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Treatment of Systemic Necrotizing Vasculitides in Patients over 65 Years

Results of the Multicenter Randomized CORTAGE Trial

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ABSTRACT

Objective. To investigate a new therapeutic strategy, with rapid corticosteroid (CS) dose-tapering and limited cyclophosphamide (CYC) exposure, for older patients with systemic necrotizing vasculitides (SNV; polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or eosinophilic GPA (EGPA)).

Methods. Multicenter, open-label, randomized-controlled trial on patients ≥65 years old with newly diagnosed SNV. The experimental treatment included, for all, CS for ~9 months and a maximum of six 500-mg fixed-dose IV-CYC pulses, every 2–3 weeks, then maintenance azathioprine or methotrexate. The control conventional treatment included ~26 months of CS for all, combined with 500 mg/m^2 IV-CYC pulses, every 2–3 weeks until remission, then maintenance for all GPA or MPA and EGPA or PAN with Five-Factor Score (FFS)≥1. The randomization used a 1:1-ratio computer-generated list and was performed centrally with sealed opaque envelopes. Primary outcome was ≥1 serious adverse events (SAEs) occurring within 3 years of follow-up. Secondary outcomes included remission and relapse rates.

Results. Among the 108 randomized (July 2005–March 2008) patients, 4 were excluded (early consent withdrawal or protocol violation). Mean age at diagnosis was 75.2±6.3 years. At 3 years, for experimental and conventional arms, respectively, analysis concerned 53 (21 GPA, 21 MPA, 8 EGPA, 3 PAN) and 51 patients (15 GPA, 23 MPA, 6 EGPA, 7 PAN); 32 (60%) versus 40 (78%) had ≥1 SAEs (P=0.04), most frequently infections; 6 (11%) versus 7 (14%) failed to achieve remission (P=0.71); 9 (17%) versus 12 (24%) died (P=0.41); 20/45 (44%) versus 12/41 (29%) survivors who had achieved remission relapsed (P=0.15).

Conclusion. For older SNV patients, an induction regimen limiting CS exposure and with fixed low-dose IV-CYC pulses reduced SAEs versus conventional therapy, and did not affect

the remission rate. Three-year relapse rates remained high for both arms. (Funded by the Ministry of Health institutional grant, PHRC 2004–AOM04008; ClinicalTrials.gov number, NCT00307671).

A previous retrospective study by our group showed that patients ≥65 years old diagnosed with systemic necrotizing vasculitis (SNV; polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA, Wegener's), microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis (EGPA, Churg–Strauss) had poorer outcomes than their younger counterparts, mainly because they develop more frequent and/or serious adverse events (SAEs; 68% versus 13%) under conventional therapy (1). Several other groups reported similar findings (2-6). Therefore, it is a common recommendation or practice to diminish, by up to one-third, the dose of the most potent induction immunosuppressant, e.g. as cyclophosphamide (CYC) for patients ≥65 years (7-9). However, no one has ever really studied this approach and demonstrated that it could lower the SAE rate without negatively impacting the sustained-remission rate.

The objective of the open-label, randomized–controlled CORTAGE (CORTicosteroid and cyclophosphamide-based induction therapy for SNV patients AGEd ≥65 years) trial was to investigate a newly defined therapeutic strategy, with lower cumulative doses of corticosteroids (CS) and CYC than conventional treatment, for SNV patients ≥65 years old. The primary aim was to decrease the morbidity and mortality rates using this specific induction regimen, without diminishing the remission rate.

PATIENTS AND METHODS

Patients. To be eligible, patients had 1) to have newly diagnosed PAN not related to hepatitis B virus infection, EGPA, GPA or MPA; 2) to satisfy the 1990 American College of Rheumatology criteria and/or 1994 Chapel Hill nomenclature definitions (10-13); 3) to be in or after the year of their 65th birthday at the time of SNV diagnosis; and 4) to provide written informed consent. They could have started CS, but for no more than 1 month prior to

enrollment, and should not have started CYC and/or received any other immunosuppressant before inclusion.

Study design and treatments. Eligible patients were randomized at diagnosis to receive, the experimental or the conventional (control) treatment, in a nonblinded manner.

The experimental regimen consisted of CS for a duration of ~9 months, combined for all patients with intravenous (IV) CYC pulses at a fixed 500-mg dose, every 2 weeks for the first 3 pulses then every 3 weeks until remission, then switched, after a maximum of 6 pulses, to azathioprine or methotrexate (or mycophenolate mofetil for patients with a contraindication for or intolerance to azathioprine or methotrexate) for a minimum 18 months of maintenance. Prednisone was started at 1 mg/kg, possibly after daily IV methylprednisolone pulses for 1–3 consecutive days, then progressively tapered after 3 weeks, following a predefined regimen schedule (online **Appendix B**), to achieve a daily dose of 30 mg at 7 weeks, then 7 mg/day at 6 months, and discontinued at month 9 (hence, a theoretical cumulative dose, not including initial methylprednisolone pulses, of 5,152 mg for a patient weighing 60 kg).

Conventional treatment for SNV is based on the original 1996 Five-Factor Score (FFS), which is a prognostic score for SNV survival (14, 15). It includes longer CS duration and higher body-surface-area– and age–adjusted CYC doses (7, 16). Vasculitis-related cardiomyopathy, central nervous system involvement, severe gastrointestinal manifestations, serum creatinine level >140 μmol/liter and proteinuria >1 g/24 hours at diagnosis count for 1 point each in the FFS calculation. This control therapy consisted of CS for ~26 months for all patients, combined with 500 mg/m^2 IV-CYC pulses for all GPA or MPA patients and EGPA or PAN patients with FFS≥1, according to the same schedule as

above, followed by 3 additional pulses for consolidation (1 pulse every 3 weeks), before maintenance (also as for the experimental arm) for at least 18 months. Patients with FFS=0 received only CS. Prednisone dosing was as above for the first 3 weeks, then more gradually tapered to reach, for a patient weighing 60 kg, 30 mg/day at 7 weeks, then 12.5 mg/day at 6 months, and discontinued after a total of 26 months (hence, a theoretical cumulative dose, not including initial methylprednisolone pulses, of 8,305 mg).

Randomization was done centrally, using numbered sealed-and-opaque envelopes to assure allocation concealment. The randomization list was computer-generated, using random blocks of 6, with a between-arm randomization ratio of 1:1.

Patients receiving CYC were given mesna for bladder protection at each pulse and co-trimoxazole (800 mg sulfamethoxazole/160 mg trimethoprim, 3 times per week) prophylaxis against *Pneumocystis jiroveci* infection, until 3 months after their last CYC pulse (17-19). All patients took calcium and vitamin D supplements. Bisphosphonates were recommended for all patients, as were low-dose aspirin (100 mg/day) or clopidogrel (75 mg/day) and statins for those not already on such medications. Folic acid supplementation (5 mg/day, except the day of methotrexate) was mandatory for patients taking methotrexate and considered for others (treating physician's discretion).

Study evaluations. Patients' main demographics, clinical and biologic characteristics at diagnosis (baseline) were recorded using standardized record forms by each center's investigators, who also calculated the initial FFS. Subsequent study visits were scheduled on days 14 and 28, then every 3 weeks until remission (conventional arm with FFS = 0) or last CYC pulse (for patients in the experimental arm and those with FFS $\geq$ 1 in the conventional arm), then every 3 months until year 3 post-diagnosis (all). Data on SNV and patient status,

treatment and potential SAEs were collected at each visit, along with the results of the main biologic parameters (hemoglobin level, white blood cell and eosinophil counts, C-reactive protein level, serum creatinine, proteinuria and urine red blood cell count). Antineutrophil cytoplasm antibodies (ANCA) were sought at diagnosis then, for positive patients, repeated during follow-up at the treating physician's discretion. Monitoring visits at each study site were scheduled before and within the 6 months following the first patient enrollment, then at 18 months for the study Safety Committee to allow study continuation, and at study closure. All record forms were retrieved at study closure for central data analysis by the primary study investigators and statisticians.

Study endpoints and definitions. The primary outcome was the occurrence of ≥1 SAEs, including all-cause deaths, during the 3 years of follow-up. SAEs were defined as potentially life-threatening adverse events, requiring hospitalization or its prolongation, causing significant disability or resulting in death.

Secondary outcomes included remission and relapse, as defined below, and overall, SAE-free and disease-progression–free (no induction failure and no relapse) survival rates. We also planned a quality-adjusted time without symptoms and toxicity (Q-TWiST) analysis, with the aim to better portray the impact of therapy and the trade-off(s) between treatment toxicity (SAE) and disease activity (treatment induction-failure or relapse) (20).

Patients were considered to be in complete remission when clinical and biologic signs of disease activity were absent for >1 month (corresponding in practice to a Birmingham Vasculitis Activity Score of 0) (21). Induction failure (persistent disease activity) corresponded to the absence of improvement after 6 weeks of induction, worsening or development of new disease manifestations under the remission-induction regimen. Relapse

was defined as the reappearance or new onset of manifestations attributable to active vasculitis in a patient previously in remission (22). Isolated ANCA titer change and/or, for EGPA patients, asthma or sinusitis exacerbation, with or without a concurrent increase of the eosinophil count, were not considered vasculitis flares.

All outcomes (SAE, remission, induction-failure, relapse) were initially recorded and graded by each patient's coinvestigator physician, then assessed and validated by the 2 coprincipal investigators (CP and LG) and, for SAEs, by members of the independent Statistics and Methodology Department (EP and PR, both blinded to treatment allocation).

Statistical analyses. The primary study hypothesis was an absolute 30% reduction (i.e., from 70%, based on our previous retrospective study (1), to 40%) of the occurrence of ≥1 SAEs, including death at 3 years with the experimental compared to the conventional regimen. With a 2-sided 5% alpha risk and 80% power to detect that effect, a minimum of 44 analyzable patients were needed in each arm and we thus aimed, assuming a 20% dropout rate, to enroll 108 patients.

All analyses were planned on a modified intent-to-treat principle, with predefined exclusion of inappropriately included patients (early protocol violation, e.g. an erroneous SNV diagnosis) or consent withdrawal within the first week. Categorical variables are reported as numbers (percentages) and compared using a chi-square test or, when appropriate, Fisher's exact test. Continuous variables are reported as means (standard deviation) and compared using Student's *t*-test. Patient global, SAE-free and disease-progression–free survival rates for each treatment arm, estimated using life tables and the Kaplan–Meier method, were compared with log-rank tests. For the Q-TWiST analysis, 3-year overall survival was partitioned into clinical health states as follows: TOX, time in

which the patient experiences ≥1 SAE; TWiST, time without disease activity and without SAE; and PROG, time with disease activity. Q-TWiST was obtained by summing up the adjusted health-state durations, as follows:

$$\text{Q-TWiST} = (\text{uTox} \times \text{TOX}) + \text{TWiST} + (\text{uProg} \times \text{PROG})$$

where uTox and uProg are the utility coefficients attributed to TOX and PROG, i.e. the perceived weights of these health states (20). Because there is some degree of uncertainty regarding these coefficients, a threshold utility analysis was performed, with uTox and uProg assigned weighted values ranging between 0 and 1, to test the sensitivity of the results and conclusions to weight changes. Mean durations of each health-state and Q-TWiST were compared using *z*-tests, with bootstrap calculation of standard-error distribution and quantile-method determination of 95% confidence intervals (CI) (20, 23).

For all analyses, $P \leq 0.05$ was considered significant. Statistical analyses were conducted using R statistical software (R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org) and Stata Statistical Software: Release 12 (College Station, TX: StataCorp LP).

Study oversight and role of funding. The CORTAGE trial was designed by the coprincipal investigators (LG, PC, LM, AM, FR, BB, XP, CP), in collaboration with the members of the French Vasculitis Study Group (other coauthors and online Appendix A). The protocol was approved by the Cochin Hospital Institutional Review Board (Comité de Protection des Personnes) on behalf of all investigating centers, and funded by an institutional grant from the Ministry of Health (PHRC no. 2004–AOM04008).

RESULTS

Enrollment and patient characteristics. Between July 2005 and March 2008, 108 patients were enrolled from 65 medical departments throughout France and Belgium (range, 1–5 patients per center); 4 were excluded within the first week (early consent withdrawal, protocol violation, wrong diagnoses; **Figure 1**).

Mean age at diagnosis of the 104 randomized and analyzed patients (53 experimental arm, 51 conventional arm; 59 males, 45 females; 10 PAN, 14 EGPA, 36 GPA, 44 MPA) was 75.2 ± 6.3 years, with a maximum of 92 years for 1 MPA patient. SNV characteristics were evenly distributed between study arms (**Table 1**), with more than half the patients having constitutional symptoms, fever or arthralgias; more than two-thirds had kidney disease, with a mean serum creatinine at diagnosis of 233.7 ± 199.3 μmol/liter (8 patients initially required dialysis); and around 20% with alveolar hemorrhage, gastrointestinal tract and/or cardiac involvement.

Sixty patients (32 experimental arm, 28 conventional arm) had ≥1 biopsies of an involved organ that supported the SNV diagnosis, mainly renal biopsy (41/45 biopsies showed active pauci-immune glomerulonephritis).

Treatments. Seventy-seven (74%) of the patients (36 experimental arm, 41 conventional arm; $P = 0.25$) initially received IV methylprednisolone pulses, before oral prednisone. For the experimental and conventional arms, respectively, starting prednisone daily doses were 60.0 ± 11.1 mg and 65.5 ± 11.3 mg (P=0.07), with all and 42 (82%; those with MPA or GPA or FFS ≥ 1) patients receiving CYC pulses. Their respective cumulative CYC doses per patient were 2,688 and 5,586 mg (for those with MPA or GPA or FFS ≥ 1; $P < 0.01$), with respective means of 5.3 ± 1.2 and 7.4 ± 2.6 pulses per patient ($P < 0.01$). The

respective intervals from first-to-last CYC pulse were 10.5 ± 4.0 and 14.9 ± 11.1 weeks (P = 0.05), with daily prednisone doses at last CYC pulse of 24.9 ± 9.8 and 22.3 ± 11.2 mg (P = 0.92; the mean daily prednisone dose in each arm during the study is shown in online **Appendix C)**.

The maintenance immunosuppressant for survivors who achieved remission with their assigned induction CYC regimen was azathioprine for 35 in the experimental arm and 31 in the conventional arm, methotrexate for 1 patient only (in the conventional arm), mycophenolate mofetil for 3 (1 and 2, respectively), and 2 (1 and 1) had received none because of prior cancers (prostate and gastrointestinal stromal tumor, both diagnosed >5 years before SNV; cholangiocarcinoma, diagnosed 6 months after starting CYC).

In the experimental and conventional arms, respectively, 37 versus 35 patients received folic acid supplementation throughout the study, whereas 25 versus 24 received low-dose aspirin, 8 versus 4 clopidogrel, and 36 versus 34 statins.

Endpoints. ***Serious adverse events.*** At 3 years, 32 (60%) experimental-arm patients had ≥1 SAEs (primary endpoint) versus 40 (78%) in the conventional arm (P = 0.04), mainly during the first year post diagnosis, as shown in **Figure 2A**. During the 3-year study, the hazard ratio (HR) for an SAE was 0.61 for the experimental versus conventional arm (95% CI, 0.38–0.98). At 3 years, those 72 patients had experienced 183 SAEs, with infections being the most frequent (**Table 2**).

Nine (17%) experimental-arm and 12 (24%) conventional-arm patients died during the study (P = 0.41), mainly due to sepsis (3 in each arm) or uncontrolled vasculitis (1 experimental, 3 conventional). Overall survival curves per arm are shown in **Figure 2B**.

Apart from the conventional-arm MPA patient diagnosed with cholangiocarcinoma after

his 6th CYC pulse, and 1 experimental-arm patient diagnosed with a biopsy-proven pituitary craniopharyngioma, 2 years after GPA diagnosis, no other incident neoplasm was diagnosed during follow-up of the survivors.

Efficacy. Six (11%) experimental-arm (4 GPA, 1 MPA with FFS = 0, and 1 MPA with FFS ≥ 1) and 7 (14%) conventional-arm (5 MPA with an FFS ≥ 1, and 2 GPA) patients failed to achieve remission with the assigned induction regimen ($P = 0.71$). Seven patients (2 experimental, 5 conventional) died during induction, including 4 (all in the conventional arm) who failed to achieve remission prior to death.

Twenty (44%) of those 45 experimental-arm survivors who had achieved remission with their assigned regimen relapsed, versus 12/41 (29%) in the conventional arm ($P = 0.15$). Twenty-one of those 32 relapses occurred in patients still on immunosuppressant maintenance, and 4 in conventional-arm patients (3 EGPA and 1 PAN) with FFS = 0, hence taking only CS. The 7 remaining relapses occurred after stopping the maintenance immunosuppressant (5 within the following 3 months, 1 at 6 months, and 1 at 30 months). Only 1 relapser (a 73 year-old conventional-arm MPA patient) died immediately following relapse, of uncontrolled SNV with multiorgan failure and sepsis.

At 3 years, relapse–free survival rates were 47% (95% CI, 32.5–60.6) in the experimental arm and 60% (95% CI, 44.4–72.3) in the conventional arm (**Figure 2C**). Thirty-nine (47%) of the 83 survivors were off prednisone, and only 8 of those still on prednisone were taking >10 mg daily. Ten of the 14 EGPA patients were still taking oral prednisone at their last study visit (median, 6 [range, 5–10] mg/day). Twenty-nine (56%; 12/28 in the conventional and 18/41 in the experimental arm, $P = 0.93$) of the 69 survivors, who had achieved remission with a CYC-based induction regimen and been switched to maintenance therapy,

were still taking that immunosuppressant. Five of the survivors were on chronic hemodialysis.

Q-TWiST analysis. The partitioned survival curves and average amounts of time that patients spent in TOX, TwiST and PROG during the 3 years of the study are shown for each treatment arm in **Figure 3**. During the 3-year study, with an arbitrarily selected scenario using uProg = uTox = 0.8 for weighting of the relative values of time spent in each predefined health state, experimental-arm patients had 0.39 months less time with SAEs, 3.06 months more time with active disease and 0.72 months less TWiST than conventional-arm patients (P = 0.06, 0.08 and 0.76, respectively). The threshold utility analysis at 3 years (online **Appendix D**) shows that the experimental-arm Q-TWiST was longer than for conventional-arm patients for a wide range of utility values, but never differed significantly.

Patient subgroups. Outcomes according to FFS or diagnosis, and between arms, are shown in the online **Appendix E**. The respective mortality and SAE rates were 28% and 79% for patients with FFS ≥ 1 versus 8% and 48% for those with FFS = 0.

DISCUSSION

The results of this randomized–controlled trial demonstrated that a specific induction regimen limiting CS exposure and with fixed 500mg IV-CYC pulses for SNV patients ≥65 years was associated with a lower rate of SAEs, including deaths, at 3 years. The remission rates obtained with induction therapy were good and comparable between arms.

Older SNV patients are more fragile and their outcomes were reported to be worse than those of younger populations in previous series (2-6). A recent retrospective study from Spain (REVAS) and our own findings showed that SNV in this older population is severe at

diagnosis, often with advanced renal involvement, and high treatment-related morbidity and mortality (24). Reasons for those findings are various and may include longer diagnostic delay (leading to greater disease severity at diagnosis) and higher susceptibility of developing SAEs due to physiologic aging and comorbidities. Mortality was 6.7% during induction and reached 20% at 3 years in the present trial, compared to 30.2% at 5 years in our previous retrospective study on patients ≥65 years old (1), and 32.1% in REVAS (24). For comparison, mortality of SNV populations of all ages was 15% at 2 years, and 22% at 5 years, in the European Vasculitis Study Group (EUVAS) long-term follow-up study (25). For our older SNV patients, like those studied previously, SAEs were very common and occurred mainly during the first year, i.e. during and immediately after the intensive induction phase of treatment. The causes of deaths were indeed more often SAEs than vasculitis (25-27), with uncontrolled vasculitis being responsible for "only" 4 of the 21 recorded deaths in this study.

Further reducing mortality and, importantly, morbidity should therefore remain major therapeutic objectives for this older population. The "new-and-lighter" regimen investigated herein was associated with a significantly lower risk of SAEs, compared to our defined conventional regimen (7, 28-30). Although adjusting the CYC dose to patients' renal function and age had been suggested and done in several previous trials, and was also included in some published recommendations (15 mg/kg per pulse in patients <60 years old with normal renal function, down to 7.5 mg/kg per pulse in those >70 years old with serum creatinine >300 μmol/liter) (7, 8, 16, 31, 32), no study results really demonstrated that this approach was safer and as effective as conventional full-dose regimens. On the other hand, to what extent CS exposure can also be limited and/or shortened remains to be determined.

The CS regimen in most European trials on ANCA-associated vasculitis exceeded 12 months (8, 16, 32), like in our trial, as opposed to only 6 months in several US trials (33, 34). Ongoing studies investigating different CS regimens, e.g. the PEXIVAS trial (35), should provide additional information to optimize dosing.

At the same time, remission-induction rates in the 2 treatment arms were not statistically different. Hence, a "lightened" regimen, with a lower CYC dose, can help decrease SAE rates, without overly hampering the chance to achieve remission. Results of another recent but uncontrolled study on 22 patients also suggested that lower CYC doses (than those recommended by the EUVAS/European League Against Rheumatism [EULAR]), using a nomogram based on age and renal function, achieved the same remission probability at 1 year (36), but its power was insufficient to assess the impact on SAEs.

While the "new-and-lighter" regimen used in our trial was shown to be safer and as effective for remission induction, relapse rates at 3 years remained high (44%). It was not significantly higher than that of the conventional treatment (29%), but probably explains why the Q-TWiST analysis failed to demonstrate a significant gain with the experimental regimen. However, our relapse rates are close to those reported in other studies on SNV (32, 34, 37-39). Longer follow-up of our patients is required, especially since long-term follow-up results from the EUVAS NORAM and CYCLOPS studies suggested that initially lower cumulative CYC exposure could be associated with higher subsequent relapse rates (39, 40). More important, in our opinion, is the need to identify more effective maintenance therapies. Most of our patients received azathioprine, some methotrexate or mycophenolate mofetil, for 18 months per protocol, but several took it for longer. Longer maintenance therapy for all patients might be associated with an even lower relapse rate than that observed herein.

The results of a recently completed randomized trial (MAINRITSAN) suggested that, alternatively, systematic reduced-dose rituximab infusions given at regular intervals were more effective and at least as safe as azathioprine for GPA maintenance, following CS-and-CYC–based induction therapy (41).

Rituximab could also be considered an alternative to CYC for remission-induction in older patients with GPA or MPA. In the RAVE trial, rituximab and CYC were as safe and effective in the 55 GPA or MPA patients ≥65 years as in the younger patients (33, 42, 43). However, those older patients developed more SAEs, and all 4 patients who died in this study were aged more than 65 years (42, 43). In addition, rituximab is not yet approved or available in every country, and the concerns about CYC and infertility or late cancer that have both become rarer with shorter exposures to CYC, do not apply to the same degree to this older population. At present, experience with rituximab for PAN or EGPA remains very limited.

Our study has several strengths, including its pragmatic design, in order to achieve practical conclusions, its 3 years of follow-up and the relatively large number of patients enrolled and analyzed. Because of the low dropout rate, that number was higher than anticipated, thereby achieving sufficient power to detect a significant difference in our primary endpoint, although smaller than initially hypothesized. This unanticipated excellent retention of patients in the study provided greater statistical power than the original effect-size estimates sought. Our study has some other limitations, including its nonblinded design, the between-arm differences of both CS and CYC doses, and the pooling of 4 SNVs of different disease severity. However, all these diseases are SNV and were largely, at the time this study was designed, treated with the same therapeutic strategies and drugs. Treating

SNV patients with FFS = 0 with a combination of CS and CYC could be viewed as being contradictory to some previous FVSG studies, whose results demonstrated good survival with CS alone. However, long-term data recently revealed that relapses were common in patients treated with CS alone (44). Importantly, the systematic but low-dose CYC pulses of the experimental regimen were devised to limit the long-term exposure to CS, and hence its potentially related-SAEs. We did not observe any blatant increase of the SAE rates in the patients with FFS = 0 and treated with CYC, but the small size of study subsets precludes any statistical analyses and firm conclusions. Finally, consolidation pulses, which were still routine practice when this trial was initiated, are no longer given, since the results of the CYCAZAREM study have been widely disseminated (16). However, and although they were part of the conventional arm, the difference in the mean number of CYC pulses received per patient between study arms was much smaller than 3, suggesting that not all 3 consolidation pulses had systematically been given by treating physicians.

To conclude, the results of this pragmatic trial suggest that a regimen combining CS for a shorter duration and CYC for all, but at a limited dose of 500-mg per pulse, for a maximum of 6 pulses, before switching to maintenance with azathioprine or methotrexate, could limit SAE frequency in newly diagnosed SNV patients ≥65 years old without impeding their chances of remission. Future studies may identify even superior alternative strategies, especially for maintenance, as relapses remain frequent.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Pagnoux and Guillevin had full access to all the study data and take responsibility for their integrity and the accuracy of their analysis.

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Statistical analysis. Pagnoux, Perrodeau, Guillevin.

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Figure legends

Figure 1. Flow diagram of the trial enrollment. AZA = azathioprine; CS = corticosteroids; CYC = cyclophosphamide pulse; EGPA = eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); FFS = Five-Factor Score; GPA = granulomatosis with polyangiitis (Wegener's); MMF = mycophenolate mofetil; MPA = microscopic polyangiitis; MTX = methotrexate; PAN = polyarteritis nodosa; SAEs = serious adverse events; SNV = systemic necrotizing vasculitis.

Figure 2. Comparisons of the experimental (Exp)- versus conventional (Conv)-arm patients' curves for (A) survival without serious adverse event (SAE), (B) overall survival, and (C) survival without active disease (induction failure or relapse).

Figure 3. Partitioned survival curves and average amounts of time that patients spent with a serious adverse event (toxicity; TOX), time without symptoms or toxicity (TwiST) and time with disease progression (activity; PROG) during the 3 years of the study (see text for details).

Table 1. Baseline patient characteristics according to treatment arm.

Characteristic	Experimental arm (n = 53)	Conventional arm (n = 51)
Age at diagnosis, mean ± SD years	75.1 ± 6.2	75.3 ± 6.4
Sex ratio, (M/F)	27/26	32/19
Diagnosis, n (%)		
GPA	21 (39.6)	15 (29.4)
MPA	21 (39.6)	23 (45.1)
EGPA	8 (15.1)	6 (11.8)
PAN	3 (5.7)	7 (13.7)
Patients with FFS =0, n (%)*		
MPA	6 (11.3)	3 (5.9)
EGPA	4 (7.5)	5 (9.8)
PAN	3 (5.7)	4 (7.8)
ANCA positivity†	41 (77.4)	41 (80.4)
Comorbidities		
Hypertension	22 (41.5)	22 (43.1)
Coronary artery disease	7 (13.2)	9 (17.6)
Diabetes	2 (3.8)	4 (7.8)
Dyslipidemia	15 (28.3)	14 (27.5)
Smoker (past or present)	13 (24.5)	17 (33.3)
Clinical manifestations, n (%)		
Constitutional symptoms		
Arthralgias/arthritis	21 (39.6)	18 (35.3)
Fever	26 (49.1)	29 (56.9)
Weight loss >5 kg	42 (79.2)	33 (64.7)
Cutaneous	17 (32.1)	18 (35.3)
Ear, nose & throat	24 (45.3)	18 (35.3)
Cardiovascular	7 (13.2)	14 (27.5)
Cardiomyopathy	0	3 (5.9)
Pericarditis	3 (5.7)	3 (5.9)
Gastrointestinal tract	12 (22.6)	10 (19.6)
Defining FFS = 1§	2 (3.8)	0
Pulmonary	35 (66.1)	32 (62.7)
Alveolar hemorrhage	9 (17)	11 (21.6)
Renal	32 (60.4)	39 (76.5)
Serum creatinine level ± SD, μmol/liter	213 ± 170	260 ± 224
Serum creatinine >140 μmol/liter	26 (49.1)	30 (58.8)
Glomerular filtration rate, ml/min/1.73 m^2	43.0 ± 35.5	33.6 ± 29.8
Proteinuria > 1 g/24 hours	13 (26.4)	17 (33.3)
Hematuria on urinary dipstick	31 (58.5)	29 (56.9)
Nervous system		
Peripheral	14 (26.4)	14 (27.5)
Central	4 (7.5)	0
C-reactive protein ± SD, mg/liter	111.4 ± 92.4	91.5 ± 80.2
Hemoglobin level ± SD, g/dl	11.35 ± 10.88	12.21 ± 12.38

* The original FFS applies only to patients with PAN, MPA or EGPA. ANCA = antineutrophil cytoplasm antibody; EGPA = eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome); ELISA = enzyme-linked immunosorbent assay; FFS = Five-Factor Score; GPA = granulomatosis with polyangiitis (Wegener's); MPA = microscopic polyangiitis; PAN = polyarteritis nodosa; SD = standard deviation.

† Detected by indirect immunofluorescence (P-, with perinuclear, or C-, with cytoplasmic, immunofluorescence-labeling pattern, with anti-myeloperoxidase [MPO] or anti-proteinase 3 [PR3] specificity by ELISA).

§ FFS-gastrointestinal manifestations yielding FFS = 1 include bowel infarction, ischemia, and/or perforations (but not isolated appendicitis, pancreatitis or cholecystitis).

Table 2. Serious adverse events according to treatment arm

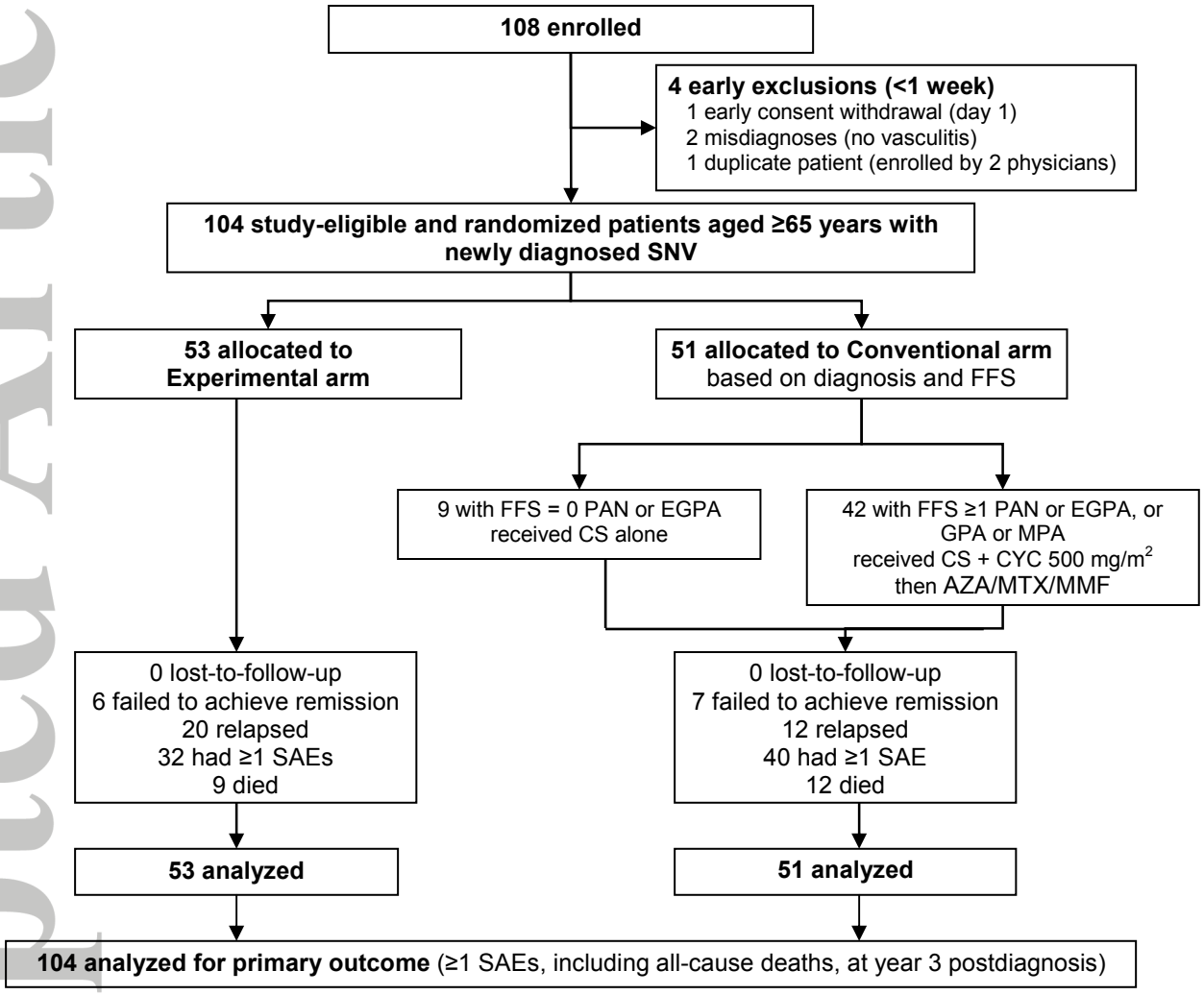
	Experimental arm (n = 53)		Conventional arm (n = 51)	
Adverse event	Patients	Events	Patients	Events
Serious adverse events*	32	73	40	110
Infections	10	13	17	30
Lung†	3	4	9	10
Zona	0	0	5	5
Sepsis	3	4	8	11
Cardiovascular	3	3	10	12
Cytopenia(s)	3	5	8	10
Fractures	6	8	4	4
Miscellaneous§	21	35	28	46
Deaths	9		12	

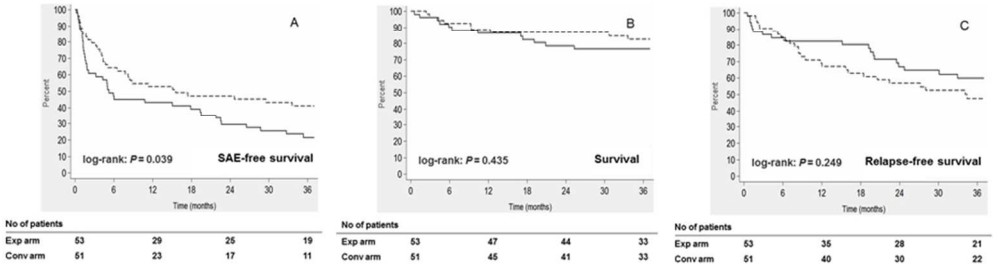
* Serious adverse events correspond to trial definitions (i.e., any adverse event that is life-threatening, requires either hospitalization or its prolongation, is responsible for a persistent or significant disability/incapacity, results in death, or other important medical events, based upon appropriate medical judgment).

† No pulmonary *Pneumocystis jiroveci* infection occurred. One experimental-arm patient died, 2.5 years after his GPA diagnosis, of lung tuberculosis with esophageal–bronchial fistulas.

§ Miscellaneous adverse events included very diverse complications at low frequencies, such as diabetes, diarrhea, fever episode, hospitalization for dyspnea, nausea/vomiting, fall with contusion, bleeding due to anticoagulant therapy all requiring hospitalization or prolongation of hospitalization.

Figure 1.





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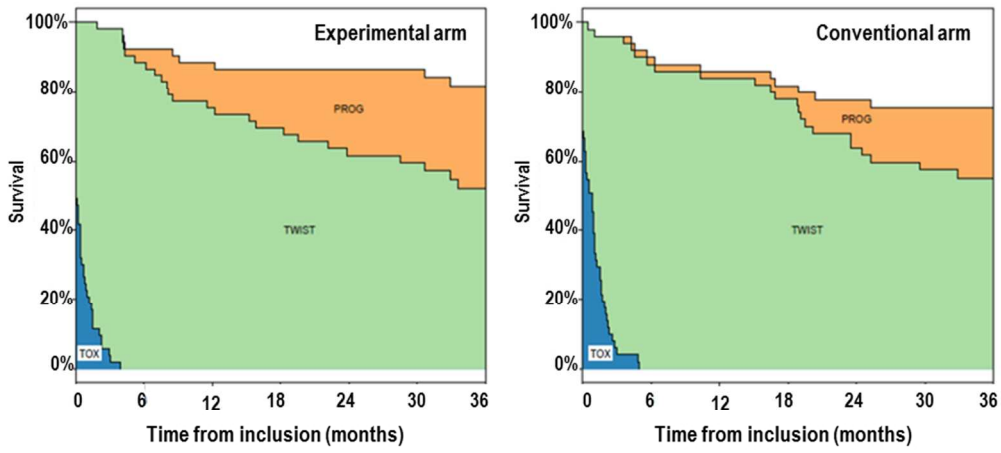

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