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ABSTRACT

Objective The randomised–controlled MAINRITSAN2 trial was designed to compare an individually-tailored (randomisation day 0 (D0)), with reinfusion only when CD19+ lymphocytes or ANCA had reappeared, or the latter's titer rose markedly) to five fixed-schedule 500-mg rituximab infusions (D0+D14, then months (M) 6, 12 and 18) to maintain ANCA-associated vasculitis (AAV) remissions. Relapse rates did not differ at M28. This ancillary study was undertaken to evaluate the effect of omitting the D14 rituximab infusion on AAV-relapse rates at M12.

Methods MAINRITSAN2-trial data were subjected to post-hoc analyses of M3, M6, M9 and M12 relapse-free survival rates in each arm as primary endpoints. Exploratory sub-group analyses were run according to cyclophosphamide or rituximab induction and newly-diagnosed or relapsing AAV.

Results At M3, M6, M9 and M12, respectively, among the 161 patients included, 79/80 (98.8%), 76/80 (95%), 74/80 (92.5%) and 73/80 (91.3%) from D0, and 80/81 (98.8%), 78/81 (96.3%), 76/81 (93.8%) and 76/81 (93.8%) from D0+D14 groups were alive and relapse-free. No between-group differences were observed. Results were not affected by cyclophosphamide or rituximab induction, or newly-diagnosed or relapsing AAV.

Conclusions We were not able to detect a difference between the relapse-free survival rates up to M12 of the D0 and D0+D14 rituximab-infusion groups, which could suggest that omitting the D14 rituximab remission-maintenance dose did not modify the short-term relapse-free rate. Nevertheless, results at M12 may also have been influenced by the rituximab-infusion strategies for both groups.

Key words: ANCA vasculitis, ANCA, CD19+ B lymphocytes, granulomatosis with polyangiitis, microscopic polyangiitis

Key messages

1 Omitting the day-14 500-mg rituximab remission-maintenance dose in an individually tailored rituximab-infusion regimen did not seem to impact the relapse-free survival rate at M12. Lack of power prevents us from drawing firm conclusions.

2 It did not affect rituximab's ability to delete circulating B cells.

3 Rituximab infusions (500 mg) on day 0, and at months 6, 12 and 18 could be envisaged.

Introduction

Rituximab, a chimeric murine human monoclonal IgG1 antibody directed against CD20+ lymphocytes, has become the cornerstone of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) treatment for both remission-induction and -maintenance therapies. It was shown to be non-inferior to cyclophosphamide to achieve remission [1, 2]; and a recent randomised–controlled trial (MAINRITSAN) demonstrated its superiority to azathioprine to maintain remission [3]. In that trial, all patients had received cyclophosphamide and glucocorticoids as induction therapy, and 500 mg of rituximab were infused on days 0 (D0) and 14 (D0+D14), then at months (M) 6, 12 and 18. Those results led to US Food and Drug Administration and European Medicines Agency approvals of that rituximab-administration schedule for AAV maintenance therapy. Although rituximab's efficacy at maintaining remission is now certain, questions remain about the modalities of its use.

Different rituximab-infusion schedules have been used for many years to maintain remission in retrospective studies: 500 mg every 6 months, 375 mg/m^2 every 6 months, 500 mg every 12 months, 1000 mg every 6 months, 1000 mg every 4 months only when patients experienced a relapse, infusion based on CD19+ B-cell reconstitution and/or ANCA-test results [4–9]. The results of a recent retrospective study that included 114 patients who had received rituximab induction, followed by maintenance therapy with 500-mg infusions on D0, then at M6, M12 and M18 [10], suggested that D14 infusion after rituximab induction could be omitted. The MAINRITSAN2 trial compared an individually-tailored rituximab-infusion schedule based on ANCA- and CD19+ B–cell-monitoring to five rituximab infusions at a pre-defined schedule [11]. The tailored-regimen group received a 500-mg rituximab infusion at randomisation (D0), with reinfusion only when CD19+ lymphocytes or ANCA had reappeared or their titer rose markedly, based on testing every 3 months until

M18. The fixed-schedule group received rituximab (500 mg) on D0+D14, then at M6, M12 and M18. AAV-relapse rates did not differ significantly between the two groups at M28. In the tailored-regimen group, the D14 rituximab infusion was systematically omitted. Despite the trial not being designed to evaluate the effect of that omission, we thought that studying the initial MAINRITSAN2-trial data might be informative about the effect of lowering the initial rituximab dose.

The objective of this post-hoc analysis was to evaluate the effect of omitting the D14 500-mg rituximab infusion on AAV-relapse rates at M3, M6, M9 and M12. CD19+ B-cell repopulation starts between 6 and 9 months post-infusion in patients with rheumatoid arthritis [12], but long-lasting B-cell depletion has been observed in AAVs [13]. In a prospective study, sustained CD19+ B-cell depletion persisted in 75% of AAV patients at M12 after rituximab administration [1]. Therefore, we decided to analyse our data until M12, even though, at that time, the direct impact of omitting the D14 rituximab infusion could be difficult to discern from that of the MAINRITSAN2 infusion schedule (individually tailored *vs* fixed).

Methods

An exploratory post-hoc analysis of MAINRITSAN2-trial data was conducted.

Patients

The detailed MAINRITSAN2-trial design was reported previously [11]. Briefly, patients with newly-diagnosed or relapsing granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA), in complete remission after induction therapy, combining glucocorticoids and cyclophosphamide, rituximab or methotrexate, were randomised to receive maintenance therapy with either the “individually-tailored” (according to laboratory

findings every 3 months) or “fixed-schedule” (control) rituximab regimen. In this ancillary study, the only patient who received methotrexate-induction therapy was excluded from the analyses.

Study interventions

Tailored-infusion–arm patients (D0 group) always received 500 mg of rituximab at randomisation; then ANCA and circulating CD19+ B lymphocytes were assessed every 3 months. Another 500 mg were infused when ANCA status differed from the previous test (i.e., reappearance after being negative, indirect immunofluorescence-determined ≥2-dilution–titer increase and/or at least doubled enzyme-linked immunosorbent assay anti-proteinase-3 (PR3) or anti-myeloperoxidase (MPO)) arbitrary units or circulating CD19+ B-cell counts exceeded 0/mm^3.

The D0+D14 (control) group received 500-mg rituximab infusions on D0+D14 post-randomisation, and at M6, M12 and M18 after the first infusion.

Assessments

MAINRITSAN2-trial visits were scheduled at enrollment, then every 3 months until the primary endpoint, M28 post-randomisation. At each visit, Birmingham Vasculitis Activity Score (BVAS) was calculated, ANCA were tested and CD19+ B-cell counts were determined.

This ancillary analysis focused on early relapse or mortality rates up to M12.

The endpoints of this study were the composite endpoint of relapse or death at M3, M6, M9 and M12. Relapse was defined as reappearance or worsening of AAV symptoms, i.e., BVAS > 0. Other endpoints were ANCA status and titer, and CD19+ B-cell–count evolutions.

Statistical analyses

Descriptive statistics are expressed as numbers (%) for qualitative variables and mean (standard deviation (S.D.)) or medians (interquartile range (IQR)) for quantitative variables. Exploratory statistical tests compared the composite-endpoint rates at each assessment time using χ^2 or Fisher's exact tests, as appropriate. Sub-group analyses were pre-defined according to induction therapy (rituximab *vs* cyclophosphamide) and AAV type (newly-diagnosed *vs* relapsing). The α-risk was set at 5% for all statistical analyses. Because all analyses were considered exploratory, no correction was applied for multiple statistical tests. We used SAS v9.4 (Gary, NC, USA) and R version 3.4.3.

Results

Enrollment and baseline characteristics

Between November 2012 and November 2013, 162 patients were randomized in 59 centers participating in the MAINRITSAN2 trial. The patient who received methotrexate as induction therapy was excluded from this study. Briefly, among the 161 remaining patients: 116 (72.0%) had GPA and 45 (28%) MPA; 104 (64.6%) and 57 (35.4%), respectively, were in remission after a first flare or at least one relapse. Pre-inclusion induction treatment included cyclophosphamide for 100 (62.1%) and rituximab for 61 (37.9%).

Relapse or death at M3, M6, M9 and M12

Among the 161 patients included in this study, those alive and relapse-free at M3, M6, M9 and M12, respectively, were distributed as follows: 79/80 (98.8%), 76/80 (95%), 74/80 (92.5%), 73/80 (91.3%) in the D0-infusion group, and 80/81 (98.8%), 78/81 (96.3%), 76/81 (93.8%) and 76/81 (93.8%) in the D0+D14-infusion group. No statistically significant

between-group difference was observed, but the study was not sufficiently powered to detect a difference at these times. Having received cyclophosphamide or rituximab for induction, being newly-diagnosed or experiencing a relapse did not change those results (see Table 1 and Supplementary Tables S1–S3).

Two D0+D14-infusion–group patients died during this period: one of carcinomatous meningitis 7 months post-randomisation and one of nosocomial pneumonia 6 months post-randomisation.

Circulating CD19+ B-lymphocyte evolution

Median (IQR) circulating CD19+ B-cell counts/mm^3 on D0, and at M3, M6, M9 and M12, respectively, were: 10 (1–40), 0 (0–0), 0 (0–1), 0 (0–5) and 0 (0–2) for the D0-infusion group; and 11.5 (0–35), 0 (0–1), 0 (0–2), 0 (0–1) and 0 (0–2) for the D0+D14-infusion group. Those results remained unchanged in the sub-group analyses (Fig. 1A–C). The frequencies of patients without circulating CD19+ B cells are reported in Supplementary Table S4. Similar between-group findings were obtained except at M9 and M12, when D0-infusion patients were less likely to have no circulating CD19+ B cells. That observation is explained by the fact that all D0+D14-infusion patients received an infusion at M6 while D0-infusion patients only received an infusion if CD19+ B lymphocytes or ANCA had reappeared, or ANCA titer rose markedly. Sub-group analyses yielded consistent results.

ANCA evolution

The frequencies of patients with detectable ANCA are reported in Supplementary Table S5. On D0, a higher percentage of D0-infusion patients were ANCA-positive and that difference remained stable at M12.

Discussion

Our ancillary, post-hoc analyses were not able to detect differences between the relapse-free survival rates of AAV patients who received 500 mg of rituximab on D0 or D0+D14 as their first maintenance therapy dose(s). These are the first prospective data comparing the two treatment protocols for patients given cyclophosphamide or rituximab and glucocorticoid induction therapy, and the results did not differ within these sub-groups. Eliminating the D14 infusion also did not seem to lower rituximab's ability to diminish the number of circulating CD19+ B cells at M12.

Rituximab has been used to maintain AAV remissions for many years [5, 7], has demonstrated superiority to azathioprine [3] and should be the preferred agent for this indication. Historically, limiting toxicity related to immunosuppressants dramatically improved AAV prognosis. The MAINRITSAN trial validated that rituximab effectively maintained remission with a 500-mg dose at D0, D14, M6, M12 and M18 [3]. In the MAINRITSAN2 trial, patients assigned to an individually-tailored regimen received fewer rituximab infusions without experiencing more relapses [11]. These post-hoc analyses of that trial's data suggest that the D14 rituximab infusion may be omitted, regardless the induction regimen that had been administered.

This study has several limitations. The trial was not designed to evaluate the effect of suppressing the D14 rituximab infusion and the results, particularly after 6 months, might be explained by the rituximab-infusion strategies: individually tailored vs fixed schedule. It is a post-hoc analysis of a randomised–controlled trial, not powered to detect difference(s) at M3, M6, M9 and M12. Pertinently, the absence of difference does not mean equivalence. It also carries over the limitations of the main study [11], e.g. open-label trial, absence of centralisation of biological parameter determinations (ANCA testing and CD19+ B-cell counts).

Conclusion

Eliminating the D14 500-mg–rituximab remission-maintenance dose in an individually tailored rituximab regimen did not seem to impact the relapse-free survival rate of AAV patients at M3, M6, M9 and M12, which could suggest that the D14 infusion could be omitted from the treatment protocol.

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Competing interests BT has received consulting and speaking fees (Roche, LFB, Grifols, GSK). MH has received personal fees from Roche. AK has received personal fees and non-financial support from Roche. XP has received speaking fees and honoraria (Pfizer, LFB, Roche), and a research grant (Pfizer). All the other authors have no competing interest to declare.

TABLE 1 Relapse or death at month 12 according to sub-group analyses

Sub-group	D0 RTX	D0+D14 RTX	*P*-value
All patients (*n* = 161)	7/80 (8.8%)	5/81 (6.2%)	0.56
Induction therapy			
RTX (*n* = 60)	3/28 (10.7%)	2/32 (6.3%)	0.66
CYC (*n* = 101)	4/52 (7.7%)	3/49 (6.1%)	1
Newly-diagnosed AAVs			
Yes (*n* = 104)	5/53 (9.4%)	4/51 (7.8%)	1
No (*n* = 57)	2/27 (7.4%)	1/30 (3.3%)	0.60

D0 RTX, individually-tailored RTX-infusion group; D0+D14 RTX, fixed-schedule RTX-infusion group; RTX, rituximab; CYC, cyclophosphamide; AAVs, ANCA-associated vasculitides.

Figure Legend

Figure 1. Evolution of mean (S.D.) circulating CD19+ B-cell counts/mm^3 over the 12-month study period **(A)** for all AAV patients, and the sub-groups of patients **(B)** who had received rituximab (RTX) or **(C)** cyclophosphamide and glucocorticoids for remission induction. D, day; D0 RTX, individually-tailored RTX-infusion group; D0+D14 RTX, fixed-schedule RTX-infusion group.