**Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life**


**ABSTRACT**

**Objective.** To investigate the effects on health-related quality of life (HRQOL) and functional capability of rituximab vs azathioprine for ANCA-associated vasculitis (AAV) maintenance therapy.

**Methods.** In a 24-month phase III randomised-controlled trial, 115 patients over time received rituximab or azathioprine for AAV maintenance therapy. Mean changes of 36-item Short-form Health Survey (SF-36) and Health Assessment Questionnaire (HAQ) scores from baseline were analysed.

**Results.** Mean improvements of HAQ scores, from baseline to month 24 were significantly better for the rituximab (0.16 points lower) than the azathioprine group (p=0.038). As demonstrated by SF-36, study patients’ baseline HRQOL was significantly impaired compared with age- and sex-matched US norms. At month 24, mean changes from baseline of SF-36 physical component score tended to be better for the rituximab group (+3.95 points, p=0.067) whereas mean changes from baseline of the SF-36 mental component score were significantly better for the azathioprine group (+4.23 points, p=0.041).

**Conclusion.** Azathioprine-treated patients’ for AAV maintenance therapy showed a decline in physical abilities when compared to RTX at M24 in the MAINRITSAN trial.

**Trial registration:** ClinicalTrials.gov, http://clinicaltrials.gov/, NCT00748644

**Introduction**

Granulomatosis with polyangiitis (Wegener’s, GPA) and microscopic polyangiitis (MPA) belong to the group of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAVs), which are life-threatening multisystemic diseases. AAVs affect small-to-medium-sized blood vessels, with a predilection for the respiratory tract and kidney. Remission-induction treatment combines glucocorticoids (GCs) and cyclophosphamide or rituximab (RTX) (1), possibly followed by maintenance therapy. The results of several retrospective studies suggested that AAV maintenance therapy with successive RTX infusions is safe and effective for at least 2 years (2-5). However, the optimal duration and regimen remain to be validated. For GPA and MPA patients, the cumulative burden of disease and treatment-related adverse effects is formidable, impairing their quality of life (QOL) and responsible for global disability.

A key goal for the management of GPA and MPA patients is to improve and preserve health-related QOL (HRQOL). The results of several studies indicated that AAV patients have poorer HRQOL (6-8). Using instruments directly originating from patients, e.g. the Medical Outcome Study 36-item Short-form Health Survey (SF-36) and Health Assessment Questionnaire (HAQ), as outcome measures in clinical trials on AAV, is essential to understanding how patients’ perceive the impact of different treatments on their lives. Using QOL measurements to differentiate between treatments is difficult and has been done in only few studies in vasculitis so far. The MAINRITSAN trial was a non-blinded, randomised-controlled, remission-maintenance study which compared systematic RTX infusions versus azathioprine (AZA), for patients with GPA, MPA or pauci-immune cres-
centic glomerulonephritis, in pulse-cyclophosphamide and corticosteroid-induced remission. Primary safety and efficacy data were recently reported (9). We report herein the results of the analysis of HRQOL and global disability.

**Patients and methods**

**Patients and study design**

Patients with newly diagnosed (2/3 of the inclusions) or relapsing (1/3) AAV (n=115), who fulfilled the American College of Rheumatology classification criteria (10) and/or the Chapel Hill Consensus Conference definitions classifying AAV (11), were enrolled in the MAINRITSAN trial. Briefly, once they achieved complete remission with combined GCs and pulse cyclophosphamide, they were randomly assigned, at a 1:1 ratio, to receive a 500 mg RTX infusion on days 1 and 15, 5.5 months later, then every 6 months for a total of five infusions over 18 months, or AZA maintenance therapy for 22 months at the initial dose of 2 mg/kg/d. The primary endpoint was the percentages of patients with major relapses at follow-up month 28. The appropriate regional committees approved the study. All patients gave written informed consent to participate, in accordance with the Declaration of Helsinki.

The planned analysis of patient-reported HRQOL used the intend-to-treat population (ITT) (n=115), including all randomly assigned patients who received one or more study-treatment doses. Patients were assessed at baseline and every 3 months. At each visit, HRQOL questionnaires completion was optional. When they did, patients completed the French versions of the HAQ and SF-36 questionnaire (12, 13) on paper in the presence of the study investigator who provided no coaching or suggestions regarding questionnaire content.

**Patient-reported outcomes**

HRQOL was assessed with the French version of the SF-36 (14). This self-administered questionnaire covers eight domains: physical function (PF), physical role (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), emotional role (RE) and mental health (MH). For each domain, scores range from zero (poorer) to 100 (best) health status. Scores can also be summarised with two global scores: physical component score (PCS) and mental component score (MCS). For both physical and mental health, Ware, JE Jr et al. observed an agreement between SF-36 summary measures estimated using standard and country-specific scoring algorithms in all countries. Specifically, correlations between SF-36 summary measures scored using standard (U.S.) scoring and country-specific scoring ranged from 0.980 to 0.998 across European countries. On the basis of these findings, we used US-derived scoring algorithms for our study. Baseline values and treatment-associated changes of these domain scores are depicted using histograms, which allowed comparison with age- and sex-matched US population norms (13). SF-36 is the most widely used measure of patients’ AAV HRQOL, displaying good validity, reliability and responsiveness (7, 8).

The HAQ is a standard disability index used to measure the global disability level. It is one of the most frequently used global disability measures in randomised clinical trials on rheumatic disease, including AAVs (15). HAQ contains 20 items divided into 8 domains representing a comprehensive set of functional activities; dressing, rising, eating, walking, hygiene, reach, grip and usual activities. Each score ranges from 0 (no disability) to 3 (maximal disability). The HAQ has been translated into French (16). Minimal clinically important differences (MCIDs) are the smallest changes in an instrument score that are considered clinically meaningful, and have been defined as ≥0.22 for the HAQ, >5.42 for the SF-36 PCS and >6.33 for the SF-36 MCS (15, 16) for rheumatoid arthritis (RA). No MCIDs have been defined for AAV patients.

**Statistical analyses**

Baseline characteristics, HRQOL, SF-36 (PCS and MCS) and HAQ changes from baseline to months 24 (M24), are expressed as means and standard deviation (SD) for normally distributed variables and medians and interquartile ranges (IQR) for non-normally distributed variables. Mean changes from baseline scores for RTX- and AZA-treated groups were compared at M24 using a constrained longitudinal data analysis model with random effect at centre level. In this model, the baseline value is included as part of the outcome vector, assuming group mean responses at baseline equal. Estimates of the mean differences and their 95% confidence intervals (CI) were calculated for each time. All analyses used the ITT population. For missing data, an analysis was performed on multiple imputed datasets, with m=5 imputations (17). All statistical analyses were computed with R 3.0.1.

**Results**

Baseline demographics and main AAV characteristics (Table I) were well-balanced for the two treatment groups. At study entry, 87 patients had GPA, 23 MPA and five renal-limited pauci-immune vasculitis; 92 were in remission after a first disease flare and 23 after a relapse. Seven had ANCA-negative, biopsy-proven disease. Vasculitis damage index values were comparable for the RTX and AZA groups (respectively, 1.63±1.53 vs. 2.07±1.80). At M6, M12, M18 and M24, HAQ questionnaires were missing for 17/58 (29.3%), 16/58 (27.6%), 22/58 (37.9%) and 29/58 (50%) AZA-patients, and 8/57 (14%), 14/57 (24.6%),16/57 (28.1%) and 23/57 (40.4%) RTX-patients, respectively. SF-36 questionnaires were missing for 20/58 (34.5%), 21/58 (36.2%), 20/58 (34.5%) and 32/58 (55.2%) AZA vs. 9/57 (15.8%), 17/57 (29.8%), 16/57 (28.1%) and 22/57 (38.6%) RTX recipients, respectively.

At M24, HAQ questionnaires were missing for 13 of the 17/58 AZA-patients who met the primary endpoint, and two of the 3/57 RTX-patients who met the primary endpoint. SF-36 questionnaires were missing for 14/17 AZA vs. 2/3 RTX patients who relapsed.

HAQ-assessed baseline global disability was modestly impaired: 0.24±0.38 vs. 0.33±0.53 for RTX and AZA groups, respectively. Global disability remained unchanged for RTX recipients but worsened significantly for the AZA group (mean difference: 0.16
and sex-matched US norms (Fig. 1). Significantly impaired compared with age-

Baseline SF-36 PCS was severely impaired: 44.0±8.1 for the RTX group vs.

Baseline SF-36 MCS was severely impaired: 41.9±10.2 for RTX recipients vs. 41.7±10.1 for the AZA group. SF-36 MCS improved for both groups. Mean SF-36 MCS changes from baseline were larger for the AZA group (4.23 [8.29; 0.17] points lower; p=0.041). From baseline to M24, RTX-treated patients reported improvement of all four SF-36 PCS domains, with the most for BP and PF domains. AZA-treated patients also reported improvement for three SF-36 MCS domains, with the greatest for MH and RE domains (Fig. 2). But neither RTX- nor AZA-treated patients’ scores represented MCIDs.

**Discussion**

The MAINRITSAN trial results showed that RTX was superior to AZA at maintaining AAV remission and safe (9). In the present analysis of MAINRITSAN-trial disability and HRQOL data, HAQ did not change in RTX-arm patients, whereas it significantly decreased in AZA-arm patients between enrolment and M24. On the other hand, SF-36 PCS domain scores slightly improved in RTX-arm patients, whereas SF-36 MCS domain did in the AZA-arm patients. AAV had a marked impact on HRQOL in our study, with all eight domain scores differing significantly at baseline between the trial population and normal ≥50.

**Table 1.** Baseline demographics and AAV-patient-reported outcome scores for HRQOL and global disability, according to maintenance therapy.

<table>
<thead>
<tr>
<th>Disease status</th>
<th>AZA (n=58)</th>
<th>RTX (n=57)</th>
<th>Total (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed</td>
<td>47 (81.0)</td>
<td>45 (78.9)</td>
<td>92 (80)</td>
</tr>
<tr>
<td>Relapsing</td>
<td>11 (19)</td>
<td>12 (21.1)</td>
<td>23 (20)</td>
</tr>
<tr>
<td>ANCA+ at diagnosis or last flare</td>
<td>54 (93.1)</td>
<td>54 (94.7)</td>
<td>108 (93.9)</td>
</tr>
<tr>
<td>By indirect immunofluorescence</td>
<td>38 (65.5)</td>
<td>44 (77.2)</td>
<td>82 (71.3)</td>
</tr>
<tr>
<td>C-ANCA</td>
<td>15 (25.9)</td>
<td>9 (15.8)</td>
<td>24 (20.9)</td>
</tr>
<tr>
<td>Proteinase-3</td>
<td>0</td>
<td>1 (1.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Vasculitis damage index</td>
<td>2.07 ± 1.80</td>
<td>1.63 ± 1.53</td>
<td>1.85 ± 1.68</td>
</tr>
<tr>
<td>GFR at inclusion, ml/min/1.73 m²</td>
<td>59.4 ± 29.7</td>
<td>68.3 ± 29.3</td>
<td>63.9 ± 29.7</td>
</tr>
<tr>
<td>Proteinuria, g/24 h</td>
<td>1.6 ± 1.5</td>
<td>1.8 ± 1.8</td>
<td>1.7 ± 1.7</td>
</tr>
<tr>
<td>HAQ score*</td>
<td>0.33 ± 0.53</td>
<td>0.24 ± 0.38</td>
<td>0.28 ± 0.46</td>
</tr>
<tr>
<td>SF-36 score†</td>
<td>42.7 ± 10.7</td>
<td>44.0 ± 8.1</td>
<td>43.4 ± 9.5</td>
</tr>
<tr>
<td>PCS</td>
<td>41.7 ± 10.1</td>
<td>41.9 ± 10.2</td>
<td>41.8 ± 10.1</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or n (%). GFR glomerular filtration rate (calculated according to the Modification of the Diet in Renal Disease equation). *HAQ scores ranged from 0 to 3 (higher scores indicate more severe disability). †SF-36 PCS and MCS ranged from 0 (worst) to 100 (best) status, with normal ≥50.

**Table 2.** ANCA, proteinase-3, and proteinuria values at diagnosis.

<table>
<thead>
<tr>
<th>ANCA specificity</th>
<th>AZA (n=58)</th>
<th>RTX (n=57)</th>
<th>Total (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By ELISA, ANCA specificity</td>
<td>53 (91.4)</td>
<td>53 (92.9)</td>
<td>106 (92.2)</td>
</tr>
<tr>
<td>Proteinase-3</td>
<td>36 (67.9)</td>
<td>44 (83.0)</td>
<td>80 (75.5)</td>
</tr>
<tr>
<td>Myeloperoxidase</td>
<td>17 (32.1)</td>
<td>9 (17)</td>
<td>26 (24.5)</td>
</tr>
<tr>
<td>Proteinuria, g/24 h</td>
<td>1.6 ± 1.5</td>
<td>1.8 ± 1.8</td>
<td>1.7 ± 1.7</td>
</tr>
</tbody>
</table>

**Table 3.** Clinical characteristics of MAINRITSAN patients.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>AZA (n=58)</th>
<th>RTX (n=57)</th>
<th>Total (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>56 ± 14</td>
<td>54 ± 13</td>
<td>55 ± 13</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>28 (48.3)</td>
<td>37 (64.9)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>30 (51.7)</td>
<td>20 (35.1)</td>
</tr>
<tr>
<td>AA V</td>
<td>40 (69)</td>
<td>47 (82.5)</td>
<td>87 (75.7)</td>
</tr>
<tr>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
<td>15 (25.9)</td>
<td>8 (14.0)</td>
<td>23 (20)</td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>3 (5.2)</td>
<td>2 (3.5)</td>
<td>5 (4.3)</td>
</tr>
</tbody>
</table>

**Table 4.** GFR, creatinine, and proteinuria values at inclusion.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
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<tr>
<td>Glomerular filtration rate (ml/min/1.73 m²)</td>
<td>59.4 ± 29.7</td>
<td>68.3 ± 29.3</td>
<td>63.9 ± 29.7</td>
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<tr>
<td>Proteinuria, g/24 h</td>
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**Table 5.** HAQ and SF-36 scores at enrolment and M24.

<table>
<thead>
<tr>
<th>HAQ and SF-36 scores at enrolment and M24</th>
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<td>PCS</td>
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Health-related quality of life in ANCA-associated vasculitides / G. Pugnet et al.

Although HRQOL scores differed significantly, MCIDs, i.e. clinical differences, are what really matter, especially in routine practice. If we apply the thresholds validated for RA patients none of our results had clinical relevance. However, because no reference or consensus MCID values of HRQOL exist for AAVs, those for RA are used. Compared with RA, AAAs can have a wide variety of clinical features, which may affect various HRQOL items and no published studies have ever investigated any MCID relationship between RA and AAV. Studies are needed to evaluate the AAV MCIDs for SF-36 and/or HAQ. Thereafter, validation studies will have to assess SF-36 and HAQ relevance for AAAs.

Fig. 1. Norm-based mean changes from baseline to M24 of health-related quality of life mean (±SD) changes of (A) Health Assessment Questionnaire scores, and SF-36 (B) physical component and (C) mental component scores over the 24 months of follow-up.

Fig. 2. SF-36 item (PF: physical function; RP: physical role; BP: bodily pain; GH: general health; VT: vitality/energy; SF: social function; RE: emotional role; MH: mental health/emotional well-being) scores and PCS and MCS for RTX- or AZA-treated AAV patients, and age- and sex-matched normal US-population values (+) at M24.
The goal of AAV treatment should extend beyond the induction of remission and its maintenance. As mentioned in the EULAR and OMERACT recommendations (22, 23), HRQOL or patient-reported outcomes should be included as outcome measures of clinical studies on vasculitides, as for other conditions, like RA. The impact of AAV on the patient’s life is one of the major concerns for the clinicians but they do not evaluate QOL well and/or consistently in daily practice. Neither SF-36 nor HAQ scores can be used routinely. PF and HRQOL improvements should be included systematically as major therapeutic goals and should be more consistently assessed in routine practice and trials, with tools simple to use and analyse, for the patients and treating physicians.

In conclusion, in the MAINRITSAN trial, AZA for maintenance therapy was associated with a greater decline in physical abilities, based on SF36, when compared to RTX. Although this finding would strengthen the superiority of RTX over AZA for maintenance in AAV, as the former was already shown superior in preventing major relapses, it should be interpreted with caution, as an important amount of HRQOL data was missing.

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Conflict of interest statements
G. Pugnet reports receiving travel support from Abbvie and Actelion.
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L. Guillemin reports receiving fees for serving on an advisory board from GlaxoSmithKline and lecture fees from Roche, Actelion, Pfizer, CSL Behring, LFB Pharma, and Octapharma.

References


