SUPPLEMENTARY TEXT. Additional Results

Demographic Characteristics

At diagnosis, patients classified as GPA or PR3-AAV were approximately 15 years younger (mean age ~45 years) compared to those classified as MPA or MPO-AAV (mean age ~60 years), respectively ($P < 0.01$ for both comparisons). There were also significantly more male subjects within the GPA group compared with the MPA group (54% versus 38%; $P = 0.04$) and within the PR3-AAV group compared to the MPO-AAV group (58% versus 36%; $P < 0.01$).

Baseline Disease Characteristics

The baseline disease characteristics for the four groups are shown in **Table 1**. Patients with GPA were more likely than those with MPA to have relapsing disease at baseline (62% versus 19%; $P < 0.01$). The same finding was true for PR3-AAV patients compared to MPO-AAV patients (62% versus 30%; $P < 0.01$).

Patients with MPO-AAV had a greater frequency of vasculitic neuropathy compared to patients with PR3-AAV (27% versus 15%, $P = 0.04$), even after adjusting for differences in age, serum creatinine concentration, and the presence of diabetes mellitus (OR 2.33, 95% CI 1.03 to 5.30; $P = 0.04$). In contrast, the frequency of vasculitic neuropathy was equivalent between the MPA and GPA groups (19% versus 18%, $P = 0.95$). Renal disease was more common and more severe among patients with MPA and MPO-AAV. The mean (SD) serum creatinine concentration at

baseline was 1.8 (0.9) in MPA and 1.3 (0.7) in patients with GPA ($P < 0.01$). Corresponding values in patients with MPO-AAV and PR3-AAV were 1.7 (0.8) and 1.3 (0.7), respectively ($P < 0.01$). In contrast, the GPA and PR3-AAV subsets had significantly more constitutional, ocular, and ear, nose and throat (ENT) manifestations than did those with MPA and MPO-AAV, respectively. The baseline prevalence of lung nodules and cavities was significantly higher in patients classified as GPA as opposed to MPA (29% versus 2%; $P < 0.01$). The same was true for PR3-AAV patients compared to those with MPO-AAV (28% versus 12%; $P = 0.02$). Alveolar hemorrhage, however, was similar across all four subsets (20-24%).

Effect of Treatment on ANCA titers in PR3-AAV and MPO-AAV patients

All of the patients were ANCA-positive at baseline but fewer than half (36%) became ANCA-negative over the first six months on their original treatment assignments. ANCA negativity was achieved at 6 months 40% and 41% of the MPO-AAV patients treated with RTX and CYC/AZA, respectively. In contrast, ANCA negativity by 6 months occurred in 50% of PR3-AAV patients treated with RTX but only 17% of those treated with CYC/AZA ($P < 0.01$). However, no statistically significant association between the achievement of ANCA-negativity and the achievement of complete remission by 6 months was detected in any of the four subgroups (data not shown).

Disease Relapse

A higher proportion of patients with GPA and PR3-AAV experienced disease exacerbations during the trial compared to patients with MPA and MPO-AAV (**Supplementary Table 1**). By 18 months, at least one relapse had occurred in 25% and 10% of the patients with GPA and MPA, respectively (P = 0.04); and in 25% and 12% of patients with PR3-AAV and MPO-AAV, respectively (p = 0.03). Non-severe relapses were also more common among patients in the GPA and PR3-AAV subsets compared to the MPA and MPO-AAV subsets. At least one non-severe relapse was seen in 31% of GPA patients compared with only 13% of those with MPA (P = 0.01), as well as in 31% of the PR3-AAV patients but only 15% of those with MPO-AAV (P = 0.02).

Multivariate Analyses of Relapse Risk

For a more accurate estimate of the risk of relapse associated with each classification category, we assessed the group of 146 patients who achieved complete remission at any time during the trial based on their originally assigned treatments. We built logistic regression models that included the following predictors: classification category (GPA versus MPA, PR3-AAV versus MPO-AAV), disease type at baseline (new-onset versus relapsing), renal involvement at baseline, serum ANCA status at 6 months (positive versus negative), and B-cell depletion status at 6 months (depletion [<10 $CD19^+$ B-cells/microliter] versus non-depletion)

The multivariate-adjusted OR of disease relapse from the time of complete remission through month 18 for the diagnosis of GPA as opposed to MPA was 3.1 (95% CI 1.04 - 9.14; p = 0.04). The corresponding OR for PR3-AAV as opposed to MPO-AAV was 3.2 (95% CI 1.3 - 8.05; p = 0.01).

Chronic damage

VDI scores were compared over time between pairs of groups (GPA versus MPA, PR3-AAV versus MPO-AAV) using repeated measures mixed-effect models that included a random subject intercept and other covariates such as visit number, baseline VDI value, patient group, and patient group by visit interaction.

An increase in damage from baseline through month 18 was seen in the whole cohort of patients regardless of the classification system used. By the end of follow up, patients classified as MPA and MPO-AAV demonstrated more damage than those with GPA and PR3-AAV (**Supplementary Table 1**). The mean (SD) VDI scores at baseline and 18 months in patients with GPA were 1.2 (1.6) and 2.2 (2.1), respectively. Corresponding values for patients with MPA were 0.9 (1.5) and 2.6 (2.2), respectively ($P < 0.01$ for both, group and time point comparisons). Similarly, the mean (SD) VDI scores at baseline and 18 months in patients with PR3-AAV were 1.3 (1.6) and 2.2 (2), respectively. Corresponding values in patients with MPO-AAV were 1.0 (1.7) and 2.5 (2.3), respectively ($P = 0.03$ for the group comparison and $P = 0.02$ for the comparison of time points).

Cumulative prednisone use

For the analysis of cumulative glucocorticoid use at 6, 12, and 18 months, we added the cumulative oral prednisone dose to the cumulative intravenous methylprednisolone dose converted to prednisone for each individual (1 mg of methylprednisolone = 1.25 mg of prednisone)

Glucocorticoid requirements up to 18 months were similar among groups regardless of the classification system used (**Supplementary Table 2**). Patients classified as PR3-AAV and GPA accumulated slightly larger doses of glucocorticoids at 6, 12, and 18 months, but differences did not reach the point of statistical significance. In addition, in all subsets (PR3-AAV, MPO-AAV, GPA and MPA) the cumulative prednisone dose was lower in RTX-treated patients; however, the point of statistical significance was only reached in PR3-AAV patients at 12 months. At this time point, the median cumulative prednisone dose was 4.1 grams in RTX-treated patients and 4.4 grams in CYC/AZA treated patients ($p = 0.04$).

Safety outcomes

A detailed analysis of the safety associated with each treatment arm through month 18 has already been published [1, 2]. This analysis included the incidence of leucopenia, infection, and malignancy, and the kinetics of the serum immunoglobulin G (IgG) among other safety outcomes.

Because an increased risk of venous thromboembolism (VTE) has been previously described in AAV [3], we looked into the incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) up to 18 months according to the two classification systems. Results demonstrated that within the PR3-AAV group, a PE and/or DVT occurred in 4 (3.1%) and 8 patients (6.1%), respectively. In contrast, there were no VTE events among MPO-AAV patients. When patients were classified as GPA or MPA, the results were similar. Within the GPA group, a PE and/or DVT occurred in 4 (2.7%) and 7 patients (4.8%), respectively. Among patients with MPA, there were no episodes of PE and only one case of DVT (2.1%)

Additional References

1. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK *et al*: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010, 363(3):221-232.
2. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Fessler BJ, Ding L *et al*: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013, 369(5):417-427.
3. Merkel PA, Lo GH, Holbrook JT, Tibbs AK, Allen NB, Davis JC, Jr., Hoffman GS, McCune WJ, St Clair EW, Specks U *et al*: Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) Study. *Ann Intern Med* 2005, 142(8):620-626.