EXTENDED REPORT

Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides

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ABSTRACT

Objective To compare long-term efficacy of remission-maintenance regimens in patients with newly diagnosed or relapsing antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides.

Methods The 28-month Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis trial compared rituximab with azathioprine to maintain remission in patients with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis or renal-limited ANCA-associated vasculitis. Thereafter, prospective patient follow-up lasted until month 60. The primary endpoint was the major-relapse rate at month 60. Relapse and serious adverse event-free survival were also assessed.

Results Among the 115 enrolled patients, only one was lost to follow-up at month 60. For the azathioprine and rituximab groups, respectively, at month 60, the major relapse-free survival rates were 49.4% (95% CI 38.0% to 64.3%) and 71.9% (95% CI 61.2% to 84.6%) (p=0.003); minor and major relapse-free survival rates were 37.2% (95% CI 26.5% to 52.2%) and 57.9% (95% CI 46.4% to 72.2%) (p=0.012); overall survival rates were 93.0% (95% CI 86.7% to 99.9%) and 100% (p=0.045) and cumulative glucocorticoid use was comparable. Quality-adjusted time without symptoms and toxicity analysis showed that rituximab-treated patients had 12.6 months more without relapse or toxicity than those given azathioprine (p<0.001). Antiproteinase-3-ANCA positivity and azathioprine arm were independently associated with higher risk of relapse. HRs of positive ANCA to predict relapse increased over time.

Conclusion The rate of sustained remission for ANCA-associated vasculitis patients, following rituximab-based or azathioprine-based maintenance regimens, remained superior over 60 months with rituximab, with better overall survival.

Trial registration number NCT00748644.

INTRODUCTION

Antineutrophil cytoplasm antibody (ANCA)-associated vasculitides are necrotising vasculitides affecting small-sized vessels, with potential organ-threatening or life-threatening complications.[1] They include granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss). The latter is usually studied separately because of its particularities. Staged therapeutic strategies based on disease severity have dramatically improved overall survival over the last decades.[2–5]

Rituximab was approved, combined with glucocorticoids, for remission-induction treatment of severe granulomatosis with polyangiitis and microscopic polyangiitis, based on the results of the Rituximab in ANCA-Associated Vasculitis (RAVE) trial[6] and the Rituximab versus Cyclophosphamide in ANCA-Associated Vasculitis trial.[7] Follow-up of RAVE trial patients showed the non-inferiority of the single initial rituximab cycle to cyclophosphamide then azathioprine at achieving sustained remissions.[6 8] However, only 39% of the rituximab-treated patients and 33% of the cyclophosphamide–azathioprine group remained in sustained complete remission off glucocorticoids at month 18, highlighting the persistently high relapse rate of ANCA-associated vasculitides.

The prospective, open-label, randomised, controlled Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN) trial compared systematic rituximab infusions to azathioprine for maintenance of remission.[9] Its results demonstrated that the rituximab maintenance regimen was superior to azathioprine at preventing major relapses at 28 months. However, remission duration following rituximab-based or azathioprine-based maintenance regimens and their long-term toxicities are unknown. Herein, we report MAINRITSAN trial patients' 60 month follow-up (online supplementary data).

METHODS

Study oversight

This MAINRITSAN trial was designed by the two coprincipal investigators (CP and LG). Long-term outcome data were collected by the site investigators and analysed by the Data Analysis Committee (BT, CP, EP, PR and LG) that did not include representatives from Hoffmann-La Roche, which

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provided some of the rituximab for the study. Hoffmann-La Roche was not involved in or consulted about the study design, did not review the manuscript and did not have access to the study data or provide any other support.

All manuscript drafts were written by BT, CP and LG, with input as appropriate from coauthors and other-site investigators (see online supplementary appendix). The Hôpital Cochin Comité de Protection des Personnes (Paris) approved the study, which received legal, monitoring and administrative management support from the Assistance Publique-Hôpitaux de Paris and was funded by the French Ministry of Health (NCT00748644; EudraCT 2008-002846-51).

Patients

The MAINRITSAN trial design details were reported previously.[9] Briefly, patients with newly diagnosed or relapsing granulomatosis with polyangiitis, microscopic polyangiitis or renal-limited ANCA-associated vasculitides in complete remission after combined glucocorticoids and 'pulse' intravenous cyclophosphamide were enrolled between October 2008 and June 2010. Patients were followed every 3 months for 28 months. Thereafter, patients were followed prospectively until month 60, every 3–6 months according to their clinical status.

Treatment groups

They were randomly assigned, at a 1:1 ratio, to receive rituximab or azathioprine maintenance and followed for 28 months. After induction therapy until remission, patients were randomised to receive rituximab (500 mg on days 0 and 14, and at months 6, 12 and 18 postinclusion) or azathioprine (dose: 2 mg/kg/day for 12 months; 1.5 mg/kg/day for 6 months; then 1 mg/kg/day for 4 months). Prednisone dose tapering and the decision to stop prednisone after month 18 were left to each site investigator's discretion. Co-trimoxazole prophylaxis was recommended for all patients with <250 CD4+ T cells/mm^3.

Study assessments

At each follow-up visit, information on disease activity, medications and adverse events (AEs) were collected. Each patient's serum samples were tested in each study centre for ANCA by indirect immunofluorescence and for antiproteinase 3 (PR3) and antimyeloperoxidase (MPO) ANCA with ELISAs, according to clinical status. Rituximab-treated patients' CD19+ B lymphocytes (defined as B cell count >0/mm^3) were counted locally at least before each infusion, during the initial 28-month study period, then according to clinical status.

Outcomes

The primary 60-month endpoint was the time to first major relapse (reappearance or worsening of disease with Birmingham Vasculitis Activity Score (BVAS) >0 and involvement of at least one major organ, a life-threatening manifestation or both). Secondary endpoints included time to first relapse, that is, major or minor (reappearance or worsening of disease with BVAS >0, not corresponding to a major relapse but requiring mild treatment intensification), AEs and their severity and mortality. Relapses were initially graded by each patient's site investigator, then reassessed and validated by the Data Committee. Relapses were treated according to the site investigator's decision. Grade 3/4, death (from any cause; grade 5), cancers, cardiovascular events, AEs requiring hospitalisation or infusion reactions that contraindicated further infusions defined severe AEs (SAEs). Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) analyses assessed relapse and SAE-free times for the two groups at 60 months.

Statistical analyses

Patients' data were analysed and compared according to the initial randomisation group. Kaplan-Meier survival curves described overall, major and major and minor relapse-free and event-free survival rates for each arm. Survival analyses were censored at 60 months of follow-up. Survival rates were compared using marginal Cox models to consider the centre effect. The comparison was stratified on disease status (newly diagnosed, relapsing), which was a stratification parameter at randomisation. HRs and their 95% CIs were derived from the Cox models and tested with robust-score tests. Because no rituximab-arm patient died, a stratified log-rank test was used to compare overall survival between groups. Q-TWiST analyses were also run (see online supplementary appendix).

For each patient, the cumulative glucocorticoid dose was estimated with the area under the curve (AUC) of glucocorticoid-dose evolution versus time (inclusion to month 60). AUC means were compared between groups using a linear-mixed model with a random effect at the centre level. For patients with incomplete follow-up, the AUC was divided by the real follow-up time and multiplied by 60 months.

Age at disease flare, sex, ANCA-associated vasculitis, PR3-ANCA status at disease flare, creatininemia >2.27 mg/dL (200 μmol/L), ear, nose and throat, pulmonary and/or cardiovascular involvement(s) and ANCA at inclusion were evaluated as potential factors predictive of relapse. Factors with p value <0.20 in univariate analysis were included in the multivariate analysis. These analyses were adjusted on treatment arm.

To analyse changes in ANCA and B cell count over time as predictors of relapses, we used ANCA and B cell count collected at time points s=0, 3, 6, 9, 12, 15, 18, 21, 24, 28, 36, 42 and 48 months. For each time point, we constructed a data set by selecting all individuals at risk at time *s* (ie, no relapse before s, but still followed-up at s). Data recorded at the month 54 visit were not used as there was not enough information after this time point (individuals at risk, relapses). For each data set, we fitted two Cox models, one for ANCA and one for B cell count. Treatment arm was included as an adjustment variable in each model. HRs for each separate model (one per time point) were plotted against time points. All statistical tests were two-sided with p values <0.05 defining significance.

RESULTS

Patients

Figure 1 follows the status of the 115 enrolled patients (58 randomised to azathioprine, 57 to rituximab) over 28 and 60 months. One hundred and ten (96%) patients completed the 60-month follow-up (four died, one was lost to follow-up and censored at last follow-up).

Efficacy assessments

Relapses

As previously reported, for azathioprine and rituximab arms, respectively, 17 (29%) and three (5%) patients suffered major relapses during the first 28 months, and nine (16%) and six (11%) patients had minor relapses.

Between months 28 and 60, for azathioprine and rituximab arms, respectively, among previously major relapse-free patients, 11 (19%) and 13 (23%) additional patients experienced major relapses; while three (5%) and seven (12%) had minor relapses.

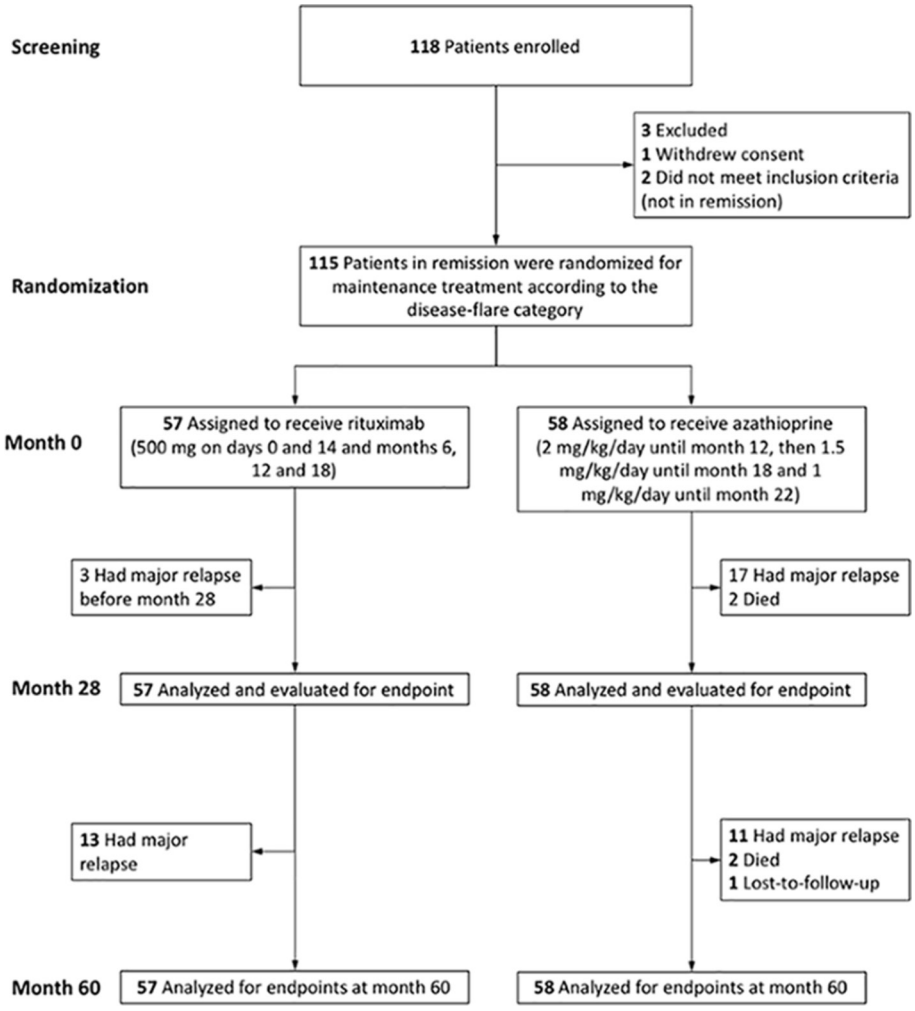

Figure 1 Randomisation and inclusion in the analysis at months 28 and 60. Patients were randomly assigned, at a 1:1 ratio, to receive rituximab or azathioprine maintenance therapy. Randomisation was stratified according to disease-flare category. Among azathioprine-treated patients, four died and one was lost to follow-up after month 28; they were censored at last follow-up. The remaining 110 (96%) patients completed the 60 months of follow-up.

Only one of the 11 azathioprine-group patients with major relapses and two of the 13 rituximab recipients had previously experienced minor relapses during the first 28 months of follow-up. Moreover, all the azathioprine-group patients with minor relapses had prior minor relapses during the first 28 months, versus only two of the seven rituximab recipients.

Hence, at month 60, for the azathioprine and rituximab arms, respectively, the major relapse-free survival rates were 49.4% (95% CI 38.0% to 64.3%) and 71.9% (95% CI 61.2% to 84.6%) (p=0.003) and all relapse-free survival rates were 37.2% (95% CI 26.5% to 52.2%) and 57.9% (95% CI 46.4% to 72.2%) (p=0.012). The azathioprine versus rituximab HRs were 2.51 (95% CI 1.35 to 4.69) (p=0.003) for major relapses and 2.11 (95% CI 1.19 to 3.73) (p=0.012) for major or minor relapses. Kaplan-Meier curves estimated the probability of remaining major or major and minor relapse free (figure 2A, B).

Cumulative glucocorticoid dose

Cumulative glucocorticoid doses, estimated with glucocorticoid-dose versus time (inclusion to month 60) AUCs, were comparable: 11 767 mg (SD 6529 mg) for the azathioprine group and 9841 mg (SD 6557 mg) for rituximab recipients (mean difference 1964 mg; 95% CI –461 to 4388; p=0.110) (online supplementary figure S1).

Adverse events

SAEs are listed in table 1. Sixteen (28%) azathioprine group and 15 (26%) rituximab-arm patients developed severe infections. Infections were mainly respiratory (bronchitis and pneumonia), most frequently in rituximab recipients, while other infections were equally distributed in the two groups. Opportunistic infections included three *Pneumocystis jiroveci* pneumonias, two aspergilloses and two mycobacterial infections. Concerning *P. jiroveci* pneumonia patients (two given rituximab and one taking azathioprine), one had discontinued co-trimoxazole 1 month before infection onset because treatment duration had been considered sufficient, another was allergic to co-trimoxazole and complied poorly with monthly pentamidine aerosolisations and the last received no prophylaxis because of pre-existing co-trimoxazole allergy.

For azathioprine-group and rituximab-group patients, respectively, five (9%) and six (11%) developed cardiovascular events, six (10%) patients had cancers (including non-melanoma skin cancer in four) and two (4%) prostate cancers (men aged 68 years and 73 years).

Overall, SAE-free survival was comparable for the two treatment groups (figure 2D). The azathioprine versus rituximab HR for SAEs was 1.02 (95% CI 0.63 to 1.62) (p=0.951).

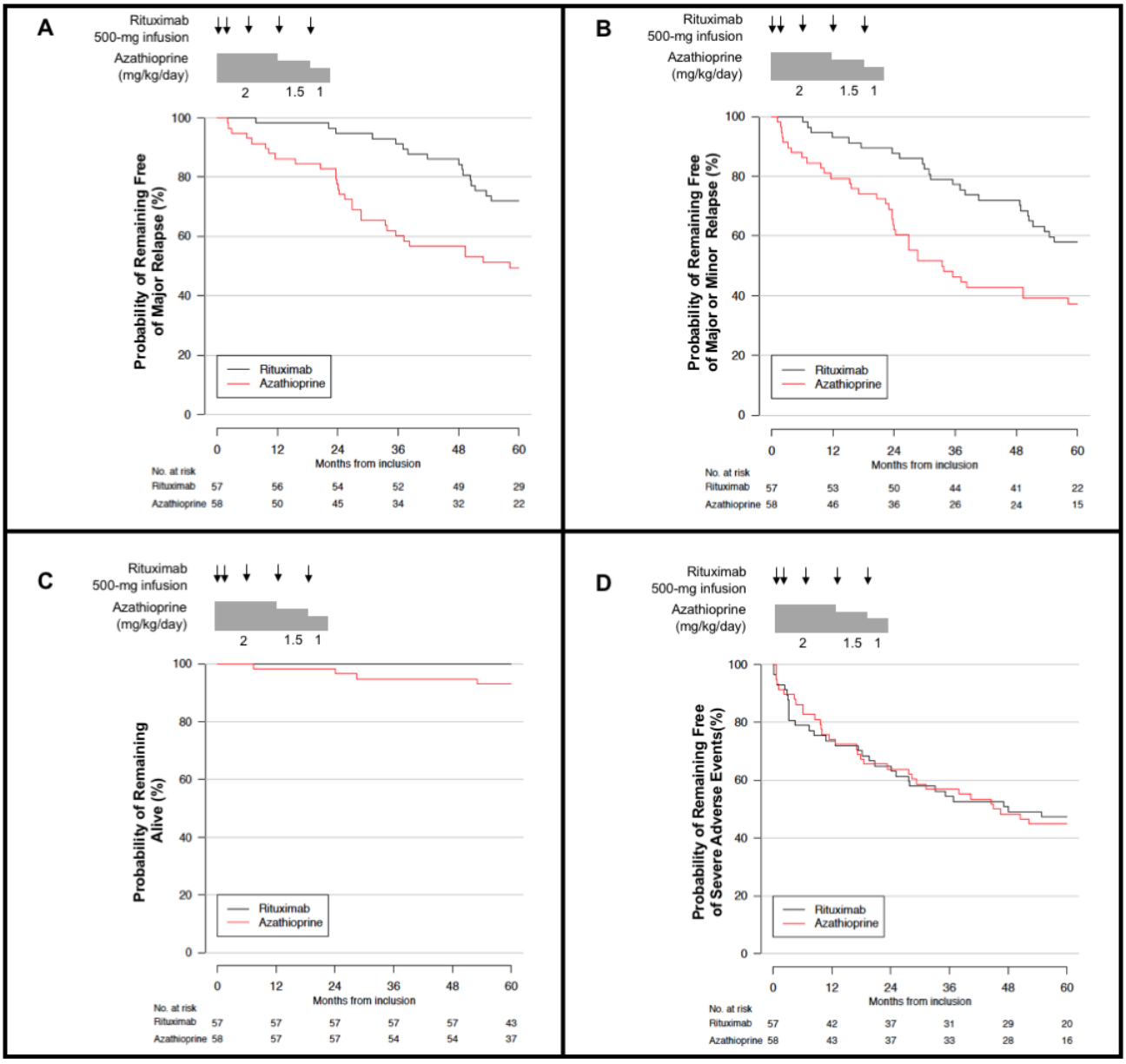

Figure 2 Kaplan-Meier curves for the probability of remaining relapse free according to treatment group. Patients were randomly assigned to receive maintenance therapy with rituximab (500 mg on days 1 and 15 and then months 6, 12 and 18 after the first infusion (arrows)) or azathioprine (2 mg/kg/day from day 1 to month 12, 1.5 mg/kg/day until month 18, then 1 mg/kg/day until the last day of month 22 (horizontal grey bars)). Shown are the postrandomisation probabilities of remaining major relapse free (A) (HR for azathioprine-group patients vs rituximab recipients was 2.51; p=0.003); remaining major or minor relapse free (B) (HR 2.11; p=0.012); surviving (C): because no rituximab-arm patient died, a stratified log-rank test was used to compare between-group overall survival. At 60 months, overall survival rates were 100% for the rituximab group and 93.0% for the azathioprine group (95% CI 86.7% to 99.9%) (p=0.045) and remaining severe adverse event free (D): rates were comparable between the two treatment arms (HR 1.02 (95% CI 0.63 to 1.62; p=0.951).

Deaths

Four azathioprine-group patients died during the trial: three with granulomatosis with polyangiitis and one with microscopic polyangiitis, all newly diagnosed. Two had already been described and occurred before month 28.[9] The third one, a 68-year-old azathioprine-treated man with microscopic polyangiitis with renal involvement (initial serum creatinine: 2.76 mg/dL), in remission after six cyclophosphamide pulses, suffered, at month 10, a major relapse treated with prednisone and rituximab; he died of mesenteric infarction at month 29. The fourth, a 72-year-old azathioprine-treated man with granulomatosis with polyangiitis in remission after six cyclophosphamide pulses developed, at month 28, a major relapse treated with prednisone and rituximab infusions and achieved remission; at month 53, he relapsed again and died of acute heart failure unrelated to vasculitis.

At 60 months, overall survival rates were 93.0% for the azathioprine group (95% CI 86.7% to 99.9%) and 100% for rituximab recipients (p=0.045) (figure 2C).

Q-TWiST analyses

During the 60-month follow-up, rituximab recipients spent 12.6 months more free of relapse or toxicity (p<0.001). The Q-TWiST period was significantly shorter for the azathioprine-treated

Table 1 Severe adverse events according to treatment group

Severe adverse event	Azathioprine group (n=58) No. of events	Rituximab group (n=57)
Infection	20	31
Bronchitis	1	10
Pneumonia with respiratory distress syndrome	3	6
Infectious diarrhoea	4	2
Cholecystitis	2	1
Acute urinary infection	2	1
Pneumocystis jiroveci pneumonia	1	2
Sepsis	1	1
Lung aspergillosis	2	0
Pleural effusion	1	0
Bacterial endocarditis	1	0
Varicella zoster virus infection	1	1
Lung tuberculosis	0	1
Lung atypical mycobacterial infection	1	0
Oesophageal candidiasis	0	1
Colon diverticulitis	0	1
Appendicitis	0	1
Bacterial orchitis	0	1
Infected elbow hygroma	0	1
Unspecified viral infection	0	1
Cardiovascular events	5	6
Cancer	6	2
Skin (non-melanoma)	4	0
Prostate	0	2
Pancreas	1	0
Gastrointestinal stromal tumour	1	0

patients than rituximab recipients (48.0 vs 55.2 months, respectively, p<0.001) (online supplementary table S1 and figure S2). Sensitivity analyses, varying utility coefficients for quality-adjusted health-state duration, yielded the same significant findings (online supplementary table S2).

ANCA testing, CD19+ B cell counts and gammaglobulin levels

Serial ANCA testing (immunofluorescence positive vs negative) and CD19+ Bcell counts for both groups during follow-up are summarised in the online supplementary figures S3 and S4, respectively. Twenty-two (81%) of the 27 azathioprine-treated patients with major relapses were ANCA positive at relapse. None of the three rituximab-arm patients with major relapses (on therapy) before month 28 had CD19+ Bcell reconstitution at the time of relapse, but two were ANCA positive. In contrast, 12 of the 13 rituximab recipients with major relapses between months 28 and 60 (post-therapy) were ANCA positive (data missing for one) at relapse, and all had CD19+ Bcell reconstitution (data missing for two), with CD19+ Bcell counts ranging from 10 to 206/mm^3.

Evolution of gammaglobulin levels was comparable in both groups before month 28 (not recorded after month 28), and is summarised in the online supplementary figure S5.

Factors predictive of relapse

Data from azathioprine and rituximab group were pooled. Risk factors of minor and major relapses were similar in patients from both groups, with no significant interaction between treatment arm and each predictor variable. Table 2 shows the results of the univariate and multivariate analyses. The HRs for relapse for patients with PR3-ANCA specificity and azathioprine arm were 2.04 (95% CI 1.06 to 3.91) (p=0.032) and 2.72 (95% CI 1.55 to 4.76) (p<0.001) in multivariate analysis, respectively.

Table 2 Univariate and multivariate analysis of factors predictive of vasculitis relapse in treated patients

Variables	HR (95% CI)	P values
Univariate analysis		
Age (years)	1.00 (0.98 to 1.02)	0.984
Male (vs female)	1.00 (0.59 to 1.68)	0.997
GPA (vs MPA or renal-limited vasculitis)	2.08 (1.07 to 4.03)	0.030
PR3-ANCA (vs MPO-ANCA or no ANCA)	2.18 (1.18 to 4.00)	0.012
Serum creatinine >2.27 mg/dL	0.58 (0.30 to 1.10)	0.093
Ear, nose and throat involvement	1.59 (0.83 to 3.02)	0.161
Pulmonary involvement	1.04 (0.61 to 1.76)	0.884
Cardiovascular involvement	1.10 (0.60 to 2.00)	0.764
Induction to remission ANCA evolution (persistence vs disappearance)	1.09 (0.65 to 1.82)	0.756
Multivariate analysis		
PR3-ANCA (vs MPO-ANCA or no ANCA)	2.04 (1.06 to 3.91)	0.032
Serum creatinine >2.27 mg/dL	0.58 (0.31 to 1.11)	0.100
Ear, nose and throat involvement	1.18 (0.59 to 2.35)	0.634
Arm (AZA vs RTX)	2.72 (1.55 to 4.76)	<0.001

ANCA, antineutrophil cytoplasmic antibodies; AZA, azathioprine; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, antiproteinase 3; RTX, rituximab.

HRs of detectable B cells to predict relapse was constant over time (figure 3A), whereas HRs of positive ANCA to predict relapse increased over time with a significant linear trend test (p<0.001, compared with p=0.716 for B cell count) (figure 3B).

DISCUSSION

According to this long-term analysis of MAINRITSAN trial patients, rituximab had a superior post-treatment efficacy than azathioprine at maintaining remissions of ANCA-associated vasculitides over 60 months, with a Q-TWiST analysis identified benefit and no safety differences with azathioprine. Our results also showed that rituximab maintenance was associated with better overall survival and that ANCA specificity and positive ANCA over time were associated with higher subsequent relapse risk.

Although the management of ANCA-associated vasculitis patients has dramatically improved since the 2000s, strategies to prevent late relapses, decrease glucocorticoid exposure and reduce disease-related and treatment-related morbidities remain suboptimal. After the 28-month MAINRITSAN trial results, the major question remains rituximab's ability to maintain long term, sustained ANCA-associated vasculitis remissions. More azathioprine-arm patients relapsed during the first 28 months of follow-up and that difference remained significant at month 60, with comparable major relapse rates between months 28 and 60 (17% for the azathioprine group vs 23% for rituximab recipients). The major-relapse frequency increased rapidly over the 12 months following azathioprine discontinuation at 22 months. Most rituximab-arm major relapses occurred 18–24 months after the last infusion (at 36–42 months), still suggesting longer and more sustained efficacy at maintaining remission. These findings suggest that rituximab could delay rather than abrogate relapses and emphasise the need to better identify patients with high-relapse risk that could benefit from longer treatment.

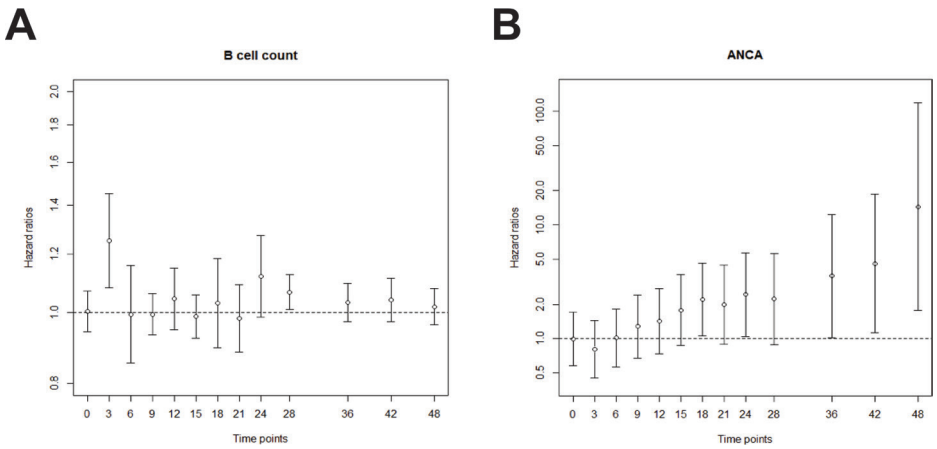

Figure 3 HRs of B cell count and antineutrophil cytoplasmic antibodies (ANCA) to predict vasculitis relapse for each separate model. HRs of detectable B cells to predict relapse was constant over time (A), whereas HRs of positive ANCA to predict relapse increased over time with a significant linear trend test (p<0.001, compared with p=0.716 for B cell count) (B).

The safety profile was comparable for both agents, except for respiratory infections that were slightly more frequent in rituximab recipients. *P. jiroveci* pneumonia occurred in three patients not receiving prophylaxis, further supporting the need for cotrimoxazole or, in case of sulfonamide allergy, pentamidine aerosolisations, oral dapsone or atovaquone to prevent *P. jiroveci* pneumonia in these patients. Cancers were infrequent but were more common in the azathioprine group.

Optimal maintenance therapy doses and durations to further improve long-term outcomes remain major challenges, as is the identification of patients who would benefit the most from prolonged treatment. Whether a rituximab dose exceeding 500 mg for maintenance, as chosen in our trial, could achieve fewer late relapses without increasing AEs, especially severe infections, warrants further investigation. The longest glucocorticoid intakes were associated with fewer relapses in a meta-analysis before rituximab was used to treat ANCA-associated vasculitides,[10] but ongoing vasculitis studies are mostly attempting to develop glucocorticoid-sparing strategies. A retrospective cohort study found that continuing azathioprine or methotrexate maintenance, respectively, for >18 or >36 months, obtained 29% or 66% HR reduction for relapse,[11] and the recently published randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis (REMAIN) trial demonstrated that prolonged remission maintenance therapy with azathioprine to 48 months from diagnosis reduced relapse risk and improves renal survival in AAV.[12] The ongoing MAINRITSAN-3 trial (NCT02433522) compares 46 versus 18 months of rituximab maintenance, like that used herein. Overall, optimal dose and duration of rituximab have still to be defined. Also, data from the Rituximab Vasculitis Maintenance Study (RITAZAREM) trial will show if higher dose of rituximab for almost the same duration show better relapse-free survival.

One secondary MAINRITSAN trial goal was to study correlation between ANCA reappearance and/or B cell reconstitution and the relapse rate. Most patients in each group were ANCA positive at relapse, and B cell reconstitution preceded relapses in most rituximab-treated patients, except for the very few early relapses that occurred during active therapy. Furthermore, our results showed that patients with PR3-ANCA-positive vasculitis were at higher risk of subsequent relapse. Also, positive ANCA over time were able to identify patients who might require longer and repeated maintenance treatment. These findings are consistent with those of previous studies on the impact of PR3-ANCA positivity in ANCA-associated vasculitides.[13–15] However, the role of ANCA monitoring in predicting relapses has always been controversial,[16–19] probably because of the heterogeneity of treatment regimens used in those studies.

This long-term trial follow-up study has several strengths. Its results should be applicable to the broad spectrum of patients seen in routine practice (eg, patients with granulomatosis with polyangiitis, microscopic polyangiitis and renal-limited vasculitis) and patients with newly diagnosed or relapsing disease were included, most with granulomatosis with polyangiitis. However, this latter high percentage of patients with granulomatosis with polyangiitis is relevant in a trial focusing on relapse prevention, because they are at a much higher risk of relapse than those with microscopic polyangiitis.[13–15] Finally, whereas the open-label study design could represent a limitation, major ANCA-associated vasculitis relapses were clearly defined, based on overt clinical manifestations.[20]

In conclusion, the long-term follow-up of MAINRITSAN trial patients showed that the lower risk of major relapses of ANCA-associated vasculitides observed at 28 months with 500 mg rituximab infusions administered on days 1 and 15 then every 6 months until month 18, compared with azathioprine, was sustained over 60 months, especially for patients with granulomatosis with polyangiitis and PR3-ANCA. PR3-ANCA specificity and positive ANCA over time were able to identify patients who might require longer and repeated maintenance treatment.

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