Further Development of Rituximab for the Treatment of Rheumatoid Arthritis
Report on EULAR 2010 presentations

- Rituximab in combination with MTX in patients with early active RA who are naïve to MTX: IMAGE two-year radiographic outcomes (Tak P-P, et al. EULAR 2010: Abstract OP0049)

- Re-treatment with rituximab based on a treatment to target approach versus treatment as needed in patients with RA (Emery P, et al. EULAR 2010: Abstract FRI0202)

- Effectiveness of rituximab versus an alternative TNF inhibitor in preventing radiographic joint damage in RA patients with inadequate response to TNF inhibitors (Finckh A, et al. EULAR 2010: Abstract FRI0204)


EULAR = European League Against Rheumatism; MTX = methotrexate; RA = rheumatoid arthritis; TNF = tumour necrosis factor
Report on EULAR 2010 presentations (cont’d)

- Predictive factors for response to rituximab in rheumatoid arthritis patients with an inadequate response or intolerance to TNF inhibitors: ancillary study of the SMART trial
  
  (Sellam J, et al. EULAR 2010: Abstract OP0050)

- Effectiveness of different DMARD co-therapies in rituximab-treated rheumatoid arthritis patients
  
  (Gabay C, et al. EULAR 2010: Abstract OP0051)

- Experience with accelerated rituximab infusion for rheumatoid arthritis in a single community practice
  
  (Faraawi R, et al. EULAR 2010: Abstract FRI0203)

DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
TNF = tumour necrosis factor
Rituximab in combination with MTX in patients with early active RA who are naïve to MTX: IMAGE two-year radiographic outcomes

Tak P-P, et al. EULAR 2010: Abstract OP0049
Background

- The International Study in Methotrexate-naïve Subjects Investigating Rituximab’s Efficacy (IMAGE) was a phase III, randomized, active comparator, placebo-controlled study.

- IMAGE was designed to evaluate clinical and radiographic outcomes with rituxumab plus MTX compared to MTX monotherapy in patients with active RA who had not received previous MTX treatment.

- Earlier data from the IMAGE study were presented at EULAR 2009 and ACR 2009.¹, ²

- At EULAR 2010, Tak and colleagues presented two-year radiographic outcomes from the IMAGE study.³

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EULAR = European League Against Rheumatism
MTX = methotrexate; RA = rheumatoid arthritis
TNFI = tumour necrosis factor inhibitor
Key inclusion criteria for the IMAGE study were as follows:

- no prior exposure to MTX, with a disease duration of <4 years;
- SJC and TJC of ≥8 each;
- CRP concentration of ≥1.0 mg/dL;
- RF-positive or erosive damage.

Patients were randomized to one of three groups:

- placebo plus MTX;
- rituximab (2 x 500 mg) plus MTX;
- rituximab (2 x 1000 mg) plus MTX.
Study design (cont’d)

- Rituximab was administered by intravenous infusion on days 1 and 15, with a 24-week repeat treatment schedule if DAS28 ≥2.6.
- MTX was initiated in all groups at 7.5 mg/week and titrated to 20 mg/week by week 8.
- Radiographs, taken at screening and weeks 24, 52, and 104, were centrally read using the GmTSS.
- Formal statistical testing of the rituximab (2 x 500 mg) dose at two years was not performed due to the absence of a statistically significant difference versus placebo for this dose at one year.

DAS28 = 28-joint disease activity score  
GmTSS = Genant-modified total Sharp score  
MTX = methotrexate
Key findings

- A total of 755 patients were randomized, and 716 were radiographically evaluable.
- At two years, patients had received a mean of three courses in each treatment group.
- 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.
- Significantly more patients receiving rituximab (2 x 1000 mg) had no joint damage progression at two years than those receiving MTX alone.
- Of the patients in the rituximab (2 x 1000 mg) arm who were non-progressive at one year, 82% remained non-progressive at 2 years.
Figure 1. Mean change in mTSS and erosion scores after 2 years of treatment with rituximab in RA patients naïve to MTX

*At two years, patients had received a mean of three courses in each treatment group.

**p < 0.0001 versus placebo + MTX
mTSS = Genant-modified total Sharp score; MTX = methotrexate
Figure 2. Percentage of patients with mTSS and erosion scores ≤0 after 2 years of treatment with rituximab in RA patients naïve to MTX

Placebo + MTX (n = 233)
Rituximab (2 x 500 mg) + MTX (n = 239)
Rituximab (2 x 1000 mg) + MTX (n = 244)

* $p < 0.0001$ versus placebo + MTX

mTSS = Genant-modified total Sharp score; MTX = methotrexate

Key findings (cont’d)

- Rituximab (2 x 500 mg) plus MTX did not significantly inhibit joint damage at the one-year primary analysis.

- Exploratory analyses suggest inhibition at two years, with a 61% relative reduction in GmTSS.

- Both doses of rituximab suggest improved clinical outcomes at week 104, compared with MTX alone, and demonstrate maintenance of response over the two-year period.

- Safety data were consistent with those previously reported.

GmTSS = Genant-modified total Sharp score
MTX = methotrexate

Table 1. Serious infection rate after 2 years of treatment with rituximab in RA patients naïve to MTX

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Serious infections (per 100 pt-yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX</td>
<td>4.97</td>
</tr>
<tr>
<td>Rituximab (2 x 500 mg) + MTX</td>
<td>4.15</td>
</tr>
<tr>
<td>Rituximab (2 x 1000 mg) + MTX</td>
<td>3.25</td>
</tr>
</tbody>
</table>

*MTX = methotrexate; pt-yrs = patient-years*
In patients with early active RA who had not previously received treatment with MTX, the significant inhibition of joint damage observed with rituximab (2 x 1000 mg) plus MTX at one year was maintained over an extended two-year time period.
Re-treatment with rituximab based on a treatment to target approach versus treatment as needed in patients with RA

Background

- Two re-treatment strategies have been employed in clinical trials of rituximab in RA: treatment to target and treatment as needed.
- Assessing differences in efficacy and safety profiles for these two treatment approaches may be useful in determining an optimal treatment regimen.
- At EULAR 2010, Emery and colleagues presented findings from their study, which compared the efficacy of treatment to target and treatment as needed approaches for rituximab therapy in RA patients with an inadequate response to MTX.
Study design

- RA patients with an inadequate response to MTX recruited into phase II or III studies received open-label rituximab (2 x 1000 mg) intravenously 2 weeks apart plus MTX based on two approaches:
  - treatment to target (TT): patients were assessed 24 weeks after each course and were re-treated if and when not in remission, defined as DAS28 ≥2.6;
  - treatment as needed (PRN): patients were re-treated at the physician’s discretion after ≥16 weeks if both SJC and TJC were ≥8.

- Regardless of treatment strategy, study visits were at least every 8 weeks.

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

- Data were pooled across the following trials:
  - MIRROR\(^1\)
  - SERENE\(^2\)
  - Phase IIa\(^3\)
  - DANCER\(^4\)

- Data were analyzed according to treatment strategy.

- Clinical outcomes, including ACR, DAS28-ESR, and HAQ-DI responses, and safety data were evaluated over time.


ACR = American College of Rheumatology
DAS28 = 28-joint disease activity score
ESR = erythrocyte sedimentation rate
HAQ-DI = health assessment questionnaire-disability index
Key findings

- Over multiple courses of rituximab, responses were maintained or improved in both treatment groups, compared with baseline.

- TT provided tighter control of disease activity than PRN, indicated by greater improvements in DAS28-ESR, lower HAQ-DI, and greater ACR response.

- TT also resulted in more patients achieving a major clinical response (ACR70 ≥6 months) compared with PRN (12.3% vs. 5.1%).

- PRN resulted in recurrence of disease symptoms between courses:
  - DAS28-ESR scores returned close to pre-rituximab treatment levels.
  - Rates of withdrawals from the trial due to RA flare were higher.


ACR = American College of Rheumatology
DAS28 = 28-joint disease activity score
ESR = erythrocyte sedimentation rate
HAQ-DI = health assessment questionnaire-disability index
PRN = treatment as needed; RA = rheumatoid arthritis
TT = treatment to target
Figure 1. DAS28-ESR scores after treatment with rituximab (2 x 1000 mg) using TT and PRN strategies in RA patients with an inadequate response to MTX

Key findings (cont’d)

- TT resulted in more frequent re-treatment, with a median time between courses of approximately 25 weeks, compared with approximately 62 weeks for PRN.

- Safety profiles of the regimens were comparable.

- TT had a numerically reduced rate of serious infections (2.2 vs. 3.5 per 100 patient-years) and serious adverse events (12.0 vs. 16.2 per 100 patient-years), compared to PRN.

- No clinically relevant differences at any time in the proportion of patients with Ig levels below the lower limit of normal were reported across the two treatment groups.

Table 1. SIE and SAE rates after treatment with rituximab (2 x 1000 mg) using TT and PRN strategies in RA patients with an inadequate response to MTX

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Serious infections (SIEs) / per 100 pt-yrs</th>
<th>Serious adverse events (SAEs) / 100 pt-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment to target (TT)</td>
<td>2.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Treatment as needed (PRN)</td>
<td>3.5</td>
<td>16.2</td>
</tr>
</tbody>
</table>

*MTX = methotrexate; pt-yrs = patient-years*
Key conclusion

- Repeat treatment with rituximab to a target of DAS28 remission led to tighter control of disease activity compared with PRN treatment.

DAS28 = 28-joint disease activity score
PRN = treatment as needed
Effectiveness of rituximab versus an alternative TNF inhibitor in preventing radiographic joint damage in RA patients with an inadequate response to a TNF inhibitor

Background

- Observational studies have suggested that RA patients who experience an inadequate response to TNFIs may respond more favourably to a different class of biologic therapy, such as rituximab, than to an alternative TNFI.\(^1\)

- Relative effectiveness of these agents on long-term outcomes, such as radiographic damage, remains unclear.\(^1\)

- At EULAR 2010, Finckh and colleagues presented results from their study comparing the effectiveness of rituximab versus TNFI agents in preventing joint damage progression in RA patients who have had an inadequate response to at least one prior TNFI.\(^2\)

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EULAR = European League Against Rheumatism
RA = rheumatoid arthritis
TNFI = tumour necrosis factor inhibitor
Study design

- The study was a prospective cohort study nested within the Swiss Clinical Quality Management in rheumatoid arthritis (SCQM-RA) cohort of the Swiss RA registry.

- Inclusion criteria included the following:
  - RA diagnosis by a rheumatologist;
  - TNFI failure while on infliximab, etanercept, or adalimumab;
  - initiation of either a second or third alternative TNFI or rituximab.

- Primary outcome of the analysis was the progression of radiographic joint damage over time.

- Secondary outcome was the evolution of functional disability measured by the HAQ.

HAQ = health assessment questionnaire
RA = rheumatoid arthritis
TNFI = tumour necrosis factor inhibitor
Joint erosions (ERO) were assessed in 38 joints of hands and feet with a validated scoring method (Ratingen score, expressed in percentage of the maximum score).

Semi-quantitative scoring for percentage of eroded area over total joint was done.

Scoring was carried out by a single reader, blinded to clinical history and film order.

The evolution of ERO was analyzed using regression models for longitudinal data, adjusting for potential confounders.
Key findings

- A total of 644 RA patients were included in the study:
  - 255 patients on rituximab;
  - 389 patients on an alternative TNFI (adalimumab 51%, etanercept 30%, infliximab 19%).

- Patients were followed over a median duration of 18 months and assessed on average with two sets of hand and feet X-rays.

- Both therapeutic groups were similar for most disease characteristics, but some differences were seen in disease duration, baseline DAS28, HAQ levels, and number of previous TNFI failures.
<table>
<thead>
<tr>
<th>Baseline disease characteristics</th>
<th>Rituximab (n = 255)</th>
<th>Alternative aTNF (n = 389)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median symptom duration (years)</td>
<td>13</td>
<td>11</td>
<td>0.04</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>77</td>
<td>81</td>
<td>0.24</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>57</td>
<td>54</td>
<td>0.08</td>
</tr>
<tr>
<td>Rheumatoid factor positive (%)</td>
<td>86</td>
<td>82</td>
<td>0.17</td>
</tr>
<tr>
<td>Median baseline ERO score (%)</td>
<td>7.8</td>
<td>7.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Median DAS28</td>
<td>4.4</td>
<td>4.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median function (HAQ)</td>
<td>1.37</td>
<td>1.17</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median number of prior TNFIs</td>
<td>2</td>
<td>2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Concomitant DMARDs (&gt;1 allowed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– methotrexate (%)</td>
<td>48</td>
<td>50</td>
<td>0.53</td>
</tr>
<tr>
<td>– other DMARDs (%)</td>
<td>31</td>
<td>24</td>
<td>0.07</td>
</tr>
<tr>
<td>– none (%)</td>
<td>29</td>
<td>32</td>
<td>0.42</td>
</tr>
<tr>
<td>Concomitant glucocorticoid use (%)</td>
<td>53</td>
<td>50</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*DAS28 = 28-joint disease activity score; DMARD = disease-modifying anti-rheumatic drug; ERO = joint erosion score; HAQ = health assessment questionnaire; TNFI = tumour necrosis factor inhibitor*
Key findings (cont’d)

- After adjusting for prognostic factors, no significant differences existed in the rates of ERO progression or HAQ evolution between patients on alternative TNFI s and those on rituximab ($p = 0.52$).

- The ERO score progressed at an annual rate of +0.17% (95% CI: –0.18, 0.52) in the TNFI group versus –0.01% (95% CI: –0.51, 0.49) in the rituximab group.

- No evidence was found for effect modification by concomitant methotrexate or glucocorticoids.
Figure 1. ERO scores in RA patients receiving rituximab or alternate TNFI treatment

ERO = joint erosion score; TNFI = tumour necrosis factor inhibitor
Figure 2. HAQ scores in patients receiving rituximab or alternate TNFI treatment

HAQ = health assessment questionnaire; TNFI = tumour necrosis factor inhibitor
Key conclusion

- This observational study suggests that rituximab is as effective as alternative TNF inhibitors in preventing radiographic joint damage and functional deterioration in RA patients with an inadequate response to a TNF inhibitor.


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

Van Vollenhoven RF, et al. EULAR 2010: Abstract OP0046
Background

- Rituximab, a chimeric monoclonal antibody that selectively targets CD20-positive B cells, has been shown to be effective, with a favourable safety profile, in patients with RA.\(^1,2\)

- At EULAR 2010, van Vollenhoven and colleagues presented data from a pooled analysis evaluating the long-term safety of rituximab in RA patients who participated in clinical trials.\(^3\)

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

- The study was a pooled analysis of safety data from patients treated with rituximab in combination with MTX in a global clinical trial program.
- All patients were offered rituximab re-treatment based on physicians’ decisions of clinical need.
- Patients receiving placebo during placebo-controlled study periods were pooled to provide a placebo population.


MTX = methotrexate
Key findings

- A total of 3,189 patients had been treated with rituximab as of September 2009, providing 9,342 patient-years of exposure.
- The analysis included more than 9 years of follow-up, with up to 15 courses of rituximab.
- More than 1,500 patients were followed for >3 years, and received up to 6 courses of treatment.

### Table 1. Number of courses received in >3 years of rituximab treatment

<table>
<thead>
<tr>
<th>Rituximab courses</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 courses</td>
<td>2417</td>
</tr>
<tr>
<td>≥3 courses</td>
<td>1724</td>
</tr>
<tr>
<td>≥4 courses</td>
<td>1392</td>
</tr>
<tr>
<td>≥5 courses</td>
<td>1036</td>
</tr>
<tr>
<td>≥6 courses</td>
<td>656</td>
</tr>
</tbody>
</table>
Key findings *(cont’d)*

- In the rituximab group, the most frequent AEs (35.6%) were infusion-related reactions (IRRs).
- Most IRRs were CTC grade 1 or 2 and occurred after the first infusion of the first course (23.0%), with 0.5% over all courses considered serious.
- Rates of SAEs and infections generally remained stable over time and over multiple rituximab courses.
- The overall serious infection rate was 4.35 events/100 patient-years, comparable to that observed in the placebo population (4.29 events/100 patient-years).
- The numerically higher serious infection rate at course 5 was not seen at course 6.

Key findings (cont’d)

- The most frequent serious infections were of the lower respiratory tract, predominantly pneumonia (2%).
- No cases of tuberculosis or reactivation of hepatitis B were reported.
- Serious opportunistic infections were rare, but included:
  - one confirmed case of *Pneumocystis jiroveci* pneumonia in each of the rituximab and placebo groups;
  - one previously reported case of PML in the rituximab group.
- Rates of myocardial infarction (0.49 events/100 patient-years) and stroke (0.25 events/100 patient-years) were consistent with rates in the general RA population (0.34–0.59 per 100 patient-years and 0.112–0.76 per 100 patient-years, respectively).


PML = progressive multifocal leukoencephalopathy
RA = rheumatoid arthritis
Table 2: Adverse event rates per 100 patient-years by course in RA patients treated with rituximab

<table>
<thead>
<tr>
<th></th>
<th>Course 1 (n = 3189)</th>
<th>Course 2 (n = 2417)</th>
<th>Course 3 (n = 1724)</th>
<th>Course 4 (n = 1392)</th>
<th>Course 5 (n = 1036)</th>
<th>Course 6 (n = 656)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total patient-years</strong></td>
<td>3166</td>
<td>2574</td>
<td>1484</td>
<td>1029</td>
<td>607</td>
<td>313</td>
</tr>
<tr>
<td><strong>Any AEs (95% CI)</strong></td>
<td>361 (355–368)</td>
<td>278 (272–285)</td>
<td>280 (271–288)</td>
<td>280 (270–290)</td>
<td>294 (281–308)</td>
<td>285 (267–304)</td>
</tr>
<tr>
<td><strong>Any SAEs (95% CI)</strong></td>
<td>17.4 (16.0–19.0)</td>
<td>16.2 (14.7–17.8)</td>
<td>15.0 (13.1–17.1)</td>
<td>14.8 (12.6–17.3)</td>
<td>16.6 (13.7–20.2)</td>
<td>15.3 (11.5–20.3)</td>
</tr>
<tr>
<td><strong>Infections (95% CI)</strong></td>
<td>95 (91–98)</td>
<td>89 (86–93)</td>
<td>98 (93–103)</td>
<td>93 (88–100)</td>
<td>100 (93–109)</td>
<td>93 (82–104)</td>
</tr>
<tr>
<td><strong>Serious infections (95% CI)</strong></td>
<td>4.58 (3.89–5.39)</td>
<td>3.69 (3.02–4.51)</td>
<td>4.04 (3.14–5.21)</td>
<td>4.37 (3.26–5.85)</td>
<td>7.25 (5.39–9.74)</td>
<td>3.51 (1.94–6.34)</td>
</tr>
</tbody>
</table>

*AE = adverse event; CI = confidence interval; SAE = serious adverse event*
Key conclusions

- In prolonged follow-up of RA patients treated with rituximab in clinical trials, rituximab has remained well tolerated over time and over multiple courses.
- Rituximab has a safety profile similar to that of the placebo population and consistent with published data on patients with moderate-to-severe RA.
Predictive factors for response to rituximab in RA patients with an inadequate response or intolerance to TNF inhibitors: ancillary study of the SMART trial

Sellam J, et al. EULAR 2010: Abstract OP0050
Background

- The SMART study is a randomized, open-label clinical trial evaluating two re-treatment strategies in patients responding to rituximab after an inadequate response or intolerance to TNFIs.¹

- At EULAR 2010, Sellam and colleagues presented data from an ancillary study of the SMART trial, designed to identify biological parameters predictive of response to a first course of rituximab.²

1. SMART Study: clinicaltrials.gov/show/NCT01126541.

EULAR = European League Against Rheumatism
TNFI = tumour necrosis factor inhibitor
Study design

- A total of 208 RA patients fulfilling ACR criteria were included in the ancillary study.
- All patients had been treated with MTX.
- Patients were refractory or intolerant to TNFIs (n = 194), or had a counter-indication to TNFIs (n = 14).
- Patients received one course of rituximab (2 x 1000 mg) by intravenous infusion on days 1 and 15 plus MTX.
- At week 24, a blood sample was taken before the first rituximab infusion to identify biological predictive factors of EULAR response.


ACR = American College of Rheumatology
EULAR = European League Against Rheumatism
MTX = methotrexate; RA = rheumatoid arthritis
TNFI = tumour necrosis factor inhibitor
Study design \((cont’\text{d})\)

- B-cell activation biomarkers assessed included:
  - rheumatoid factor;
  - CCP antibodies;
  - serum kappa (UL 19.4 mg/L) and lambda FLC (UL 26.3 mg/L);
  - serum IgG (UL 12.7 g/L), IgA (UL 2.7 g/L), and IgM (UL 2.1 g/L) levels;
  - BAFF or BLyS level (a cytokine involved in B-cell activation).

- Univariate analysis was performed to identify predictive factors of good or partial EULAR response in comparison with non-response at week 24.

- Results with a \(p\)-value <0.15 obtained in this univariate analysis were then included in a multivariate analysis adjusted on a DAS28 level.


BAFF = B-cell activating factor; BLyS = B lymphocyte stimulator
CCP = cyclic citrullinated peptide; DAS28 = 28-joint disease activity score
EULAR = European League Against Rheumatism; FLC = free light chain
Ig = immunoglobulin; UL = upper limit
Key findings

- Of the 208 patients, 85% were women and median age was 56 years (± 11).

- A total of 149 patients (72 %) responded to the first course of treatment, of whom 44 (21 %) were good responders.

- Baseline factors associated with response at week 24 in univariate analyses were:
  - DAS28-CRP >5.1 (p = 0.01);
  - presence of radiographic erosions (p = 0.13);
  - positive RF or anti-CCP antibodies (p = 0.002);
  - absence of steroid treatment (p = 0.05);
  - time <6 months since the last TNFI (p = 0.14);
  - serum IgG (p = 0.02) and IgA (p = 0.07) level above normal.

CCP = cyclic citrullinated peptide; CRP = C-reactive protein
DAS28 = 28-joint disease activity score
Ig = immunoglobulin; RF = rheumatoid factor
TNFI = tumour necrosis factor inhibitor

Key findings (cont’d)

- Response was not significantly associated with age, disease duration, sex, baseline HAQ, CRP level, type of previous TNFI, IgM, BAFF, or FLC levels.

- Multivariate analyses indicated that RF and anti-CCP positivity, and IgG levels above normal were predictive of response to rituximab.

- The combination of the two factors increases the probability of response to rituximab.


BAFF = B-cell activating factor  
CCP = cyclic citrullinated peptide  
CRP = C-reactive protein  
FLC = free light chain  
HAQ = health assessment questionnaire  
Ig = immunoglobulin; RF = rheumatoid factor  
TNFI = tumour necrosis factor inhibitor
Figure 1. Predictive factors at 24 weeks for a EULAR good or partial response to rituximab plus MTX in a multivariate analysis adjusted on DAS28

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF + or anti-CCP+</td>
<td>3.48</td>
<td>1.60–7.58</td>
<td>0.0017</td>
</tr>
<tr>
<td>IgG &gt;12.7 g/L</td>
<td>2.11</td>
<td>1.02–4.33</td>
<td>0.043</td>
</tr>
</tbody>
</table>

CI = confidence interval; CCP = cyclic citrullinated peptide; DAS28 = 28-joint disease activity score; EULAR = European League Against Rheumatism (score); Ig = immunoglobulin; MTX = methotrexate; RF = rheumatoid factor
Figure 2. Response to rituximab plus MTX according to the presence of independent predictive factors (UL of IgG level 12.7 g/L)

CCP = cyclic citrullinated peptide; EULAR = European League Against Rheumatism (score); Ig = immunoglobulin; MTX = methotrexate; RF = rheumatoid factor; UL = upper limit
Key conclusions

- In patients failing TNFI therapy, the presence of RF or anti-CCP positivity predicted the response to rituximab plus MTX, confirming similar results found in early RA patients naïve of treatments.

- The study demonstrated for the first time that a serum IgG level above normal was predictive of response to rituximab plus MTX, independently of autoantibody presence.

- Conversely, serum BAFF and FLC levels are not predictive of response to rituximab plus MTX.

Effectiveness of different DMARD co-therapies in rituximab-treated RA patients

Gabay C, et al. EULAR 2010: Abstract OP0051
Rituximab is efficacious in RA patients when prescribed in combination with MTX.

Some patients do not tolerate MTX and are treated with other DMARDs, such as leflunomide (LEF), or without co-therapy.

At EULAR 2010, Gabay and colleagues presented results of a one-year follow-up study from the CERRERA Collaboration, designed to compare the effectiveness and safety of rituximab alone or in combination with either MTX or LEF.\(^1\)

DMARD = disease-modifying anti-rheumatic drug
EULAR = European League Against Rheumatism
LEF = leflunomide; MTX = methotrexate
RA = rheumatoid arthritis
Study design

- Ten European registries submitted anonymized datasets for patients who started rituximab therapy.

- Baseline and follow-up data included disease duration, number of previous biologic agents, DAS28, HAQ, concomitant DMARDs, corticosteroid use, and rituximab re-treatment.

- Patients were separated into three groups:
  - rituximab plus MTX;
  - rituximab plus LEF;
  - rituximab monotherapy.

- EULAR good response rates were compared across groups.


DAS28 = 28-joint disease activity score  
DMARD = disease-modifying anti-rheumatic drug  
EULAR = European League Against Rheumatism  
HAQ = health assessment questionnaire  
LEF = leflunomide; MTX = methotrexate
Key findings

- A total of 1,901 patients were analyzed: 1,026 treated with rituximab plus MTX, 146 with rituximab plus LEF, and 429 with rituximab monotherapy.

- LEF was significantly associated with a good EULAR response:
  - Significantly more patients achieved a EULAR good response at 6 months when treated with rituximab plus LEF (33.3%), as compared to rituximab plus MTX (21.1%) and rituximab monotherapy (20.2%), $p = 0.01$ and $p = 0.005$, respectively.
  - A similar trend was observed at 12 months.
<table>
<thead>
<tr>
<th>Measure</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LEF vs. MTX</td>
<td>LEF vs. None</td>
</tr>
<tr>
<td>Co-efficient</td>
<td>0.96</td>
<td>1.11</td>
</tr>
<tr>
<td>Overall response</td>
<td>2.61 (1.18–5.75)</td>
<td>3.05 (1.3–7.13)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.02</td>
<td>0.010</td>
</tr>
</tbody>
</table>

CI = confidence interval; LEF = leflunomide; MTX = methotrexate
Key findings (cont'd)

- Co-treatment with LEF was still predictive of a good EULAR response when taking into account the disease duration and number of previous biological agents in a multivariate analysis.

- Fewer patients with rituximab plus LEF were re-treated during the first 12 months (10.9%), compared with rituximab plus MTX (20.2%) or rituximab monotherapy (18.9%).

- Adverse events occurred in 7.5%, 11.8%, and 12.4% of patients receiving rituximab plus LEF, rituximab plus MTX, and rituximab monotherapy, respectively.
Key conclusion

The results of this large multinational cohort of patients show that LEF is an effective and safe alternative concomitant treatment with rituximab in patients intolerant to MTX.


LEF = leflunomide; MTX = methotrexate
Experience with accelerated rituximab infusion for RA in a single community practice

Faraawi R, et al. EULAR 2010: Abstract FRI0203
Background

- Rituximab is administered as a slow infusion (255 minutes [4.25 hours]), due to the potential for infusion reactions.¹,²
- The risk of infusion reaction is greatest with the initial infusion and is significantly diminished with subsequent infusions.
- Recently, rapid infusion protocols (60 and 90 minutes) have been shown to be well tolerated in the oncology setting.²,³
- Little data are available on accelerated infusions in the rheumatology setting.
- At EULAR 2010, Faraawi and Roth presented their study designed to evaluate the practicality, safety, and tolerability of a rapid-infusion rituximab protocol in RA patients in a community practice.⁴


EULAR = European League Against Rheumatism
RA = rheumatoid arthritis
RA patients meeting the criteria for rituximab treatment were recruited to participate in evaluation of the rapid-infusion protocol.

Each treatment course consisted of two rituximab (1000 mg) infusions, given two weeks apart.

The first infusion followed the recommended schedule (255 minutes).

Second and subsequent infusions were administered over 120 minutes (2 hours).
Study design (cont’d)

- Administration of the second and subsequent infusions was as follows:
  - 0–30 min: 100 mg;
  - 30–60 min: 200 mg;
  - 60–90 min: 300 mg;
  - 90–120 min: 400 mg.

- Premedication for all infusions consisted of acetaminophen (1000 mg), oral diphenhydramine (50 mg), and methylprednisolone (100 mg).

- Vital signs were recorded at baseline and at 15, 30, 60, 90, and 120 minutes.
Study design

INITIAL RITUXIMAB INFUSION (DAY 1)
Duration of first infusion: 4 hours 15 minutes

Initial rate 50 mg/hr — escalated in 50 mg/hr increments every 30 minutes with a maximum rate of 400 mg/hr

ALL SUBSEQUENT RITUXIMAB INFUSIONS
Duration of all subsequent infusions: 4 hours

Initial rate 200 mg/hr — escalated in 200 mg/hr increments every 30 minutes with a maximum rate of 800 mg/hr
Key findings

- To date, 10 patients have been recruited; baseline characteristics are typical of the patient population with RA.
- All patients had been treated with and had failed or did not tolerate at least one TNFI; three patients had received more than one agent.
- Forty (40) infusions have been administered, of which 30 followed the rapid-infusion protocol.

RA = rheumatoid arthritis
TNFI = tumour necrosis factor inhibitor
Key findings (cont’d)

- Mean duration between rituximab infusion courses was 9.1 months.
- Rapid infusion was safe and well tolerated by all patients.
- One patient experienced a minor infusion reaction (headache, chest tightness, and shortness of breath), which resolved during the infusion.
- No infections were reported, and no additional adverse events have occurred.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Population (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year, mean ± SD</td>
<td>49.2 ± 10.8</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>70</td>
</tr>
<tr>
<td>RA disease duration, yr, mean ± SD</td>
<td>8.9 ± 8.3</td>
</tr>
<tr>
<td>RF positive at baseline*, %</td>
<td>66</td>
</tr>
<tr>
<td>Tender/swollen joint count, mean</td>
<td>16.4/11</td>
</tr>
<tr>
<td>Concomitant steroid use, %</td>
<td>60</td>
</tr>
<tr>
<td>Concomitant methotrexate, %</td>
<td>60</td>
</tr>
<tr>
<td>Mean methotrexate dose, mg</td>
<td>19.16</td>
</tr>
<tr>
<td>DAS, mean, ± SD†</td>
<td>6.1 ± 0.98</td>
</tr>
<tr>
<td>HAQ, mean‡</td>
<td>1.58</td>
</tr>
<tr>
<td>Previous number biologics, mean ± SD</td>
<td>1.5 ± 0.8</td>
</tr>
</tbody>
</table>

*RF result unavailable for 1 patient (n = 9); †DAS result unavailable for 1 patient (n = 9); ‡DAS results unavailable for 2 patients (n = 8); DAS = disease activity score; HAQ = health assessment questionnaire; MTX = methotrexate; RF = rheumatoid factor; SD = standard deviation
### Table 2. Reason for discontinuation of previous TNF inhibitor(s)

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary failure (inefficacy)</td>
<td>2</td>
</tr>
<tr>
<td>Loss of effect</td>
<td>2</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
</tr>
</tbody>
</table>
Key conclusions

- An accelerated rituximab infusion is safe and well tolerated in the community setting.
- All patients were satisfied with the short infusion duration.
- Rapid rituximab infusion is a practical option in a community setting, and the accelerated protocol optimizes patient, nurse, and physician time.