin cancers) was similar to rates in the general RA population.

AEs = adverse events; IRRs = infusion-related reactions; RA = rheumatoid arthritis; SAEs = serious adverse events

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### Summary of adverse events rates per 100 patient-years

<table>
<thead>
<tr>
<th></th>
<th>RTX All-Exposure (n = 3,595)</th>
<th>RTX long-term (&gt;5 years) (n = 1,145)</th>
<th>Pooled placebo (n = 818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure (pt-years)</td>
<td>14,008</td>
<td>7,716</td>
<td>1,107</td>
</tr>
<tr>
<td>AE rate (95% CI)</td>
<td>249.34 (246.74–251.97)</td>
<td>237.25 (233.83–240.71)</td>
<td>315.43 (305.14–326.06)</td>
</tr>
<tr>
<td>SAE rate (95% CI)</td>
<td>14.03 (13.42–14.66)</td>
<td>12.25 (11.49–13.05)</td>
<td>13.82 (11.79–16.19)</td>
</tr>
<tr>
<td>Infection rate (95% CI)</td>
<td>78.60 (77.14–80.08)</td>
<td>75.10 (73.19–77.06)</td>
<td>90.39 (84.96–96.17)</td>
</tr>
<tr>
<td>SIE rate (95% CI)</td>
<td>3.8 (3.50–4.14)</td>
<td>2.76 (2.41–3.16)</td>
<td>3.79 (2.80–5.13)</td>
</tr>
</tbody>
</table>

*AE = adverse event; CI = confidence interval; SAE = serious adverse event; SIE = serious infection event; RTX = rituximab*
Incidence of infusion-related reactions by treatment course

In courses 1–10, 17 patients reported 19 serious IRRs. The proportion of patients experiencing serious IRRs was 0.5% (17/3,595), with 11, 5, 0, 1, 1, 1, 0, 0, and 0 events occurring per course, respectively.

INF = infusion; IRR = infusion-related reactions
Rates of adverse events over time: one-year increments (all-exposure population)

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<table>
<thead>
<tr>
<th></th>
<th>All patients receiving any biologic following RTX treatment (n = 331)</th>
<th>Subset of patients receiving a TNF-I following RTX treatment (n = 268)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before other biologic</td>
<td>After other biologic</td>
</tr>
<tr>
<td>Total exposure (pt-years)</td>
<td>593.45</td>
<td>445.58</td>
</tr>
<tr>
<td>SIEs, n</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>SIEs/100 pt-years (95% CI)</td>
<td>4.89 (3.40–7.03)</td>
<td>4.26 (2.72–6.69)</td>
</tr>
</tbody>
</table>

CI = confidence interval; pt-years = patient-years; RTX = rituximab; SIE = serious infection events; TNF-I = tumour necrosis factor inhibitor
### Rate of malignancy and incidence ratio for malignancy in rituximab all-exposure population and published data in adults with RA

<table>
<thead>
<tr>
<th></th>
<th>Rate (per 100 pt-years)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Any site*</td>
</tr>
<tr>
<td>RTX (All-Exposure) (95% CI)</td>
<td>0.72 (0.59–0.87)</td>
</tr>
<tr>
<td>RA observational studies</td>
<td></td>
</tr>
<tr>
<td>Danish Cancer Registry</td>
<td>1.17</td>
</tr>
<tr>
<td>National Databank for Rheumatic Diseases</td>
<td>1.30</td>
</tr>
</tbody>
</table>

### Standardized incidence ratio

<table>
<thead>
<tr>
<th></th>
<th>Rate (per 100 pt-years)</th>
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<tbody>
<tr>
<td></td>
<td>Any site*</td>
</tr>
<tr>
<td>Malignancy incidence in RTX-treated RA All-exposure population (95% CI)</td>
<td>1.01 (0.83–1.23)</td>
</tr>
<tr>
<td>Meta-analysis of malignancy incidence in adult patients with RA (95% CI)</td>
<td>1.05 (1.01–1.09)</td>
</tr>
</tbody>
</table>

* Excluding non-melanoma skin cancer and non-malignant events
† Only female patients
‡ Surveillance Epidemiology and End Results database was used to obtain age- and sex-specific incidence ratio of malignancies for the U.S. general population for standardized incidence ratio calculations

CI = confidence interval; pt-years = patient-years; RA = rheumatoid arthritis; RTX = rituximab

van Vollenhoven RF, et al. EULAR 2012: Abstract THU0120
Key conclusions

- No new safety signals were observed with increasing duration of exposure, including among patients with >five years of follow up.
- Rituximab remains well tolerated over time as well as multiple treatment courses.
- IRRs predominantly occurred during the first infusion of the first course and were rarely serious.
- Serious and non-serious infection rates were similar to previous analyses and did not increase over time or course.
Key conclusions (cont’d)

- The use of subsequent biologics, including TNF-Is, in patients with RA previously treated with rituximab, was not associated with an increased SIE rate.

- Rates of MIs and malignancies were consistent with those observed in epidemiological data from other RA cohorts.

- Apart from IRRs, the overall safety profile of rituximab remains similar to that of the pooled placebo population and consistent with the published data of patients with moderate-to-severe RA.
Analysis of infection risk in patients with limited return of peripheral B cells after a period of two years or more following any rituximab treatment course in rheumatoid arthritis clinical trials

Background

- The safety of prolonged peripheral B-cell depletion in patients treated with rituximab, in particular with regard to the potential risk of serious infections, remains to be fully established.\(^1\)

- Mease and colleagues evaluated the risk of infection and the long-term safety of prolonged peripheral B-cell depletion following rituximab treatment in RA clinical trials.

- Results were presented at EULAR 2012.

Study design

- Subgroups of patients with limited return of peripheral B cells from the rituximab “all-exposure” population (all patients exposed to at least one or part of one rituximab infusion, regardless of dose, within the clinical trial program) were analyzed.

- Limited return of peripheral B cells was defined as a CD19 count below the LLN (80 cells/µL) after a period of ≥two years (104 consecutive weeks) following any course of rituximab.

- During the ≥two-year period of B-cell depletion, patients did not receive additional rituximab therapy, although some patients were subsequently re-retreated.

- B-cell (CD19+) levels were measured every four to 12 weeks, depending on the clinical study protocol.
Key findings

- The all-exposure population (September 2010) comprised 3,194 patients (11,962 patient-years, with up to 9.5 years of follow-up, and up to 17 courses of rituximab treatment).

- Overall, 345 patients (10.8%) had limited return of peripheral B cells (below LLN) after ≥two years.

- Limited return of peripheral B cells over ≥two years was not associated with an increased risk of infections in terms of rates, clinical pattern, or severity.

- Infection rates per 100 patient-years were lower in patients with low CD19 for ≥two years vs. all-exposure and patients with an IR to a TNF-I
Key findings (cont’d)

- SI rates in patients were similar to those in other populations (overlapping 95% CI) and were most comparable with rates in patients who were TNF-IR (rituximab-indicated population).

- In the subgroups of patients with limited return to peripheral B cells, there were no apparent differences in types or outcomes of SIs.
<table>
<thead>
<tr>
<th>Summary of infection and serious infection rates</th>
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<tbody>
<tr>
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<td></td>
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<tr>
<td>Observation, pt-year</td>
</tr>
<tr>
<td>Infections, events/100 pt-years (95% CI)</td>
</tr>
<tr>
<td>Serious infections (n) pt-years (95% CI)</td>
</tr>
<tr>
<td>Serious infections/100 pt-years (95% CI)</td>
</tr>
</tbody>
</table>

*For ≥2 years after any rituximab course

CI = confidence interval; LLN = lower limit of normal; LLQ = lower limit of quantification; pt-years = patient-years; TNF-IR = tumour necrosis factor inadequate response.
Key conclusions

- Analysis of 345 patients with limited return of peripheral CD19 + B cells ≥ two years after any rituximab treatment course showed no clear association with an increased risk of infections, including SIs.

- Rates and infection profiles were comparable with those in other patients who received rituximab, with baseline disease characteristics and SI rates most closely resembling those of the TNF-IR population.

- No clinically relevant differences were evident in baseline demographics or disease characteristics that could help predict which patients may potentially have limited return of peripheral B cells following one or more rituximab treatment courses.

SIs = serious infections; TNF-IR = tumour necrosis factor inadequate response

Relative effectiveness of rituximab versus an alternative TNF inhibitor in patients with RA and an inadequate response to a single previous TNF inhibitor: results from SWITCH-RA, a global, comparative effectiveness, observational study

Background

- Although TNF-Is are effective in improving the signs and symptoms of RA, and slowing or preventing structural damage in RA, approximately 20% to 40% of patients experience an IR to TNF-I treatment.

- The objective of this study was to compare the effectiveness of rituximab and an alternative TNF-I following an IR with a first TNF-I in patients with RA in a real-world clinical practice.

- Results were presented at EULAR 2012.
Study design

- SWITCH-RA is an ongoing prospective, multicentre, global, observational study.

- A total of 1,107 patients from 11 countries were enrolled:
  - N = 602 (54.4%) received rituximab;
  - N = 505 (45.6%) received an alternative TNF-I.

- The majority of enrolled patients were female (79.0%), mean age was 55.5 years, and mean disease duration was 8.3 years.
Study design (cont’d)

- Eligible patients were ≥18 years old and starting rituximab or an alternative TNF-I therapy following an IR to a first TNF-I.
- Patients were enrolled up to four weeks after commencing the second biologic therapy.
Key findings

- The mean change in DAS28-3-ESR from baseline to six months was significantly greater in the rituximab group compared with the alternative TNF-I group ($p = 0.008$).
  - Mean decreases in DAS28-3-ESR at six months were greater in patients who switched to rituximab owing to inefficacy but not intolerance.

- A greater decrease in ESR least squares mean was noted in the rituximab vs. alternative TNF-I group overall ($-15.0$ vs. $-9.0$; $p = 0.014$).

DAS28-3 = disease activity score in 28 joints based on DAS-3 which excludes the patient’s global health component; ESR = erythrocyte sedimentation rate; TNF-I = tumour necrosis factor inhibitor
Key findings (cont’d)

- A numerically greater change in CRP was observed in the alternative TNF-I group vs. the rituximab group (−11.6 vs. −8.2; \( p = 0.509 \)).

- Swollen and tender joint counts showed greater improvements with rituximab than with an alternative TNF-I treatment, although the differences were not statistically significant.

CRP = C-reactive protein; TNF-I = tumour necrosis factor inhibitor
Changes in DAS28-3-ESR over six months, overall, and by means for discontinuation of initial TNF-\(\text{I}^*\)

* Analyses adjusted for baseline value, propensity score, and other covariates found to be statistically significantly different between the two groups at baseline. DAS28-3-ESR least squares means.

DAS28 = 28-Joint disease activity score; ESR = erythrocyte sedimentation rate; TNF-\(\text{I}\) = tumour necrosis factor inhibitor
<table>
<thead>
<tr>
<th>Clinical Characteristics, mean (SE)</th>
<th>Rituximab</th>
<th>Alternative TNF-I</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAS28-3-ESR</strong></td>
<td>−1.5 (0.2)</td>
<td>−1.1 (0.2)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td><strong>DAS28-3-CRP</strong></td>
<td>−1.2 (0.2)</td>
<td>−1.1 (0.3)</td>
<td>0.776</td>
</tr>
<tr>
<td><strong>ESR (mm/h)</strong></td>
<td>−15.0 (3.3)</td>
<td>−9.0 (3.6)</td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td><strong>CRP (mg/L)</strong></td>
<td>−8.2 (7.4)</td>
<td>−11.6 (8.2)</td>
<td>0.509</td>
</tr>
<tr>
<td><strong>Swollen joint count</strong></td>
<td>−4.3 (0.9)</td>
<td>−3.8 (0.9)</td>
<td>0.449</td>
</tr>
<tr>
<td><strong>Tender joint count</strong></td>
<td>−5.2 (1.1)</td>
<td>−3.9 (1.2)</td>
<td>0.104</td>
</tr>
<tr>
<td><strong>Physician Global Assessment of Disease (mm)</strong></td>
<td>−22.9 (5.4)</td>
<td>−18.7 (5.7)</td>
<td>0.248</td>
</tr>
<tr>
<td><strong>Patient Global Assessment of Disease (mm)</strong></td>
<td>−18.2 (4.9)</td>
<td>−12.3 (5.1)</td>
<td>0.086</td>
</tr>
<tr>
<td><strong>Patient VAS pain score (mm)</strong></td>
<td>−12.3 (6.0)</td>
<td>−6.7 (6.4)</td>
<td>0.148</td>
</tr>
<tr>
<td><strong>HAQ-DI</strong></td>
<td>−0.6 (0.2)</td>
<td>−0.6 (0.2)</td>
<td>0.541</td>
</tr>
<tr>
<td><strong>Duration of morning stiffness (mins)</strong></td>
<td>−15.8 (22.6)</td>
<td>−3.1 (24.2)</td>
<td>0.405</td>
</tr>
</tbody>
</table>

*Least squares means and p-values were based on analysis of covariance (ANCOVA) models with change in outcome as the dependent variable and treatment group as the independent variable and controls for the baseline value on the outcome variable, including propensity to receive treatment along with other covariates. Characteristics in bold were statistically significantly different between groups (p < 0.05).

**CRP** = C-reactive protein; **DAS28-3** = disease activity score in 28 joints based on DAS28-3 which excludes the patient’s global health component; **ESR** = erythrocyte sedimentation rate; **HAQ-DI** = Health Assessment Questionnaire Disability Index; **SE** = standard error; **TNF-I** = tumour necrosis factor inhibitor; **VAS** = visual analogue scale.
Key conclusions

- Following discontinuation of a first TNF-I, patients who started treatment with rituximab achieved improved effectiveness compared with patients switching to an alternative TNF-I, as demonstrated by significantly greater decreases in DAS28-3-ESR over six months.

- Decreases in DAS28-3-ESR were particularly significant for patients who switched owing to inefficacy.

DAS28-3 = disease activity score in 28 joints based on DAS-3 which excludes the patient’s global health component; ESR = erythrocyte sedimentation rate; TNF-I = tumour necrosis factor inhibitor