Efficacy and Safety of Rituximab in the Treatment of Rheumatoid Arthritis and ANCA-associated Vasculitis
Multiple courses of rituximab produce sustained efficacy in RA patients with an inadequate response to one or more TNF inhibitors (Keystone E, et al. ACR/ARHP 2010: Abstract 321)


Rituximab maintenance therapy for relapsed Wegener's granulomatosis and microscopic polyangiitis (Roubaud-Baudron C, et al. ACR/ARHP 2010: Abstract 2041)
Multiple courses of rituximab produce sustained efficacy in RA patients with an inadequate response to one or more TNF inhibitors

Background

- At ACR/ARHP 2010, Keystone and colleagues presented data from a pooled analysis of efficacy data collected from RA patients with a prior IR to TNF inhibitors who were treated with repeat courses of rituximab during open-label extensions of several international double-blind clinical trials.
Patients with active RA and a prior IR to a TNF inhibitor were recruited into the following phase II or III international clinical trials with rituximab: REFLEX/WA17531, DANCER, WA16291, WA16855, MIRROR, SIERRA, and SUNRISE.1–7

Eligibility for open-label re-treatment included active disease, defined as either ≥8 SJC/TJC or DAS28 ≥2.6, and a response to the first or second course of rituximab, defined as at least 20% reduction in SJC and TJC.

In the majority of studies, re-treatment occurred at a minimum interval of 24 weeks for the second course and 16 weeks for subsequent courses, based on patients having significant inflammation (both SJC and TJC ≥8) and at the discretion of the treating physician.


DAS28 = 28-joint disease activity score
IR = inadequate response; RA = rheumatoid arthritis
SJC = swollen joint count; TJC = tender joint count
TNF = tumour necrosis factor
Each course of rituximab consisted of 2 x 500 mg or 2 x 1000 mg, given as IV infusions 2 weeks apart, with concomitant MTX (10–25 mg/week) at a stable dose.

Prior to infusion with rituximab, patients received prophylactic treatment with methylprednisolone (100 mg IV), and were permitted to receive additional background NSAIDs.

Disposition, demography, and safety analyses were based on all available data using both doses, but efficacy data analyses were limited to patients who received a rituximab dose of 2 x 1000 mg.
Study design (cont’d)

- Patients from the SIERRA and SUNRISE studies were not included for efficacy data analyses due to incompatible study designs.
- All data were observed, with no imputation methods applied.
- All responses, together with mean changes, were calculated from the first treatment course baseline.
- Efficacy data per course were presented for the following populations:
  - Within patient, within visit (WW): data for patients who received at least 5 courses of rituximab and had efficacy data at week 24 after each course; the number of patients was constant over courses/visits in this analysis;
  - All patients, all visits, all courses (observed population): all data available at a given time point were presented; the number of patients decreased over courses/visits in this analysis.

Key findings

Baseline characteristics and disposition

- Of the 1,324 TNF-IR patients exposed to at least one course of rituximab, 595 patients (44.9%) were exposed to at least one course of rituximab (2 x 1000 mg) in the long-term efficacy TNF-IR population.
- A total of 500 patients (37.7%) had evaluable efficacy assessments at week 24 following the first course.
- The majority of withdrawals occurred during the first two courses of treatment, principally for non-safety reasons.
- A large number of patients did not receive >1 or >2 courses as they completed treatment in the SIERRA and SUNRISE studies.
- A total of 79 patients withdrew over five courses of rituximab due to adverse events (AEs), with no further patients withdrawing because of AEs after this.
- Most withdrawals due to AEs occurred during the first treatment course and decreased with subsequent courses.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TNF-IR patients (n = 1324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>81</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.9 (± 11.55)</td>
</tr>
<tr>
<td>RA disease duration (years)</td>
<td>11.49 (± 8.39)</td>
</tr>
<tr>
<td>Median number of prior DMARDs (excluding MTX)</td>
<td>3.00</td>
</tr>
<tr>
<td>Median number of previous biologic DMARDs</td>
<td>1.00</td>
</tr>
<tr>
<td>Swollen joint count (66 joints)</td>
<td>22.9 (± 12.6)</td>
</tr>
<tr>
<td>Tender joint count (68 joints)</td>
<td>34.6 (± 15.74)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>3.41 (± 3.69)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR; mm/h)</td>
<td>46.9 (± 25.48)</td>
</tr>
<tr>
<td>DAS28-ESR</td>
<td>6.88 (± 1.00)</td>
</tr>
<tr>
<td>HAQ-DI</td>
<td>1.86 (± 0.60)</td>
</tr>
</tbody>
</table>

*DAS28 = 28-joint disease activity score; DMARD = disease-modifying anti-rheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = health assessment questionnaire-disability index; MTX = methotrexate; RA = rheumatoid arthritis; TNF-IR = inadequate response to tumour necrosis factor inhibitor*
Key findings (cont’d)

Efficacy

▪ The proportion of patients in the WW or observed population with ACR20/50/70 responses was sustained over multiple courses of treatment.

▪ EULAR responses showed a similar trend to those seen for ACR responses over multiple courses.

▪ The proportion of patients with DAS28-ESR low disease activity and DAS28 remission mirrored EULAR and ACR responses.

▪ The proportion of patients in DAS28 remission doubled between the first and fifth courses.

ACR = American College of Rheumatology (score)
DAS28 = 28-joint disease activity score
ESR = erythrocyte sedimentation rate
EULAR = European League Against Rheumatism (score)
Figure 1. ACR response 24 weeks after each course of rituximab in the within patient, within visit long-term efficacy (2 x 1000 mg) TNF-IR population

Key findings (cont’d)

- Similar trends were seen in the WW population for EULAR responses and DAS28 low disease activity and remission.

- Improvements in physical function were maintained in the observed population receiving repeated courses of rituximab (2 x 1000 mg), indicated by mean change in HAQ-DI scores and the proportions of patients achieving MCID decreases of $\geq 0.22$ or $\geq 0.5$.

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DAS28 = 28-joint disease activity score  
HAQ-DI = health assessment questionnaire-disability index  
EULAR = European League Against Rheumatism (score)  
MCID = minimal clinically important difference
Figure 2. EULAR response 24 weeks after each course of rituximab in the within patient, within visit long-term efficacy (2 x 1000 mg) TNF-IR population.

Figure 3. DAS28-ESR low disease activity and remission 24 weeks after each course of rituximab in the within patient, within visit long-term efficacy (2 x 1000 mg) TNF-IR population.
### Table 2. HAQ-DI response 24 weeks after each course in TNF-IR patients receiving 2 x 1000 mg rituximab (all observed data)

<table>
<thead>
<tr>
<th></th>
<th>Course 1</th>
<th>Course 2</th>
<th>Course 3</th>
<th>Course 4</th>
<th>Course 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ-DI (n) Mean change (SD)</td>
<td>499 -0.45 (0.55)</td>
<td>364 -0.48 (0.57)</td>
<td>286 -0.52 (0.59)</td>
<td>219 -0.52 (0.60)</td>
<td>148 -0.54 (0.63)</td>
</tr>
<tr>
<td>MCID (%) HAQ-DI decrease ≥0.22</td>
<td>65.5</td>
<td>65.4</td>
<td>67.1</td>
<td>68.0</td>
<td>66.9</td>
</tr>
<tr>
<td>HAQ-DI decrease ≥0.5</td>
<td>43.3</td>
<td>44.0</td>
<td>45.8</td>
<td>47.0</td>
<td>47.3</td>
</tr>
</tbody>
</table>

Note: Median time between courses in weeks: 1st and 2nd 44.2; 2nd and 3rd 49.9; 3rd and 4th 50.1; 4th and 5th 44.1.

HAQ-DI = health assessment questionnaire-disability index; MCID = minimal clinically important difference; SD = standard deviation; TNF-IR = inadequate response to tumour necrosis factor inhibitor
Key findings (cont’d)

Safety

- Safety over repeat courses did not show any unexpected findings, with consistent rates of infection and serious infection.*
- In 3,786.49 pt-yrs of observation in all TNF-IR patients (both doses), the overall rates of SAEs was 20.10/100 pt-yrs, and the overall rate of serious infection events was 5.57/100 pt-yrs.

*Safety data for rituximab by course are shown in van Vollenhoven FR, et al. ACR/ARHP 2010: Abstract 391 (following)
Key conclusion

- In TNF-IR patients with an initial response to rituximab, repeated courses of rituximab were associated with sustained levels of efficacy.


IR = inadequate response; TNF = tumour necrosis factor
Long-term safety of rituximab: follow-up of the rheumatoid arthritis clinical trials and re-treatment population

van Vollenhoven RF, et al. ACR/ARHP 2010: Abstract 391
Background

- At ACR/ARHP 2010, van Vollenhoven and colleagues presented safety data, including AEs and infections, from several global clinical trials of RA patients treated with repeat courses of rituximab after a previous inadequate response to MTX and/or to a TNF inhibitor.


AE = adverse event; MTX = methotrexate
RA = rheumatoid arthritis; TNF = tumour necrosis factor
Study design

- Safety data for this observed case analysis were pooled from RA patients treated with rituximab plus MTX in eight randomized controlled clinical trials and two long-term open-label extensions, including the phase II (IIa) DANCER and SIERRA trials, and the phase III REFLEX, SUNRISE, SERENE, and IMAGE trials.\(^1\)–\(^8\)

- Patients who received placebo in placebo-controlled study periods were pooled to provide a placebo population.

- Repeat treatment with rituximab was based on physician decision of clinical need; criteria for re-treatment included assessment of active disease, defined as either a SJC and TJC ≥8, or a DAS28 ≥2.6.

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DAS28 = 28-joint disease activity score
MTX = methotrexate; RA = rheumatoid arthritis
SJC = swollen joint count; TJC = tender joint count
Study design (cont’d)

- The all-exposure population consisted of all patients exposed to rituximab and included a subset of patients with longer term follow-up of >5 years from first exposure who, in many cases, had received multiple repeat treatment.

- Each rituximab course consisted of IV infusions of either 2 x 500 mg or 2 x 100 mg, given two weeks apart with concomitant MTX (10–25 mg/week) at a stable dose.

- Prior to each infusion with rituximab, patients received methylprednisolone (100 mg IV) and, in some cases, additional oral corticosteroids (≤10 mg/day prednisone or equivalent). NSAIDs were also permitted, depending on the study.

Key findings

Patient characteristics and demographics

- As of September 2009, a total of 3,189 patients had been treated with rituximab providing 9,342 pt-yrs of exposure.
- More than 1,500 patients were followed for >3 years and 587 patients for >5 years, with 1724, 1392, 1036, and 656 patients receiving ≥3, ≥4, ≥5, and ≥6 courses, respectively.
- The analysis included >9 years of follow-up with up to 15 courses of rituximab.
- The pooled placebo population consisted of 818 patients providing placebo exposure of 979 pt-yrs.


pt-yrs = patient years
Key findings (cont’d)

- Baseline demographics and disease characteristics of patients in the all-exposure population, patients with long-term (>5 years) follow-up, and the placebo population were comparable.

- The mean RA disease duration was notably longer in the patient group with >5 years follow-up, compared with the all-exposure and placebo populations (11.13 years versus 8.3 and 7.1 years, respectively).
  - Patients in this subset had received an average of three previous DMARDs, excluding MTX.

DMARD = disease-modifying anti-rheumatic drug
MTX = methotrexate; RA = rheumatoid arthritis

Key findings (cont’d)

Overall adverse events

- Other than IRRs, the overall rates of AEs, SAEs, and serious infections in the long-term population (>5 years follow-up) were comparable to the all-exposure and placebo populations.

- In the all-exposure population, the AE rate over time was highest during the first 6 months after the first rituximab infusion.

- The high AE rate was due partly to IRRs in 733 patients (23%), the majority of which were grade 1/2 and occurred primarily during the first infusion of the first treatment course; this incidence was reduced to 0%–12% for subsequent infusions.
### Table 1. Summary of adverse events and infection rates in all safety populations

<table>
<thead>
<tr>
<th></th>
<th>All exposure (n = 3189) 9342 pt-yrs</th>
<th>Long-term (&gt;5 years) (n = 587) 3386 pt-yrs</th>
<th>Pooled placebo (n = 818) 979 pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AE rate/100 pt-yrs</strong></td>
<td>309.4 (305.9–313.0)</td>
<td>285.1 (279.5–290.9)</td>
<td>353.1 (341.5–365.0)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SAE rate/100 pt-yrs</strong></td>
<td>16.2 (15.4–17.0)</td>
<td>15.5 (14.2–16.9)</td>
<td>15.5 (13.2–18.2)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infection rate/100 pt-yrs</strong></td>
<td>94.3 (92.3–96.3)</td>
<td>83.2 (80.2–86.3)</td>
<td>100.8 (94.7–107.3)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Serious infection rate/100 pt-yrs</strong></td>
<td>4.35 (3.94–4.79)</td>
<td>3.19 (2.64–3.85)</td>
<td>4.29 (3.17–5.80)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**AE** = adverse event; **CI** = confidence interval; **pt-yrs** = patient-years; **SAE** = serious adverse event
Figure 1. Rate of all adverse events in all patients per 100 patient-years

AE = adverse event; pt-ys = patient-years; SAE = serious adverse event
Figure 2. Incidence of infusion-related reactions by treatment course

Key findings (cont’d)

- Serious IRRs were reported in 17 patients (0.5%), with eight of the IRRs reported during the first infusion of the first course; no grade 4 IRRs or deaths due to IRRs were observed.

- The most common SAEs (occurring in ≥1% of patients) were exacerbations of RA (n = 66; 2%), pneumonia (n = 52; 2%), falls (n = 47; 1%), and myocardial infarction (n = 33; 1%).


IRR = infusion-related reaction
SAE = serious adverse event
Key findings (cont’d)

Infections

- The overall serious infection rate in the all-exposure population was 4.35 events/100 pt-yrs, which was comparable to the 4.29 events/100 pt-yrs observed in the pooled placebo population; patients with long-term follow-up had a rate of 3.19 events/100 pt-yrs.

- Serious opportunistic infections were rare in the all-exposure population, with a rate similar to that of the placebo population (0.04/100 pt-yrs versus 0.1/100 pt-yrs).

- The most frequent serious infections in the all-exposure population were of the lower respiratory tract, predominantly pneumonia (2%).

- The rate of serious infection generally remained stable over time and over multiple courses of rituximab treatment; the numerically higher rate at course 5 was not seen at course 6.


pt-yrs = patient-years
Figure 3. Rate of serious infections over time in all patients per 100 patient-years

Figure 4. Rate of serious infections per 100 patient-years by treatment course

Key findings (cont’d)

Viral hepatitis

- No cases of hepatitis B reactivation were observed in the rituximab RA clinical development program; transient rises in HBV DNA were observed in 5/130 HBcAb positive patients.
- AEs, SAEs, and liver function test abnormalities were consistent with those in the all-exposure population, and there were no liver-related SAEs.

Tuberculosis

- In the clinical trial safety database, there were two cases of pulmonary TB, both treated with anti-TB medication.
- No cases of extra-pulmonary TB, atypical mycobacterial infection, or multi-drug resistant TB cases were reported.

Key findings (cont’d)

Herpes family of viruses

- In the all-exposure population, there were 102 AEs of herpes zoster reported in 94 patients, including two events of ophthalmic herpes zoster; five of these events were SAEs.
- In the placebo population, 12 AEs of herpes zoster were reported.
- The rate of herpes zoster (10.9 events/1000 pt-yrs) was consistent with the placebo population (12.3 events/1000 pt-yrs) and the general RA population (11.5 events/1000 pt-yrs).


AE = adverse event; pt-yrs = patient-years
RA = rheumatoid arthritis; SAE = serious adverse event;
Key findings (cont’d)

Cardiovascular events

- Myocardial infarction (MI) was the most frequent cardiac AE (46 patients, 1%) in the all-exposure population.
- Most patients who experienced MI had at least one conventional risk factor for MI (such as prior MI, coronary artery disease, hypertension, diabetes, or smoking).
- Rates of MI (0.49 events/100 pt-yrs) and stroke (0.25 events/100 pt-yrs) in the all-exposure population were consistent with rates observed in the placebo population and with epidemiological data from the general RA population.

Malignancies

- The rate of confirmed malignancies (excluding non-melanoma skin cancers) in the all-exposure population was (0.82 events/100 pt-yrs, n = 77), which is comparable with epidemiological data from the general RA population.

- As expected in a predominately female study population, the most frequently reported malignancy was breast cancer (SIR 0.63, 95% CI: 0.34–1.08), which is consistent with the general RA population.
Key conclusions

- Rituximab has remained well tolerated over time and over multiple courses, with a safety profile similar to that of the pooled placebo population and consistent with published data on patients with moderate-to-severe RA.

- In long-term follow-up of RA patients treated with rituximab in clinical trials, no new safety signals were observed in all exposed patients or in patients with >5 years follow-up.

- The serious infection rate was similar to previous analyses and generally remained stable over time and over multiple courses; the serious opportunistic infection rate was low and was comparable to the pooled placebo population.

- The long-term safety profile of rituximab is similar to that observed in the placebo population; rates of infection, MI, stroke, and malignancies are consistent with those observed in epidemiological data from other RA cohorts.

Rituximab versus a second TNF inhibitor in the treatment of RA patients after failure of a first TNF inhibitor

Background

- Treatment with biologics has led to a fundamental change in therapy for RA. A significant proportion of patients, however, still do not respond sufficiently to therapy with a first TNF inhibitor.

- Switching to a second TNF inhibitor rather than a second generation biologic, such as rituximab, remains a matter of debate as to which option is superior.

- At ACR/ARHP 2010, Kekow and colleagues presented data from their retrospective observational cohort study comparing the efficacy of one course of rituximab to a second TNF inhibitor in RA patients with one previous inadequate response to a TNF inhibitor.
Study design

- This analysis was a multicentre, non-interventional, retrospective cohort study with a mean observation period of 6.6 months (median 6.3, range: 1.6–20.8) after initiation of a second biologic.

- The study population consisted of 196 patients (77% females) with active RA (DAS28 $\geq 3.2$), despite TNF inhibitor treatment.

- Of the 196 patients, 90 (45.9%) were treated with rituximab (2 x 1000 mg), while 106 (54.1%) received a second TNF inhibitor.

- Of the 196 patients, 156 patients were found to be sero-positive for RF, 132 were sero-positive for CCP antibodies, and 23 were sero-negative.
Key findings

Baseline characteristics and disposition

- The rituximab cohort was comparable to the TNF inhibitor cohort with regard to:
  - age (56.6 years ± 11.1 versus 57.4 years ± 13.1);
  - duration of disease (10.0 years ± 7.8 versus 9.7 years ± 7.6);
  - DAS28 (5.6 ± 1.0 versus 5.4 ± 1.0);
  - concomitant DMARD therapy (77.8% versus 77.4%) at initiation of second treatment (baseline).

- In the second TNF inhibitor cohort, 47 patients (44.3%) received etanercept, 43 patients (40.6%) were given adalimumab, and 16 (15.1%) were treated with infliximab.
Key findings (cont’d)

Efficacy

- After 6.6 months of treatment, the rituximab cohort had a significantly greater mean DAS28 reduction compared to the TNF inhibitor group: –1.64 (95% CI: –1.92, 1.36) versus –1.19 (95% CI: –1.42, –0.96) (p = 0.01).

- The difference in mean DAS reduction was similar in the subgroup of patients sero-positive for RF (n = 156), with a mean reduction of –1.66 (95% CI: –1.98, –1.34) in the rituximab group versus –1.17 (95% CI: –1.43, –0.91) in the TNF inhibitor group (p = 0.02).

- The cohort difference was more pronounced in the subgroup sero-positive for anti-CCP antibodies (n = 132), with a significant improvement in DAS28 in the rituximab group of –1.75 (95% CI: –2.07, –1.43) compared to –1.06 (95% CI: –1.34, –0.78) in the TNF inhibitor group (p <0.01).

Figure 1. Mean reduction in DAS28 from baseline to end of observation in all patients following treatment with rituximab or a second TNF inhibitor.

CCP = cyclic citrullinated peptide; DAS28 = 28-joint disease activity score; RF = rheumatoid factor; TNF = tumour necrosis factor.
Key findings (cont’d)

- With regard to TJC, a significant cohort difference was noted in the anti-CPP positive subgroup favouring rituximab: –5.28 (95% CI: –6.78, –3.79) versus –3.06 (95% CI: –4.28; –18.5), \( p = 0.02 \).

- A numerical cohort difference in improvement of SJC favouring rituximab was also seen in the anti-CCP positive subgroup: rituximab –3.67 (95% CI: –4.99, –2.35) versus TNF inhibitor –2.94 (95% CI: –4.06, –1.81) (\( p = 0.40 \)).

- Results from the 23 sero-negative patients also favoured rituximab, but this difference was not significant.

- More rituximab than TNF inhibitor patients reached moderate/good EULAR response (82.2% versus 71.7%, \( p = 0.14 \)), with a significant difference in the CCP subgroup (85.3% versus 67.2%, \( p = 0.01 \)).


CI = confidence interval; CCP = anti-cyclic citrullinated peptide
DAS28 = 28-joint disease activity score; RA = rheumatoid arthritis
EULAR = European League Against Rheumatism (score)
RF = rheumatoid factor; TJC = tender joint count
TNF = tumour necrosis factor; SJC = swollen joint count
Figure 2. EULAR response at end of observation in all patients treated with rituximab or a second TNF inhibitor

Figure 3. EULAR response at end of observation in anti-CCP positive patients treated with rituximab or a second TNF inhibitor

Key findings (cont’d)

Safety

- Safety data were collected from 124 patients in the rituximab cohort and 123 patients in the TNF inhibitor cohort.

- Adverse events suspected to be related to treatment occurred in 12 patients: 7 patients (5.6%) in the rituximab cohort (14 AEs, with 1 patient having 3 different events) and 5 patients (4.1%) in the TNF inhibitor cohort (5 AEs, 1 event each).

- No SAEs occurred during the complete observation period.
Key conclusions

- Study results indicate that treatment with rituximab is clinically superior to a second TNF inhibitor therapy in RA patients after failure of the first TNF inhibitor, as reflected in clinically significant improvement in DAS28 scores, especially in patients sero-positive for antibodies to CCP.

- Results from this real-life retrospective study confirm the REFLEX study findings, which demonstrated the efficacy of rituximab in RA patients after failure of a TNF inhibitor.

- The study also supports the idea that anti-CCP antibodies may be a useful predictive biomarker for response to rituximab in patients with TNF inhibitor failure.


CCP = anti-cyclic citrullinated peptide
DAS28 = 28-joint disease activity score
RA = rheumatoid arthritis
TNF = tumour necrosis factor
Rituximab versus cyclophosphamide for generalized ANCA-associated vasculitis: RITUXVAS two-year follow-up

Jones RB, et al. ACR/ARHP 2010: Abstract 676
Background

- Early data from the RITUXVAS trial, which compared rituximab with a cyclophosphamide regimen for newly diagnosed ANCA-associated renal vasculitis (AAV), demonstrated that rituximab is just as effective as cyclophosphamide for the treatment of AAV.1

- At the ACR/ARHP 2010, Jones and colleagues presented updated results from a two-year follow-up of the RITUXVAS trial.2


ANCA = anti-neutrophil cytoplasmic antibody
Study design

- RITUXVAS was an international, randomized, controlled, prospective, open phase II/III trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine regimen in the treatment of active, generalized AAV.

- Forty-four (44) patients with newly diagnosed AAV and renal involvement were randomly assigned in a 3:1 ratio to rituximab or control groups.
  - Both groups received a standard glucocorticoid regimen.
Study design (cont’d)

- **Induction regimen:**
  - The rituximab group \((n = 33)\) received rituximab, 375 mg/m\(^2\) body-surface area per week for 4 weeks, with 2 intravenous cyclophosphamide pulses.
  - The control group \((n = 11)\) received intravenous cyclophosphamide for 3 to 6 months, followed by azathioprine.

- **Remission maintenance regimen:**
  - Cyclophosphamide was switched to azathioprine after 3–6 months, when remission \((BVAS = 0\) for 2 months\) was achieved.
  - Azathioprine was continued until trial end.
  - Prednisone 5 mg/day was given to patients in both groups up until month 18.


BVAS = Birmingham vasculitis activity score
RITUXVAS study design

44 AAV patients:
- newly diagnosed
- renal involvement
- ANCA positivity

Randomized
3:1

**Rituximab group**
(n = 33)
- rituximab: 375 mg/m² x 4
- cyclophosphamide: 15 mg/kg IV x 2
- methylprednisolone: Ig IV
- prednisolone PO

Remission/maintenance: continue on oral steroids as per protocol

**Cyclophosphamide (control) group**
(n = 11)
- IV cyclophosphamide (min. 3 months, max. 6 months)
- methylprednisolone: Ig IV
- prednisolone PO

Remission/maintenance: azathioprine: 2 mg/kg

Trial end at 2 years

**Analyses:**
- 6 weeks: initial response evaluation;
- 6 months: efficacy/safety evaluation;
- 24 months: trial end and efficacy/safety evaluation
Study design (cont’d)

- The median age of patients in this study was 68 years.
- GFR was 18 mL/minute/1.73 m² body-surface area.
- The main study outcomes were sustained remission (defined as BVAS = 0 at 6 months and sustained for 6 months) and SAEs.
- Secondary outcomes included change in GFR, all adverse events, prednisolone cumulative dose, and cyclophosphamide cumulative dose.
- Correlation of B cells with disease activity, change in ANCA and disease activity, and histopathology predictors of outcome were also studied.

Key findings

Primary outcomes

- At two years, there were no significant differences in primary outcomes between the two groups:
  - Relapse: 26% rituximab-treated versus 20% cyclophosphamide-treated patients, \( p = 0.82 \);
  - SAEs: 42% rituximab-treated versus 36% cyclophosphamide-treated patients;
  - End-stage renal failure: 6% rituximab-treated versus 0% cyclophosphamide-treated patients, \( p = 0.57 \);
  - Death: 18% rituximab-treated versus 27% cyclophosphamide-treated patients, \( p = 0.62 \).


SAE = serious adverse event
Table 1. Two-year outcomes for newly diagnosed AAV patients treated with rituximab versus cyclophosphamide

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rituximab group (n = 33) (%)</th>
<th>Cyclophosphamide group (n = 11) (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>42</td>
<td>36</td>
<td>–</td>
</tr>
<tr>
<td>Infections</td>
<td>39</td>
<td>21</td>
<td>–</td>
</tr>
<tr>
<td>Death</td>
<td>18</td>
<td>18</td>
<td>0.62</td>
</tr>
<tr>
<td>Relapse</td>
<td>26</td>
<td>20</td>
<td>0.82</td>
</tr>
<tr>
<td>major relapse</td>
<td>3</td>
<td>18</td>
<td>0.82</td>
</tr>
<tr>
<td>minor relapse</td>
<td>18</td>
<td>0</td>
<td>0.82</td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td>6</td>
<td>0</td>
<td>0.57</td>
</tr>
</tbody>
</table>

AAV = ANCA-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody
Key findings (cont’d)

Secondary outcomes:

- Median estimated GFR was 20 mL/min/m$^2$ with rituximab versus 16 mL/min/m$^2$ with cyclophosphamide.
- No significant difference in the AE incidence was seen between the two groups.
- By 24 months, 21% rituximab-treated and 18% cyclophosphamide-treated patients had withdrawn from prednisolone.
- Effective depletion of CD20 B cells was seen with rituximab.


AE = adverse event
GFR = glomerular filtration rate
Figure 1. Change in glomerular filtration rate in newly diagnosed AAV patients treated with rituximab versus cyclophosphamide

AAV = ANCA-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody; GFR = glomerular filtration rate

Figure 2. Change in detectable peripheral blood B cells in newly diagnosed AAV patients treated with rituximab versus cyclophosphamide

AAV = ANCA-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody
Key conclusion

- Rituximab-based induction appears efficacious for patients with AAV and is non-inferior to intravenous cyclophosphamide at two years in terms of combined relapse, mortality, and end-stage renal failure outcome.


AAV = ANCA-associated vasculitis
Rituximab maintenance therapy for relapsed Wegener's granulomatosis and microscopic polyangiitis

Background

- Rituximab has been shown to effectively induce remission for first relapses and refractory disease in ANCA-associated vasculitis (AAV).\(^1\)

- At ACR/ARHP 2010, Roubaud-Baudron and colleagues reported findings from their retrospective analysis of rituximab efficacy and safety as maintenance therapy in AAV.\(^2\)


ANCA = anti-neutrophil cytoplasmic antibody
Study design

- Patients with AAV registered in the database of the National Referral Centre for Necrotizing Vasculitides and Systemic Sclerosis in Paris, France, who had received ≥2 rituximab maintenance infusions, regardless of induction regimen, between 2003 and 2010 were selected.

- Main clinical characteristics and outcomes were analyzed, as well as rituximab tolerance.
Key findings

- Four MPA and 24 WG patients were included in the analysis.
  - Median age was 55.5 years (range: 18–78 years); 17 patients (61%) were men.
  - Median disease duration was 71 months (range: 0–222 months).
- Follow-up as of November 2010 was 38 months (range: 21–97 months) from last relapse.
Key findings (cont’d)

- Relapses:
  - The cumulative median cyclophosphamide dose was 48 g (range 10–250 g).
  - At last relapse, patients had several organ involvements: 19 ENT, 17 lung, 11 arthralgias, 11 fever, 9 nephropathy, 3 neuropathy and/or 4 eyes.

- Induction treatment:
  - Induction treatment was rituximab for 21 patients, conventional corticosteroids plus cyclophosphamide for 5 patients, and IV Ig for 2 patients (1 patient was also treated with MTX).
Key findings (cont’d)

- Maintenance treatment:
  - Rituximab maintenance was as follows: 375 mg/m² biannually for 13 patients, 1 g biannually for 4 patients, 1 g yearly for 3 patients, and different regimens for 8 other patients.
  - Median number of rituximab maintenance infusions was 4 (range: 2–10).
  - PR3-ANCA levels significantly decreased under maintenance rituximab in 19 patients.
  - Total Ig levels decreased with rituximab treatment in 18 patients (decrease of Ig 7.78 ± 2.5 versus 6.97 ± 1.9, \( p = 0.041 \)).
  - At last evaluation of 21 patients, there was a decrease in IgM in 15 patients and a decrease in IgG in 12 patients.
Figure 1. PR3-ANCA levels after rituximab maintenance treatment

AAV = ANCA-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody; PR3 = proteinase-3

Figure 2. Gammaglobulin levels after rituximab maintenance treatment

AAV = ANCA-associated vasculitis; ANCA = anti-neutrophil cytoplasmic antibody
Key conclusion

- Rituximab maintenance therapy in patients with AAV was effective and well tolerated.


AAV = ANCA-associated vasculitis