New Evidence reports on presentations given at EULAR 2011

Rituximab for the Treatment of Rheumatoid Arthritis and Vasculitis
Report on EULAR 2011 presentations


- Seropositivity, and in particular ACPA positivity is a strong predictor of response to treatment with rituximab: Pooled data from 10 European registries *(Chatzidionysiou K, et al. EULAR 2011: Abstract FRI0371)*

- Retreatment with rituximab yields better clinical outcomes, especially when it is given at a fixed interval: Data from the CERERRA collaboration *(Chatzidionysiou K, et al. EULAR 2011: Abstract FRI0372)*

- Long-term safety profile of rituximab in RA clinical trials: Pooled analysis of up to 9.5 years follow-up of the re-treatment population *(van Vollenhoven RF, et al. EULAR 2011: Abstract SAT0267)*

RA = rheumatoid arthritis; TNF = tumour necrosis factor; ACPA = anticitrullinated protein antibody status.

Long-term efficacy and safety results of rituximab in ANCA-associated vasculitis (RAVE) trial (Specks U and Stone JH. EULAR 2011: Abstract OP0054)

RA = rheumatoid arthritis; ANCA = antineutrophil cytoplasmic antibody.
Anti-TNF failure and response to rituximab in seropositive and seronegative RA

Background

- Patients with RA with an inadequate response to anti-TNF therapy may switch to an alternative anti-TNF or initiate treatment using a different class of drugs such as rituximab.

- Data are emerging showing that patients with seropositive RA respond better to rituximab than those with seronegative RA.\(^1\)\(^-\)\(^3\)

- Khan and Leak analyzed the response to one course of rituximab therapy in RA patients treated in the Kent and Medway Rheumatology Network and compared responses of seropositive and seronegative patients to rituximab in primary and secondary anti-TNF failure.\(^4\)

- Results were presented at EULAR 2011.

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EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; TNF = tumour necrosis factor.
Study design

- This analysis was carried out in a group of 140 patients known to have at least six months of follow-up after their first course of rituximab for active RA.

- It was previously demonstrated that patients with seropositive RA had significantly higher pre-treatment 28-joint DAS28 than seronegative patients, but achieved a significantly greater decrease in DAS28 after six months of therapy.

- For this analysis, this group of patients was further subdivided into primary and secondary TNF failure. The number of previous anti-TNFs was also noted.

RA = rheumatoid arthritis; DAS = disease activity score; TNF = tumour necrosis factor.
Key findings

Of 85 seropositive patients, 63 had primary anti-TNF failure, 16 had secondary anti-TNF failure, and six had not been previously treated with anti-TNF therapy:

- There were no differences in baseline DAS28 between the two groups.
- Following treatment with rituximab, primary anti-TNF failure patients had significantly lower DAS28 scores than secondary anti-TNF failure patients.
- Only patients receiving rituximab (2 x 1000 mg) saw a statistically significant reduction in GmTSS compared with placebo plus MTX, with a 79% relative reduction in GmTSS at two years.


TNF = tumour necrosis factor; DAS = disease activity score; GmTSS = Genant-modified total Sharp score; MTX = methotrexate.
Key findings (cont’d)

- Of 85 seropositive patients, 63 had primary anti-TNF failure, 16 had secondary anti-TNF failure, and six had not been previously treated with anti-TNF therapy:
  - Patients with no prior anti-TNF therapy had the best mean DAS28 following rituximab treatment (mean ± standard deviation: 2.9 ± 0.9) and a significant reduction in DAS28 when compared with baseline (3.4).
  - There was a relationship between the lower number of anti-TNFs, and a better response to rituximab and a reduction in DAS28 scores.

TNF = tumour necrosis factor; DAS = disease activity score.

### Table 1. Primary and secondary anti-TNF failure response to rituximab

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Variable</th>
<th>Primary anti-TNF failure</th>
<th>Secondary anti-TNF failure</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive</td>
<td>Baseline DAS28</td>
<td>6.0 (0.9)</td>
<td>6.3 (1.2)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Post-treatment DAS28</td>
<td>3.8 (1.2)</td>
<td>4.5 (1.3)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Decrease in DAS28</td>
<td>2.2 (1.2)</td>
<td>1.8 (1.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Seronegative</td>
<td>Baseline DAS28</td>
<td>5.8 (0.8)</td>
<td>5.8 (0.8)</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>Post-treatment DAS28</td>
<td>5.1 (1.0)</td>
<td>5.2 (0.9)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>Decrease in DAS28</td>
<td>0.7 (1.0)</td>
<td>0.6 (1.1)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Data are shown as mean (standard deviation)

DAS28 = 28-joint disease activity score; TNF = tumour necrosis factor
<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 anti-TNF failure</th>
<th>2 anti-TNF failure</th>
<th>3 anti-TNF failure</th>
<th>No anti-TNF</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive</td>
<td>n = 28</td>
<td>n = 45</td>
<td>n = 6</td>
<td>n = 6</td>
<td></td>
</tr>
<tr>
<td>Baseline DAS28</td>
<td>6.3 (1.0)</td>
<td>6.1 (0.9)</td>
<td>5.5 (0.9)</td>
<td>6.3 (0.6)</td>
<td>0.38</td>
</tr>
<tr>
<td>Post-treatment DAS28</td>
<td>3.3 (0.8)</td>
<td>4.9 (1.3)</td>
<td>3.7 (0.6)</td>
<td>2.9 (0.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>Decrease in DAS28</td>
<td>2.7 (1.0)</td>
<td>2.1 (1.2)</td>
<td>2.0 (0.3)</td>
<td>3.4 (1.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Seronegative</td>
<td>n = 15</td>
<td>n = 32</td>
<td>n = 4</td>
<td>n = 4</td>
<td></td>
</tr>
<tr>
<td>Baseline DAS28</td>
<td>5.9 (0.7)</td>
<td>5.7 (0.9)</td>
<td>6.0 (1.1)</td>
<td>5.2 (0.5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Post-treatment DAS28</td>
<td>5.5 (0.7)</td>
<td>5.0 (1.1)</td>
<td>5.1 (0.9)</td>
<td>5.3 (0.4)</td>
<td>0.38</td>
</tr>
<tr>
<td>Decrease in DAS28</td>
<td>0.4 (0.6)</td>
<td>0.7 (1.0)</td>
<td>1.0 (1.7)</td>
<td>-0.1 (0.4)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are shown as mean (standard deviation)
DAS28 = 28-joint disease activity score; TNF = tumour necrosis factor
Key findings (cont’d)

- Of 55 seronegative patients, 32 had primary anti-TNF failure, 19 had secondary anti-TNF failure, and four had not been previously treated with anti-TNF therapy:
  - There were no differences in baseline DAS28 between the two groups.
  - Following treatment with rituximab, there were no significant differences in DAS28 or in reduction in DAS28 scores in patients with primary and secondary anti-TNF failure.

- There were no significant differences following rituximab therapy in DAS28 according to the number of prior anti-TNF drugs.

TNF = tumour necrosis factor; DAS = disease activity score.
Key conclusions

- Seropositive RA patients respond more effectively to rituximab than seronegative RA, even when matched for disease activity, disease duration, and prior treatment.

- Seropositive RA patients who have not been treated with anti-TNF therapies or have primary anti-TNF failure respond best to rituximab but even those with secondary failure had a mean decrease in DAS28 scores of 1.8.

- Additionally, the use of fewer anti-TNF drugs prior to rituximab therapy was associated with better rituximab response.


RA = rheumatoid arthritis; TNF = tumour necrosis factor; DAS = disease activity score.
Key conclusions (cont’d)

- By contrast, patients with seronegative RA had poor response to rituximab with no significant difference according to primary or secondary failure, or according to the number of anti-TNF drugs tried.


RA = rheumatoid arthritis; TNF = tumour necrosis factor.
Seropositivity, and in particular ACPA positivity is a strong predictor of response to treatment with rituximab: Pooled data from 10 European registries

Chatzidionysiou K, et al. EULAR 2011: Abstract FRI0371
Background

- Predictors of response to biologic therapy in RA are needed to achieve a more individualized therapy. To date, seropositivity has been associated with better response to rituximab.

- At EULAR 2011, Chatzidionysiou and colleagues presented their findings after assessing the three and six-month responses to the first course of RTX in RA according to RF and ACPA status.¹

- The results were presented at EULAR 2011.


EULAR = European League Against Rheumatism; RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anticitrullinated protein antibody status.
Study design

- Pooled data from 10 European registries were used in this analysis.

- The registries submitted anonymized datasets (baseline and for three- and six-month follow-up) for patients who began rituximab treatment.

- The data were pooled and analyzed using Chi-square test for comparison of categorical variables and t-test for continuous data.

- Predictors of response were identified by logistic regression analysis.
2,265 patients were included in this analysis, which included their RF and ACPA status.

Improvement in the 28-joint DAS28; measured by the ΔDAS28 at three and six months were compared amongst various subgroups of patients:

- At three and six months, ΔDAS28 was slightly better for RF-positive patients than for RF-negative patients (1.77 ± 1.38 vs. 1.6 ± 1.35, $p = 0.07$ and 1.87 ± 1.53 vs. 1.78 ± 1.49, $p = 0.4$, respectively).

- For ACPA-positive, ΔDAS28 at three and six months was significantly greater than for ACPA-negative patients (1.88 ± 1.49 vs. 1.16 ± 1.37, $p < 0.0001$ and 1.92 ± 1.58 vs. 1.38 ± 1.44, $p = 0.003$, respectively).

RF = rheumatoid factor; ACPA = anticitrullinated protein antibody status; DAS = disease activity score.
Key findings (cont’d)

• The same was true for double positive and double negative patients in that the double positive patients had significantly greater improvements in DAS28 (1.85 ± 1.46 vs. 1.05 ± 1.27, \(p < 0.0001\) and 1.93 ± 1.57 vs. 1.24 ± 1.47, \(p = 0.007\), respectively).

• ΔDAS28 at three and six months for patients who were RF- or ACPA-positive were significantly better compared with patients who were double negative (1.78 ± 1.37 vs. 1.05 ± 1.27, \(p = 0.001\) and 1.82 ± 1.56 vs. 1.24 ± \(p = 0.03\), respectively).

RF = rheumatoid factor; ACPA = anticitrullinated protein antibody status; DAS = disease activity score.
Key findings (cont’d)

- A trend to higher ΔDAS28 was observed for RF-negative, ACPA-positive patients compared with RF-positive, ACPA-negative patients at three and six months (1.89 ± 1.28 vs. 1.37 ± 1.44, \( p = 0.06 \) and 1.96 ± 1.26 vs. 1.85 ± 1.45, \( p = 0.7 \)).

- Similar results were observed when the disease activity was assessed using the EULAR good/moderate/no response criteria.

- In a univariate analysis adjusted for age and gender, ACPA-positivity (OR = 2.54, \( p = 0.002 \)) and double positivity (OR = 1.68, \( p = 0.03 \)) but not RF-positivity (OR = 1.36, \( p = 0.1 \)) predicted EULAR good response to therapy with RTX at six months after the first treatment.


RF = rheumatoid factor; ACPA = anticitrullinated protein antibody status; DAS = disease activity score; EULAR = European League Against Rheumatism; OR = overall response.
### Table 1. Patient rheumatoid factor and anti-citrullinated protein antibody status

<table>
<thead>
<tr>
<th>FR and ACPA status</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF +</td>
<td>1,507/1,949 (77.3%)</td>
</tr>
<tr>
<td>ACPA +</td>
<td>574/760 (75.5%)</td>
</tr>
<tr>
<td>Double +</td>
<td>453/530 (85.5%)</td>
</tr>
<tr>
<td>Double +</td>
<td>77/530 (14.5%)</td>
</tr>
<tr>
<td>RF +/- ACPA –</td>
<td>75</td>
</tr>
<tr>
<td>RF –/ ACPA +</td>
<td>82</td>
</tr>
</tbody>
</table>

ACPA = anti-citrullinated protein antibody; RF = rheumatoid factor
Figure 1. DAS28 reductions at three and six months for RA patient subgroups.

1A: DAS28 reductions for RF-positive vs. RF-negative patients; 1B: DAS28 reductions in ACPA-positive vs. ACPA-negative patients; 1C: DAS28 reductions in double positive vs. double negative patients; 1D: DAS28 reductions in RF-positive or ACPA-positive vs. double negative patients.

ACPA = anti-citrullinated protein antibody; ΔDAS28 = change in 28-joint disease activity score; RF = rheumatoid factor.
Key conclusions

- In this large observational cohort of RA patients treated with RTX, seropositive patients achieved significantly greater reductions in DAS28 at 3 and 6 months compared to seronegative patients.
- Baseline ACPA positivity may be a better predictor for good response to RTX than RF positivity.

RTX = rituximab; RF = rheumatoid factor; ACPA = anticitrullinated protein antibody status; DAS = disease activity score.

Retreatment with rituximab yields better clinical outcomes, especially when it is given at a fixed interval: Data from the CERERRA collaboration

Chatzidionysiou K, et al. EULAR 2011: Abstract FRI0372
Background

- Previous studies have shown that retreatment with rituximab can provide sustained efficacy in RA. Some studies have suggested that retreatment at fixed intervals is preferable over retreatment at flare, but both retreatment options are used in practice.

- Chatzidionysiou and colleagues evaluated the efficacy of retreatment with rituximab given five to seven months after the initial course of therapy, depending on whether the second course was given at a flare.

- Their findings were presented at EULAR 2011.¹


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

- Ten registries submitted anonymized data sets (baseline and at three-, six-, nine-, and 12-month follow-up) from RA patients who had started rituximab.

- Independent-sample t-tests and paired t-test were used for comparison of continuous data.

- Patients who received retreatment with rituximab at six months (±1 month) were identified as ‘retreated’:
  - Patients who received treatment at three or nine months were excluded from this analysis.
Flare was defined as any increase in the 28-joint disease activity score (DAS28) from three to six months.

Efficacy of retreatment was assessed by disease activity, reductions in DAS28 ($\Delta$DAS28), and EULAR response at six months after retreatment.
Key findings

- 2,265 patients were included in this study cohort.
- At five to seven months, 325 patients were retreated, either as fixed interval retreatment (n = 131) or at flare (n = 137).
  - The reason for retreatment was unknown in 57 patients.
- The overall cohort had a significant \( \Delta \text{DAS28} \) \( (1.8 \pm 1.6, p < 0.0001) \) at six months.
- DAS28 for retreated patients decreased from 6.4 ± 1.2 at baseline to 4.6 ± 1.4 at six months, and further decreased and remained stable to 4.3 ± 1.2 at nine and 12 months (i.e., three and six months after the second course of rituximab).

Key findings (cont’d)

- Paired analysis for ΔDAS28 at six and 12 months for retreated patients showed significant further reduction of DAS28 after retreatment (ΔDAS28 0–6 months = 1.9 ± 1.4 vs. ΔDAS28 0–12 months = 2.2 ± 1.4, \( p < 0.0001 \), \( n = 160 \)).

- The two subgroups of retreated patients (at fixed intervals and at flare) had similar DAS28 at baseline (6.5 ± 1.2 and 6.4 ± 1.1, respectively, \( p = 0.7 \)), but at the time of retreatment patients at flare had significantly higher DAS28 (5.2 ± 1.2) than the retreated patients (3.9 ± 1.2), as expected (\( p < 0.0001 \)).

DAS = Disease activity score.

Key findings (cont’d)

- At 12 months there was a trend for a larger mean ΔDAS28 for the group of patients who were retreated at fixed intervals than those retreated at flare (ΔDAS28 2.4 ± 1.4 vs. 2.0 ± 1.4 vs. 2.0 ± 1.3, p = 0.06).

- The proportion of EULAR good responders (compared with baseline) was 51.5% (34/66) for retreated patients at fixed intervals and 23.3% (17/73) for patients retreated at flare (p = 0.001).


DAS = Disease activity score; EULAR = European League Against Rheumatism.
Figure 1. DAS28 at baseline, 3, 6, 9 and 12 months for retreated and not retreated patients

$p < 0.0001$

DAS28 = 28-joint disease activity score

Figure 2. Mean change in DAS28 at 12 months after the first rituximab treatment for patients who were treated at 5–7 months on flare and not on flare.

Error bars = ± 2 standard error
DAS28 = 28-joint disease activity score

Figure 3. Proportions of patients with EULAR good or no response to rituximab treatment at 12 months compared to baseline

$p = 0.001$

EULAR = European League against Rheumatism

Key conclusions

- In this observational study, retreatment with rituximab at six months lead to significant efficacy.

- The reductions in DAS28 at 12 months were even greater than at six months, suggesting additional benefit for retreatment in patients who responded to the first course of therapy.

- Retreatment at fixed intervals (i.e., at six months in the absence of a flare) yielded better results than retreatment at the time of flare, suggesting that a treatment strategy based on fixed time intervals may be superior to an “on demand” treatment strategy.

DAS = Disease activity score.

Long-term safety profile of rituximab in RA clinical trials: Pooled analysis of up to 9.5 years follow-up of the re-treatment population

van Vollenhoven RF, et al. EULAR 2011: Abstract SAT0267
Studies have shown that retreatment with rituximab is effective for RA however the long-term safety profile remains to be defined.

At EULAR 2011, van Vollenhoven and colleagues presented the results of a pooled analysis of the long-term safety of RTX in the retreatment population.

Data for up to 9.5 years of follow-up were included in this analysis.

Study design

This study was a pooled observed case analysis of safety data from patients with moderate-to-severe, active RA who were treated with rituximab plus MTX in a global clinical trial program which included eight randomized clinical trials and two long-term open-label extension studies.

The patient populations that were analyzed included:

- All exposure (all patients exposed to rituximab), including a subset of patients with longer-term follow-up of more than five years from first exposure.
- Pooled placebo patients (patients who received placebo in placebo-controlled studies).

MTX = methotrexate.
Study design (cont’d)

- Each rituximab course consisted of either two 1,000 mg doses or two 500 mg doses (as IV infusions two weeks apart). All patients received methylprednisolone prior to each rituximab infusion, and many patients received acetaminophen and an antihistamine prior to each infusion.

- Rituximab retreatment was based on physician’s determination of clinical need and evidence of active RA (defined as either SJC and TJC ≥8 or 28-joint DAS28 ≥2.6).

- All patients received concomitant MTX at a stable dose (10–25 mg/week) and background oral corticosteroids and non-steroidal anti-inflammatory drugs were also permitted.


RA = Rheumatoid arthritis; MTX = methotrexate; SJC = swollen joint count; TJC = tender joint count; DAS = disease activity score.
Key findings

- As of September 2010, 3,194 patients had been treated with RTX, providing 11,962 PY of exposure, with up to 9.5 years follow-up and up to 17 courses of rituximab.
  - 627 patients were followed for more than five years.
- Placebo patients (n = 818) provided 1,107 PY of exposure.
- The baseline demographics and disease characteristics were comparable across populations, with the exception of a longer mean RA disease duration and a greater number (n = 3) of previous DMARDs including MTX in the sub-population of rituximab patients with more than five years of follow-up.


PY = patient years; RA = rheumatoid arthritis; MTX = methotrexate; DMARDs = disease-modifying anti-rheumatic drugs.
Key findings (cont’d)

- The rates of AEs and SAEs were comparable in the all-exposure group (including patients with more than five years of follow-up) and the placebo group.

- In rituximab patients, the most frequent AE was IRRs.
  - Most of the IRRs were grade 1 or 2 and were rarely serious.
  - The majority of IRRs occurred during the first infusion of the first course (734/3194 patients; 23.0%).

- Apart from IRR, the safety profile of rituximab was similar to that of the placebo group or general RA populations.

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

The rates of serious AEs, SAEs, and infections generally remained stable over time and multiple courses, and were stable even in patients through more than five years of follow-up.

The overall serious infection rate was 3.94 events/100 PY (3.26 events/100 PY in patients observed for more than five years), which was comparable to that observed in the placebo population (3.79 events/100 PY).

- The most frequent serious infection was pneumonia, affecting 2% of rituximab patients.
- Serious opportunistic infections were rare (0.06/100 PY in rituximab patients compared with 0.09/100 PY in the placebo group).


AEs = adverse events; SAEs = serious adverse events; PY = patient years.
Key findings (cont’d)

- There was no evidence of an increased risk of malignancy over time or course.
- The rate of myocardial infarction (0.41 events/100 PY) was consistent with rates in the general RA population (0.48–0.59 events/100 PY).


PY = patient years; RA = rheumatoid arthritis.
Figure 1. Incidence of infusion-related reactions by infusion course (all exposed population)

Key conclusions

- Long-term safety data from 3,194 RA patients treated with rituximab in clinical trials with 11,962 PY of exposure over 9.5 years of follow-up, demonstrate that rituximab remained well tolerated over time and over multiple courses.

- No new safety signals were observed with increasing duration of exposure and rituximab treatment, including in 627 patients with more than five years of follow-up (4,418 PY).

- The overall safety profile of rituximab remains similar to that of the pooled placebo population and consistent with published data for moderate-to-severe RA.
Safety of rituximab in patients with RA and Concomitant Lung Disease

Background

- A variety of lung diseases are more common in patients with RA including ILD and infectious conditions.
- These may be considered contraindications to or cause toxicity in patients receiving DMARDs or anti-TNF agents.
- Therefore, many of these patients may be treated with rituximab.
- The safety of rituximab in lung disease in RA has not been fully assessed and such patients are often excluded from clinical trials.

RA = rheumatoid arthritis; ILD = interstitial lung disease; DMARDs = disease-modifying anti-rheumatic drugs; TNF = tumour necrosis factor.
Background (cont’d)

- At EULAR 2011, Dass and colleagues presented their findings from an observational study aimed to evaluate the safety of patients with RA and lung disease who received rituximab.

Study design

- The records of patients who received rituximab for RA were reviewed and patients with lung disease prior to receiving rituximab were identified.

- Patients underwent CT scanning and pulmonary function tests at the time of diagnosis of lung disease.

- All patients were treated with two infusions of rituximab (1,000 mg) with methylprednisolone.
  - Treatment was repeated upon return of RA disease activity, but not at less than six monthly intervals.

- Data were recorded on type of lung disease, mortality, and serious respiratory infections (i.e., those necessitating hospital admissions or intravenous antibiotics).
Key findings

- Between 2004 and 2010, 347 patients received rituximab for RA.
- 67 patients (19.3%) had lung disease when treatment with rituximab was initiated and 34 of these (50.7%) received at least two cycles of rituximab.
  - Forty-eight patients (71.6%) had ILD
  - Fourteen patients had COPD
  - Five patients had bronchiectasis
  - Two patients had previous pulmonary emphysema
- The total follow-up duration was 173.5 PY; median 2.36, range: 0.65–6.58 years).

ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; PY = patient years.
Key findings (cont’d)

- After rituximab therapy, three deaths were recorded (two patients with ILD, one patient with COPD).
- The causes of death were:
  - Infective exacerbation of COPD (12 months after the third cycle of RTX)
  - Pneumonia and possible acute progression of ILD—clinical and CT changes attributable to either condition were observed (four weeks after the first cycle of rituximab)
  - Suicide (three months after first cycle of rituximab)
- Three patients had single episodes of serious respiratory tract infection.

ILD = interstitial lung disease; COPD = chronic obstructive pulmonary disease; CT = computed tomography.
Key conclusions

- No definite new significant safety signals were observed beyond which might be expected in this patient population (longstanding severe RA and concomitant lung disease).
- However, it was noted that one death occurred due to respiratory deterioration relatively soon after rituximab administration.
- Analysis of follow-up respiratory function and high resolution CT (HRCT) data is in progress, as is an ongoing safety review.

Long-term efficacy and safety results of rituximab in ANCA-associated vasculitis

Specks U and Stone JH. EULAR 2011: Abstract OP0054
Background

- Rituximab is equally as effective as conventional CYC therapy for remission induction in severe ANCA-associated vasculitis and it is a superior therapy for patients with relapsed disease.¹

- The long-term efficacy and safety of rituximab therapy remains unknown.

- At EULAR 2011, Specks and Stone presented their findings from a study evaluating the efficacy and safety of one course of rituximab compared with CYC followed by AZA over 18 months.²

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CYC = cyclophosphamide; ANCA = antineutrophil cytoplasmic antibody; AAV = associated vasculitis; EULAR = European League Against Rheumatism; AZA = azathioprine.
Study design

- This study was a multicentre, randomized, double-blind, placebo-controlled trial.
- Patients were randomized to receive rituximab (375 mg/m² IV weekly x 4) or CYC (2 mg/kg/day po).
- Remission was assessed at six months but patients were followed for a minimum of 18 months to gauge long-term responses and the effect of rituximab on immune tolerance.
- Patients received methylprednisolone followed by prednisone, tapered over 5.5 months.

Key findings

- CYC was replaced by AZA between months 3 and 6 if remission was achieved, and AZA was continued through 18 months.
- The rituximab group received placebo after three to six months if remission was achieved.
- The primary outcome of the trial was complete remission at six months.
Key findings (cont’d)

- 197 ANCA-positive patients were enrolled.
- The mean follow-up was 35 months (SD, 14.6).
- The primary outcome at six months (BVAS/WG of 0 and no prednisone use) was achieved by 64% of the rituximab patients compared with 53% in the CYC arm ($p = 0.13$).
- At 12 and 18 months, there were no significant differences in the number of patients in remission and off glucocorticoids.
Key findings (cont’d)

• At 12 months, 42% of patients in the rituximab arm vs. 38% in the CYC arm were in remission and free of glucocorticoids.

• At 18 months, 36% of patients in the rituximab arm vs. 31% in the CYC arm were in remission and free of glucocorticoids.

□ The number of patients suffering at least one flare, and the flare rates did not differ between treatment arms over 18 months.

□ Relapses were more common among PR3-ANCA positive patients than MPO-ANCA positive patients.


CYC = cyclophosphamide; ANCA = antineutrophil cytoplasmic antibody; PR3 = proteinase 3; MPO = myeloperoxidase.
Key findings (cont’d)

- There were no differences in the rate and frequency of overall adverse events and serious adverse events, deaths (two in each treatment arm), infections, and malignancies between the two treatment arms at 18 months.

Table 1. Disease flares at 12 and 18 months

<table>
<thead>
<tr>
<th></th>
<th>Severe disease flares</th>
<th>Limited disease flares</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RTX (n = 99)</td>
<td>CYC-AZA (n = 98)</td>
</tr>
<tr>
<td>12 months</td>
<td>14 (12)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>18 months</td>
<td>22 (19)</td>
<td>23 (21)</td>
</tr>
</tbody>
</table>

Results are expressed as cumulative number in patients (number of patients with at least one flare).
Flares following cross-over, open-label treatment with RTX or best medical judgment are excluded from this analysis.
CYC-AZA = cyclophosphamide-azathioprine; RTX = rituximab.
Key conclusions

- In patients with severe AAV, a single course of rituximab is as effective as 18 months of standard therapy of CYC followed by AZA for remission induction and maintenance.
- Ongoing studies may aid in more precisely defining which patients need to be retreated and when.