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► To cite this version:

Michele Iudici, Christian Pagnoux, Delphine Courvoisier, Pascal Cohen, Mohamed Hamidou, et al. Granulomatosis with polyangiitis: Study of 795 patients from the French Vasculitis Study Group registry. *Seminars in Arthritis and Rheumatism*, 2021, 51 (2), pp.339-346. 10.1016/j.semarthrit.2021.02.002 . hal-03257789

HAL Id: hal-03257789

<https://u-paris.hal.science/hal-03257789v1>

Submitted on 9 Mar 2023

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1 **Granulomatosis with polyangiitis: Study of 795 patients from the French Vasculitis**
2 **Study Group Registry**

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11 *Several authors of this publication are members of the European Reference Network for
12 Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases, Project ID No
13 739543.

14 †Other investigators are listed in the Appendix. We propose to list and designate all the site
15 investigators and key personnel as “collaborators” as per Medline designation. This means
16 their names are searchable on Medline. This is an important method to appropriately
17 recognize the work of the many co-investigators of this study and is consistent with
18 approaches taken by major journals for such work.

19

20 **Running head:** Granulomatosis with polyangiitis

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57 **Word count.** 2778, 3 Tables, 3 Figures, Supplementary material including 2 Tables.

58 **Keywords.** Granulomatosis with polyangiitis; ANCA-associated vasculitis; vasculitis.

59 **Abbreviations**

60 AAV. ANCA-associated vasculitis

61 EGPA. Eosinophilic granulomatosis with polyangiitis

62 GPA. Granulomatosis with polyangiitis

63 MPA. Microscopic polyangiitis

64 BVAS. Birmingham Vasculitis Activity Score

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Abstract

Objective. To describe the characteristics and long-term outcomes of patients with granulomatosis with polyangiitis (GPA) from the French Vasculitis Study Group database.

Methods. Patients' clinical and laboratory characteristics, Birmingham Vasculitis Activity Score (BVAS)-assessed disease activity, malignancies, opportunistic infections, and vital status were collected at diagnosis and each visit. Estimated probabilities and predictors of overall (OS) and relapse-free survival (RFS) were analyzed by Cox regression.

Results. We enrolled 795 newly diagnosed patients, followed for a median of 3.5 years. Initial clinical manifestations involved ear, nose & throat (ENT; 80%), lungs (68%) and kidneys (56%). Among the 728 available ELISA results, 75.0% were PR3-ANCA-positive, 16.5% MPO-ANCA-positive and 62 (8.5%) ANCA-negative. Relapses occurred in 394 (50%) patients, involving ≥ 1 organ(s) affected at onset in 179 (46%), mainly ENT, lungs and kidneys, with mean BVAS 10.2 points below that at diagnosis ($p < 0.001$). Five- and 10-year RFS rates were 37% and 17%, respectively. PR3-ANCA-positivity independently predicted relapse ($p = 0.05$) and prolonged survival ($p = 0.034$). OS—but not RFS—improved significantly over time ($p < 0.001$); 10-year OS reached 88.2% (95% CI 83.9 to 92.7) for the 660 patients diagnosed after 2000. Infections were the main causes of death. Malignancy or opportunistic infection each occurred in $\leq 5\%$ of the patients.

Conclusion. Survival has improved dramatically over the last decades but the high relapse rate remains a major concern for GPA patients, once again stressing the need for therapeutic strategy optimization to lower it. PR3-ANCA-positivity was associated with increased probability of relapse and survival.

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1. Introduction

Granulomatosis with polyangiitis (GPA) is a severe, multisystemic, antineutrophil cytoplasm antibody (ANCA)-associated granulomatous vasculitis [1] whose prevalence has been estimated in France [2], and the US [3], respectively, at ~25 and ~32 cases/million inhabitants. Clinical GPA manifestations are heterogeneous, affecting mainly the upper and lower respiratory tract, and the kidneys [1]. Most of our knowledge on GPA clinical presentation and evolution came mainly from observational studies, which represent the best tools to characterize a disease in a real-world setting [4], rather than from limited numbers of trials, most of which included patients with several distinct vasculitides, low morbidity and short follow-up [5].

Defining long-term outcomes of rare diseases, with a sufficient level of evidence, is difficult. That rarity makes collection of sufficiently robust and extensive information a challenge, as they are often underdiagnosed and seen in different clinical settings not necessarily linked by shared research interests. To obtain larger samples, analyses often included more than one disease or newly diagnosed and prevalent patients but obtained estimates could potentially be biased [6,7].

Availability of the French Vasculitis Study Group (FVSG) Registry, a large national database of prospectively entered longitudinal clinical and laboratory data from ANCA-associated vasculitis (AAV) patients since 1983, enabled some of these difficulties to be overcome. Investigators from >60 French centers regularly contribute those data. The data from 795 newly diagnosed GPA patients entered in that database were analyzed to obtain descriptions of their main initial clinical features and outcomes, particularly relapses, morbidity and mortality.

2. Methods

2.1 Patients

We studied newly diagnosed patients with GPA, satisfying the American College of

145 Rheumatology (ACR) 1990 classification criteria [8] and/or revised Chapel Hill nomenclature
146 [1], entered into the FVSG database from May 1983 to April 2018. For the patients to be
147 classified as fulfilling those criteria, their entire clinical histories were considered. All FVSG-
148 Registry patients gave their written informed consent. Only newly diagnosed patients,
149 entered in the Registry at diagnosis, and followed-up for ≥ 6 months or who died within 6
150 months of entry, were included. Patients with insufficient data (no clinical details at diagnosis)
151 were excluded.

152

153 **2.2 Demographic and GPA features collected from diagnosis onwards**

154 For the complete list of demographic and clinical items recorded at onset and each follow-up
155 visit, see the online supplement. The database collects patient's information at baseline,
156 thereafter every 6 months, or in case of refractory/relapsing disease requiring treatment
157 escalation. Electronic records were the source of information on demographics; clinical,
158 laboratory, radiological and histological findings; opportunistic infections and malignancies.
159 We defined opportunistic infections as known to occur more often in immunocompromised
160 patients and included in the list provided by Winthrop *et al* [9]; vital status at last known date
161 was obtained from clinical charts, contacting patients, or their family members or general
162 practitioners; and congestive heart failure exclusively by clinical symptoms (eg, pulmonary
163 edema), thereby corresponding to the 2009 revised Five-Factor Score (FFS) definition [10].
164 Severe gastrointestinal manifestations (including bowel perforation, bleeding and/or
165 pancreatitis) met FFS definitions.

166 The laboratory parameters included: serum creatinine level; proteinuria on dipstick
167 ($\geq 1+$); hematuria (>10 red blood cells/ mm^3); C-reactive protein (CRP) level;
168 immunofluorescence- and/or enzyme-linked immunosorbent assay (ELISA)-determined
169 ANCA status (anti-myeloperoxidase (MPO); anti-proteinase-3 (PR3)) in serum at diagnosis
170 or thereafter when positive or had not been available initially. Biopsy findings were recorded
171 as normal, or as showing evidence of vasculitis, granulomatous and/or other lesions.

172

173 **2.3 Disease activity and scores**

174 Disease activity was assessed at diagnosis and each visit using the original 1994
175 Birmingham Vasculitis Activity Score (BVAS) [11]. For patients enrolled before its publication,
176 BVAS was calculated retrospectively. The 2009 FFS score at diagnosis was calculated
177 retrospectively for each patient [10]. This prognostic tool is composed by the following 5
178 items: severe gastrointestinal involvement, cardiac insufficiency, serum creatinine level >150
179 $\mu\text{mol/L}$, age older >65, and absence of ENT involvement, with each item accorded one point,
180 for a maximum score of 5.

181

182 **2.4 Treatment procedures**

183 Patients were enrolled in randomized–controlled trials [12-18] or received standard-of-care
184 therapy. Agents used to induce and maintain disease remission, glucocorticoids (GC) use
185 and dose, initially and for relapse(s), were recorded.

186

187 **2.5 Outcomes**

188 According to the European League Against Rheumatism (EULAR) recommendations [19]
189 relapse was defined as the re-occurrence or new onset of disease attributable to active
190 vasculitis; remission as the absence of disease activity attributable to GPA manifestations for
191 >3 consecutive months, corresponding to BVAS=0. According to that definition, patients in
192 remission could still be taking immunosuppressant or prednisone. The term active disease
193 was not restricted to vasculitic manifestations; it also included other clinical signs, like
194 granulomatous manifestations, eg retro-orbital tumors or lung nodules [19]. Refractory AAV
195 was defined as failure to fully control vasculitis-related disease activity by 6 months or
196 progressive disease within the first 3 months.

197

198 **2.6 Statistical analyses**

199 Patient characteristics are reported as the number (percentage) for categorical variables and
200 as mean \pm SD or median [interquartile range; IQR] for continuous variables. Continuous

201 variables were compared with Student's t-test or Mann–Whitney test, and categorical
202 variables with chi-square test or Fisher's exact test, as appropriate. Kaplan–Meier curves
203 estimating relapse-free and overall survival were compared using log-rank tests. Relapse-
204 free survival was calculated from GPA diagnosis to relapse, death or end of follow-up,
205 whichever occurred first. Survival was calculated from GPA diagnosis to death or the last
206 follow-up visit. To identify independent predictors of relapse-free or overall survival,
207 univariable and multivariable Cox-regression analyses assessed potential associations with
208 patient demographics, clinical, laboratory and therapeutic parameters. Because few deaths
209 or relapses occurred, only variables with $p \leq 0.05$ in univariable models were tested in the
210 multivariable Cox proportional hazards model. Results are expressed as hazard ratios (HR)
211 and 95% confidence intervals (95% CI). Linear mixed models were used to compare BVAS
212 between baseline values and at relapse, while accounting for the repeated measures for
213 each patient. All statistical analyses were computed with R v3.6.1; $p \leq 0.05$ was considered
214 significant. The Ethics Committee of Cochin University Hospitals approved this study (CLEP
215 AAA-2019-08019).

216

217 **3. Results**

218 **3.1 Patient characteristics at diagnosis**

219 The study included 795 GPA FVSG-Registry patients (mean age, 53 ± 16.3 years), mostly
220 males ($n=445$; 56%). Their main demographic characteristics and clinical manifestations are
221 reported in table 1. Among the 513 with available ethnicity information, 476 (93%) were
222 white/Caucasian, 14 (3%) African/Caribbean descent, 11 (2%) Asian ancestry, and 12 (2%)
223 others.

224 The main initial clinical manifestations were ENT (80.4%) and lung (67.7%)
225 involvement; 56% had renal involvement: 193 (24%) experienced worsening of glomerular
226 filtration (eg, $>25\%$ vs pre-diagnosis), and 46 (6%) required hemodialysis. Fifty-five (7%)
227 patients had localized GPA limited to ENT tract and/or lungs. Mean BVAS was 17.4 ± 8.8 .

228 Among the 728/795 patients with available ELISA results (table 2), 75.0% were PR3-

229 ANCA-positive, 16.5% MPO-ANCA-positive and 8.5% ANCA-negative. Among the 389
230 biopsies taken from 381/795 (48%) patients, 345/389 (89%) yielded histological findings
231 supporting the GPA diagnosis: 41% vasculitis, 29% necrosis, 24% granuloma or 5% not
232 specified.

233 **3.2 Treatments**

234 Two hundred and fifty-nine (32.6%) patients were included in clinical trials (12-18). The most
235 frequently prescribed induction agents were oral GC (n=772; 97%), intravenous (n=602;
236 76%) or oral (n=53; 6.7%) cyclophosphamide, rituximab (n=52; 6.5%) or methotrexate (n=36;
237 4.5%). Among the 59 patients undergoing plasma exchange at diagnosis, 53 had renal
238 involvement (associated with alveolar hemorrhages for 25), and 6 had isolated alveolar
239 hemorrhages. After post-diagnosis induction treatment, 583 (73.3%) patients achieved
240 remission. The median follow-up duration was 3.5 [1.7–6.6] years and exceeded 1 year from
241 study entry for 687 (86.4%) with a median of 6 visits (range 2-16) per patient. After induction-
242 remission, patients received ≥ 1 dose(s) of the following maintenance agents: oral GC
243 (n=744; 93.6%), azathioprine (n=382; 48.1%), rituximab (n=269; 33.8%), methotrexate
244 (n=206; 25.9%) or mycophenolate mofetil (n=59; 7.4%).

245

246 **3.3 Relapses and main damage-related clinical manifestations at last visit.**

247 Patients (n=394, 50%) relapsed a mean \pm SD of 2.7 \pm 2.2 years post-diagnosis. Overall, with a
248 median follow-up duration of 3.5 years, we observed 652 relapses in the whole sample of
249 patients. One-hundred forty-seven (23.5%) patients experienced more than one relapse. The
250 cohort's Kaplan–Meier-estimated 5- and 10-year relapse-free–survival rates, respectively,
251 were 37% and 17% (figure 1A): 35% and 14% ANCA-PR3–positive, 46% and 25% ANCA-
252 MPO–positive ($p=0.11$); they did not differ according to diagnosis before or after 2000.

253 Mean BVAS at relapse was 10.2 (95% CI 9.39 to 10.8) points below diagnosis value
254 ($p<0.001$). Relapses affected mainly ENT (n=456), lungs (n=244), kidneys (n=186), eyes
255 (n=145), central or peripheral nervous system (n=134) and/or skin (n=99). Throughout GPA
256 evolution, about 60% of patients experienced relapse involving ≤ 2 organs: single organ in

257 117 (29.6%) patients: ENT (n=36; 9%), lungs (n=28; 7%) or kidneys (n=14; 3.5%) the main
258 targets; or two-organs in 131 (33.2%): with most frequent being ENT and systemic (n=20),
259 lung (n=14), kidneys (n=12) or eyes (n=10). The relapse patterns and numbers of affected
260 organs are schematized in figure 2. Three or more organ involvement were recorded in the
261 remaining 146 (37.2%) relapsing patients. Overall, isolated ENT (n=36), or lung (n=28), or
262 ENT relapse with systemic signs (n=20), were the main observed patterns. Relapses in ≥ 1
263 organs(s) initially affected were observed in 179/394 (46%) patients; those involving
264 previously uninvolved systems mostly affected the nervous system (n=53), eyes (n=41),
265 kidneys (n=37), skin (n=35), ENT (n=32), lungs (n=24) or cardiovascular (n=13) or
266 gastrointestinal (n=5) systems. New systemic signs and/or musculoskeletal symptoms
267 appeared in 83 patients.

268 A variety of disease sequelae were recorded in 433 (54%) patients. The main disabling GPA-
269 related manifestations were chronic renal insufficiency (n=114; 26.3%), hearing loss (n=73;
270 16.8%), peripheral neuropathy (n=55; 12.7%), saddle nose/nasal septum perforation/ENT
271 bone destruction (n=40; 9.2%), dialysis (n=29; 6.7%).

272

273 **3.4 Overall survival and causes of death**

274 Eighty-two (10.3%) patients died after a median 3.5 [7–6.6] years post-diagnosis and 33
275 (4%) within 6 months of diagnosis. The main causes of deaths (available for 72/82 patients;
276 supplementary table 1) were infections (36%), refractory disease (20%), malignancies (17%),
277 cardiovascular events (15%), suicide (4%) or others (8%). Five-year overall survival rates
278 (95% CI) for all patients and those diagnosed before or after 2000, respectively, were: 90.7%
279 (88.3 to 93.2), 72.5% (64.2 to 81.9) and 94.6% (92.5 to 96.8) (figure 1B), with respective 10-
280 year rates of 85.5% (81.8 to 89.4), 71.0% (62.4 to 80.7) and 88.2% (83.9 to 92.7).

281

282 **3.5 Malignancies**

283 Forty-one (5%) patients developed malignancies; 13 died (5 lung, 2 bladder, and 1 each:
284 hepatic, colorectal, ovary, pancreas, bladder or non-Hodgkin lymphoma). There were solid

285 tumors (14 non-melanoma skin cancer, 6 bladder, 5 lung, 3 colorectal, 2 bile duct, 2
286 urothelial, and 1 each: breast, endometrium, ovary, liver, pancreas, prostate or unspecified)
287 and 1 each mucosa-associated lymphoid tissue-lymphoma of the intestinal tract or non-
288 Hodgkin lymphoma. Thirty-six of them had received CYC, 2 another immunosuppressant and
289 3 received only GC.

290

291 **3.6 Opportunistic infections**

292 Thirty-six opportunistic infections [38.9 (95% CI 20.1 to 68.0) vs 14.6 (95% CI 9.2 to 22.2)
293 events/100 patient-years before or after 2000, respectively; $p=0.004$] were diagnosed in 30
294 (4%) patients after a median 17.5 [5.5-42.5] months post-diagnosis. Fourteen (38.8%) and
295 20 (55.5%) infections, respectively, occurred within year 1 or 2 post-diagnosis. Infection-
296 causing pathogens were: *Aspergillus* (n=12), *Pneumocystis jirovecii* (n=11; 1/7 patient taking
297 trimethoprim–sulfamethoxazole 400 mg/day; unknown for the other 4), cytomegalovirus
298 (n=6), Herpes zoster virus (n=5), *Nocardia* (n=3), *Mycobacterium tuberculosis* (n=2) *Listeria*
299 *monocytogenes* (n=1), *Legionella* (n=1) and non-tuberculous-mycobacterium (n=1). Eight
300 patients, who had received GC and intravenous (n=4) or oral (n=4) CYC, died a median of
301 5.5 [4–14] months post-GPA diagnosis.

302

303 **3.7 Univariable and multivariable predictors of relapse or death**

304 Univariable analyses (table 3) selected PR3-ANCA–positivity ($p=0.042$) as being associated
305 with higher probability of relapse and oral CYC induction ($p=0.05$) with a lower probability of
306 relapse. Multivariable analysis retained only PR3-ANCA–positivity as an independent
307 predictor of relapse ($p=0.05$).

308 Multivariable analysis retained date of diagnosis, age and congestive heart failure as
309 significant and independent predictors of death, while PR3-ANCA–positivity was protective.
310 The predictive power of the baseline 2009 FFS was confirmed for this large GPA sample
311 (supplementary table 2).

312

313 **4. Discussion**

314 Herein, we described the main GPA characteristics at diagnosis and during evolution of 795
315 patients with long-term follow-up. This large population enabled better evaluation of the initial
316 prevalences of less frequently observed manifestations, and characterization of evolution
317 and relapse patterns throughout follow-up. GPA carries a high risk of relapse, especially for
318 PR3-ANCA–positive patients, with a stable incidence rate over time. Overall, the clinical
319 picture at relapse was milder than that observed at diagnosis. Moreover, disease reactivation
320 affected organs involved initially for half the patients, mainly ENT, lungs and kidneys.
321 Notably, mortality, mostly due to infections, has gradually decreased over the last 35 years to
322 approach that of the general population.

323 Our analysis confirmed relapses in at least half of patients, a rate that has remained
324 frustratingly high and stable over time. Most previous studies grouped patients with GPA,
325 microscopic polyangiitis, kidney-limited disease or eosinophilic granulomatosis with
326 polyangiitis [20-22]. Although PR3-ANCA–positivity was found to best predict vasculitis
327 relapse [21], it remains controversial whether that parameter is specifically associated with
328 GPA relapses [23-25]. In keeping with the Glomerular Disease Collaborative Network
329 findings [21], our results further confirmed, based on more patients, that PR3-ANCA–
330 positivity was also independently associated with a higher risk of GPA relapse. Rituximab
331 has been shown to be more effective at preventing relapses than conventional treatments,
332 like azathioprine [14], but, despite having been given to more than a third of our patients, its
333 efficacy for the entire cohort could have been diluted by its more recent introduction. The
334 persistently high relapse rate, despite effective therapies, suggests that novel implementation
335 strategies aimed at better preventing relapses should be further prioritized.

336 GPA relapses have been quantified in many studies conducted in different settings
337 [21-28], but less is known about disease-reactivation patterns over time. First, we found that,
338 like at diagnosis, almost half the relapses affected ENT, lungs and kidneys, and that disease
339 extended to previously unaffected organs in the remaining half of patients, with frequent
340 involvement of the nervous system, eyes, and kidneys. Improving patient’s awareness of this

341 disease behavior is crucial to allow patients an early recognition of flares and a prompt
342 introduction of treatment. Second, ~60% of relapsing patients had a maximum of 2 organs
343 affected during follow-up, most often combining ENT and lung, renal or systemic features.
344 Moreover, mean BVAS at relapse was lower than at GPA diagnosis in a real-life setting, as
345 observed in trials when patients have easier access to their physicians [29]. That lower
346 disease activity can be explained by several factors, eg, patients better educated about GPA-
347 related relapse manifestations and how to recognize them, leading to earlier consultation, or
348 the influence of concomitant medications attenuating relapse severity. The rarity of renal
349 relapses and the predominantly nonsevere relapses might also explain why, despite
350 relapsing more frequently, our PR3-ANCA–positive GPA patients' survival was not poorer.
351 Taken together, those observations enabled better recognition of relapse patterns that can
352 be expected in daily practice; they also further inform physicians, inciting them to educate
353 patients not to delay consultation, so treatment intensification can be initiated rapidly. They
354 also highlight the need for careful follow-up of patients with milder initial GPA.

355 Our data confirmed previous observations of improved survival over time [20-22] and
356 contribute to better estimating GPA-mortality rates. They also highlighted that improvement
357 was progressive, with a $\geq 15\%$ gain of 10-year survival rates (from 71% to 88%) for patients
358 diagnosed before or after 2000, which roughly corresponds to the first rituximab use. In
359 accordance with a cluster analysis of 482 renal AAV patients [30], PR3-ANCA–positivity also
360 predicted longer survival. That finding further strengthens the concept that anti-MPO–
361 positivity might define a distinct GPA subset with the worst survival. Better GPA recognition
362 leading to earlier diagnosis, ANCA testing, the availability of effective and less toxic
363 treatments, together with improved management of cardiovascular and infectious risk factors,
364 could help explain the lowered mortality [31]. Patients now diagnosed with GPA should be
365 told that their life expectancy approaches that of the general population.

366 As reported previously [32, 33], infections were the main causes of death. Despite
367 newer agents having emerged as potential first-line therapies, their safety profiles are quite
368 similar to those of older approaches, like CYC-based regimens. Hence, even though survival

369 has improved, the percentage of patients developing severe infections has remained
370 substantial. Herein, we focused our attention only on opportunistic infections, because
371 severe infection rates were analyzed previously [34]. About 4% of our patients developed
372 opportunistic infections, with half occurring within the first 2 years post-diagnosis; when fatal,
373 patients succumbed rapidly (median 5 months post-diagnosis). Pertinently, their incidence
374 after 2000 was less than half of that recorded before. Different factors could explain that
375 observation, eg, less use of oral CYC, lower cumulative CYC exposure or the wider use of
376 trimethoprim–sulfamethoxazole prophylaxis over time. Those findings emphasize the need to
377 identify patients at high-risk of infection and constitute a strong incentive for using GC-
378 sparing strategies, less toxic immunosuppressants [17, 35] and/or trimethoprim–
379 sulfamethoxazole prophylaxis to prevent severe or life-threatening infections [36].

380 This study has several strengths including its large population, coming from different
381 specialties across France, enabling thorough qualitative descriptions of a wide range of
382 characteristics, long-term follow-up and relapse patterns.

383 However, some limitations should be acknowledged. Therapeutic strategies have
384 evolved over the 35 years of enrollment. Although patients derived from different specialties,
385 bias resulting from the inclusion of those with more severe disease consulting at tertiary
386 referral centers cannot be excluded. Furthermore, we were unable to better appraise to what
387 extent trimethoprim–sulfamethoxazole prophylaxis for CYC- or rituximab-treated patients
388 might have influenced the observed lower risk of severe infections.

389 In conclusion, GPA is a severe, relapsing, rare disease involving—at onset and at
390 relapse—mainly ENT, lungs and kidneys. Better disease-specific management over the last
391 few decades could be among the leading factors contributing to the improved survival of
392 these patients, whose life expectancy now approaches that of the general population, even
393 though the risk of relapse remains high for predominantly nonsevere events. PR3-ANCA–
394 positivity is a weak albeit still the best predictor of GPA relapse and was associated with
395 better survival. GPA monitoring over time should be driven by patient education about the
396 high risk of disease reactivation, potentially involving organs affected at diagnosis for half of

397 them.

398 **APPENDIX**

399 **In addition to the authors, the following investigators and FVSG members participated**

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412 Annecy; Audrey de Parisot de Bernecourt, H pital de la Croix-Rousse, Lyon; St phane

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416 Angers.

417

418 **Author contributions.** All authors were involved in drafting the article or revising it critically

419 for important intellectual content, and all authors approved the final version to be published.

420 Dr. Pu chal had full access to all the study data and takes responsibility for the integrity of

421 the data and the accuracy of the data analysis.

422 **Study conception and design.** MI, LG and XP.

423 **Acquisition of data.** MI, CP, PC, MH, AA, FL, MR, OA, BB, FM, OD, EH, AK, CK, NJ-C, J-

424 FV, CB-D, PG, ALQ, TQ, CdD, AR, BT, LM, LG and XP.

425 **Analysis and/or interpretation of data.** MI, CP, DSC, LG and XP.

426 **Data availability statement.** Data are available on reasonable request.

427 **Funding.** No specific funding was received from any funding bodies in the public,
428 commercial or not-for-profit sectors to carry out the work described in this manuscript.

429

430 **Competing interests.** CP has declared consultancies, speaking fees and honoraria
431 (Hoffman-La Roche, Sanofi, Chemocentryx, InflaRx GmbH and GSK <\$10,000). TQ has
432 declared receiving fees for congress inscriptions/travel/accommodations (MSD, Sanofi-
433 Genzyme, LFB <\$5,000). BT has declared consultancies, speaking fees and honoraria
434 (Roche, Grifols, LFB, AstraZeneca <\$10,000). LM has declared consultancies, speaking fees
435 and honoraria (Roche <\$10,000). XP has declared speaking fees and honoraria (Boehringer
436 Ingelheim, Sanofi <\$10,000) and for congress inscriptions/travel/accommodations (Sanofi
437 <\$5,000). All authors have been coinvestigators in academic studies for which rituximab was
438 provided by Roche Pharma. No other conflicts were reported. MI, DSC, PC, MH, AA, FL,
439 MR, OA, BB, OD, FM, EH, AK, CK, NJ-C, J-FV, CB-D, PG, ALQ, CdM, AR, and LG have no
440 conflicts of interest.

441

442 **Acknowledgments.** The authors thank Janet Jacobson for editorial assistance. Several
443 authors of this publication are members of the European Reference Network for Rare
444 Immunodeficiency, Autoinflammatory and Autoimmune Diseases, Project ID No 739543.

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567

Table 1 Main clinical characteristics and treatment at diagnosis of 795 FVSG-Registry GPA patients

Characteristic	Value
Demographic	
Sex, female	350 (44.0)
Age at diagnosis, years, mean (SD)	53 (16.3)
Age >65 years*	209 (26.3)
Year of diagnosis	
<2000	135 (17.0)
2000–2009	415 (52.2)
2010–April 2018	245 (30.8)
Smoker	207/625 (33.1)
General	628 (78.9)
Fever >38.5°C	342 (43.0)
Weight loss >3 kg within 3 months	355 (44.7)
Arthralgias	410 (51.6)
Myalgias	218 (27.4)
Ear, nose & throat	639 (80.4)
Sinusitis	331 (41.6)
Rhinitis	426 (53.6)
Nasal crusts	299 (37.6)
Epistaxis	156 (19.6)
Saddle nose	10 (1.3)
Nasal obstruction	204 (25.7)
Otitis	185 (23.3)
Lung	538 (67.7)
Alveolar hemorrhage	142 (17.9)
Massive alveolar hemorrhage and/or Hb <9 g/dL	36 (4.5)
Lung nodules	328 (41.3)
Lung infiltrate	150 (18.9)
Subglottic stenosis	13 (1.6)
Wheezing	8 (1.0)
Renal	447 (56.2)
Serum creatinine worsened >30%	193 (24.3%)
Biopsy-proven glomerulonephritis	147 (18.5)
Proteinuria	279 (35.1)
Hematuria	301 (37.9) ()
Need for dialysis	46 (5.8)
Mucocutaneous	263 (33.1)

Purpura	127 (16)
Livedo reticularis	30 (3.8)
Gangrene	17 (2.1)
Gingivitis	6 (0.8)
Eye	212 (26.7)
Exophthalmos	29 (3.6)
Episcleritis	73 (9.2)
Scleritis	30 (3.8)
Cardiovascular	119 (15)
Pericarditis	33 (4.2)
Myocarditis	11 (1.4)
Congestive heart failure*	15 (1.9)
Gastrointestinal	87 (10.9)
Abdominal pain	49 (6.2)
Perforation	2 (0.3)
Neurological	191 (24.0)
Central nervous system involvement	24 (3.0)
Peripheral neuropathy	151 (19)
Induction therapy†	
Intravenous cyclophosphamide	602 (75.7)
Oral cyclophosphamide	53 (6.7)
Rituximab	52 (6.5)
Methotrexate	36 (4.5)
Mycophenolate mofetil	1 (0.1)
Glucocorticoids	772 (97.1)
Glucocorticoid dose, mg/day, median [IQR]	60 [50–70]
Methylprednisolone pulse	215 (27.0)
Plasma exchanges	59 (7.4)
2009 FFS at diagnosis	
0	381/692 (55.1)
1	169/692 (24.4)
≥2	142/692 (20.5)
BVAS at diagnosis, mean (SD)	17.5(8.8)

Values are expressed as n (%) unless stated otherwise.

*2009 Five Factor Score item.

†In addition, trimethoprim–sulfamethoxazole was given to 249/674 (36.9) patients.

Table 2 Main laboratory findings at GPA diagnosis for FVSG-Registry patients

Parameter	Value
Serum creatinine level, median [IQR] $\mu\text{mol/L}$ *	93 [74–146]
Serum creatinine level $>150 \mu\text{mol/L}$	177/609 (29.1%)
ANCA-positivity by immunofluorescence	700/788 (88.8%)
c-ANCA	568/788 (72.1%)
p-ANCA	132/788 (16.8%)
ANCA-positivity by ELISA	666/728 (91.5%)
PR3 specificity	546/728 (75%)
MPO specificity	120/728 (16.5%)
Histology	
Patients with ≥ 1 biopsies	381 (48%)
Biopsies supporting GPA diagnosis	345/389 (89%)
Vasculitis	142 (41%)
Necrosis	101 (29%)
Granuloma	84 (24%)
Not specified	18 (6%)

*Serum creatinine levels at diagnosis were available for 609 patients. c/p-ANCA, cytoplasmic or perinuclear labeling pattern of antineutrophil cytoplasm antibodies; ELISA, enzyme-linked immunosorbent assay; PR³, p3, MPO, myeloperoxidase.

Table 3 Hazard ratios (95% CI) for the risk of death or relapse for FVSG-Registry GPA patients.

Factor	Death				Relapse			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age	1.06 (1.04-1.08)	<0.001	1.07 (1.04-1.10)	<0.001	0.95 (0.78-1.16)	0.669		
Female	0.56 (0.35-0.90)	0.017			1.00 (0.99-1.00)	0.806		
Lung	1.91 (1.10-3.30)	0.02			0.96 (0.84-1.28)	0.710		
Alveolar hemorrhage	2.19 (1.36-3.54)	0.001			0.86 (0.88-1.49)	0.289		
Renal	3.53 (2.06-6.03)	<0.001			0.97(0.83-1.24)	0.837		
Serum creatinine >150 µmol/L*	2.51 (1.56-4.02)	<0.001			0.92 (0.70-1.19)	0.538		
Hemodialysis	3.12 (1.54-6.28)	0.001			1.27 (0.81-1.97)	0.287		
Skin	2.21 (1.21-4.03)	0.009			0.97 (0.83-1.26)	0.814		
Ear, nose & throat*	0.74 (0.44-1.24)	0.26			0.91 (0.84-1.41)	0.490		
Eye	0.79 (0.48-1.31)	0.36			0.95 (0.84- 1.30)	0.648		
Cardiovascular	1.94 (1.17-3.22)	<0.01			0.98 (0.76-1.34)	0.916		
Congestive heart failure*	9.28 (4.20-20.24)	<0.0001	3.15 (1.04-9.05)	0.041	0.65 (0.20-2.03)	0.463		
Gastrointestinal*	2.24 (1.22-4.05)	0.009			0.97 (0.72-1.44)	0.906		
Neurological	1.40 (0.88-2.20)	0.146			1.02 (0.82-1.27)	0.826		
BVAS	1.06 (1.04-1.09)	<0.001			0.99 (0.98-1.00)	0.48		
Anti-myeloperoxidase°	2.05 (1.18-3.54)	0.010			0.81 (0.61-1.09)	0.173		
Anti-proteinase-3°	0.48 (0.29-0.79)	0.004	0.42 (0.18-0.95)	0.038	1.30 (1.01-1.68)	0.042	1.29 (0.99-1.67)	0.05
Date of diagnosis before 2000			Ref.					

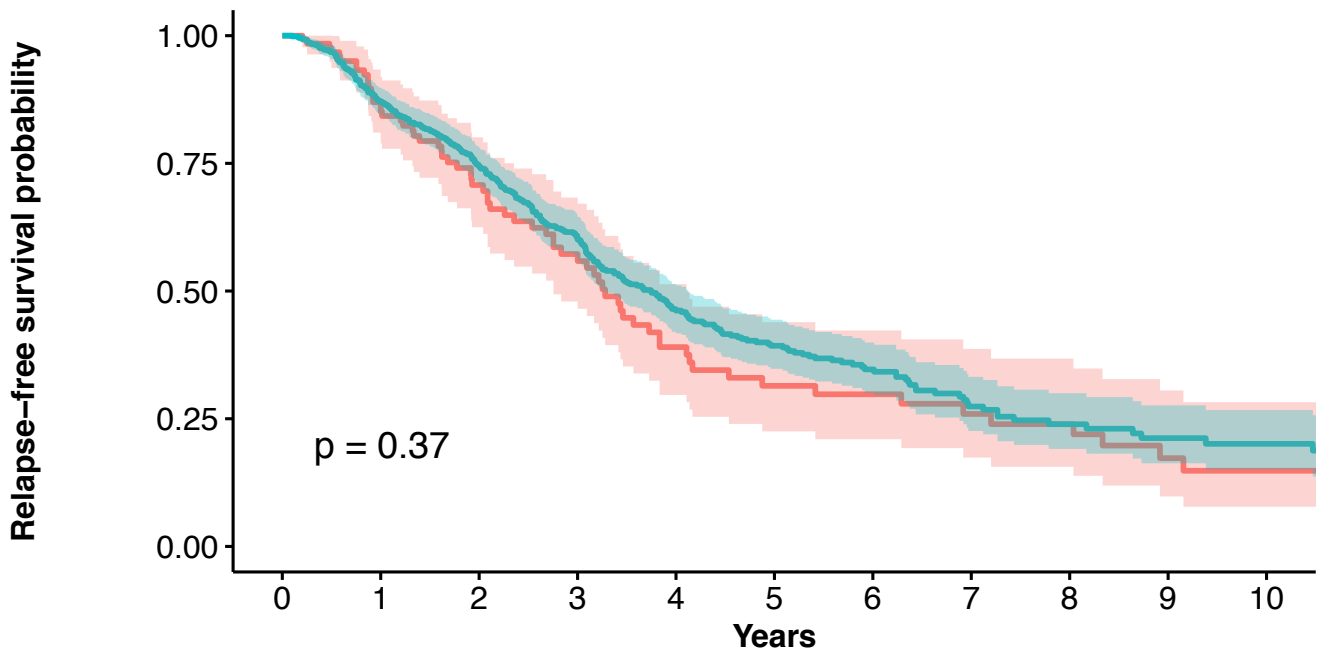
2000-2004	0.39 (0.20 - 0.77)	0.006		
2005-2009	0.19 (0.08 - 0.44)	<0.001		
since 2010	0.17 (0.06 - 0.49)	0.001		
IV CYC			0.88 (0.69-1.12)	0.313
Oral CYC			0.60 (0.36-1.00)	0.05
Rituximab			0.77 (0.44-1.35)	0.375
Methotrexate			0.96 (0.61-1.51)	0.885

Survival was calculated from the time of GPA diagnosis to death, relapse or the last follow-up visit. ° As single variable within ANCA status.

*2009 Five Factor Score item. IV CYC, intravenous cyclophosphamide; BVAS, Birmingham Vasculitis Activity Score.

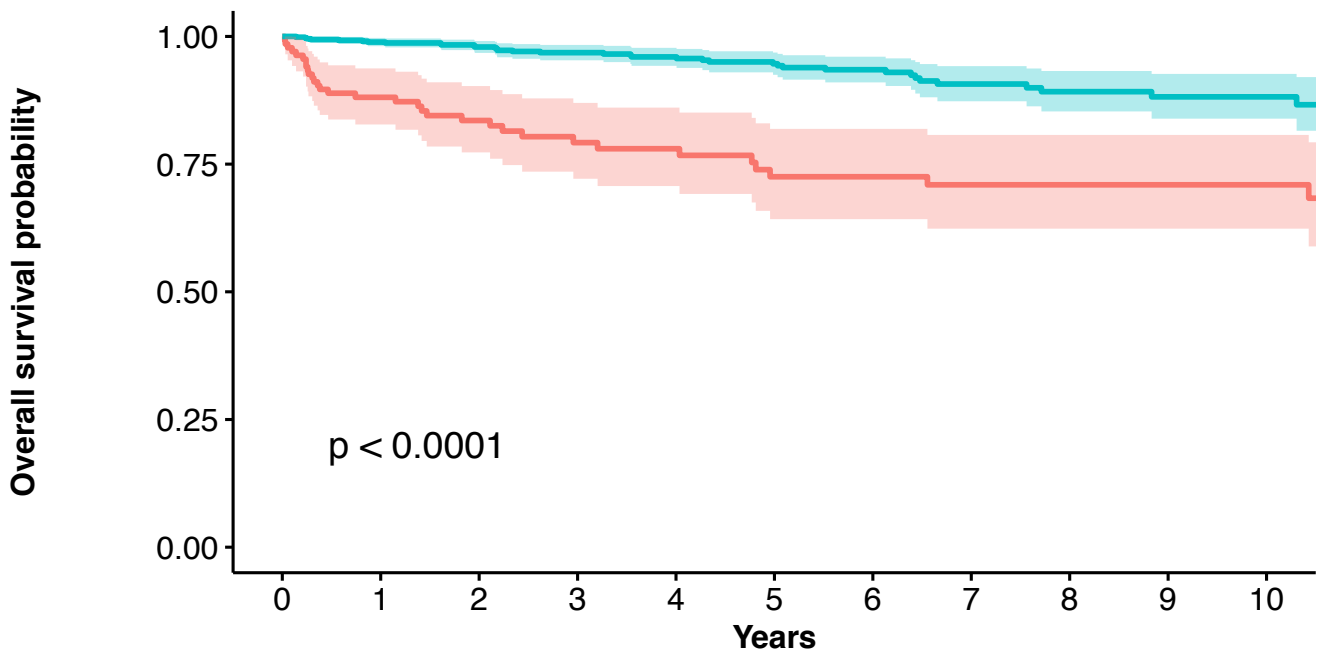
Figure 1 Kaplan–Meier curves of (A) relapse-free survival and (B) overall survival for 795 FVSG-Registry GPA patients, according to year of diagnosis (before or after 2000).

Figure 2 Number of relapsing patients (A) according to the most frequently observed relapse patterns or (B) ordered by the number of relapse-involved organs. Each patient’s pattern over time after diagnosis is illustrated by “connecting the dots” (affecting 1 or several organ(s)). For each patient, one pattern is recorded over time as the cumulative combination of involvements (eg, affecting one or several of organs) observed after diagnosis. In panel A, for example, reading from left to right, you can see that the majority of patients experienced isolated ENT (n=36), or lung (n=28) relapses, followed by a combination of lung, ENT relapses with systemic signs (n=24) (connected dots at the bottom of the graph). The number of patients with each relapse pattern is expressed in a decreasing order from left to right. In panel B, from left to right, we show the number of patients with relapses involving a single organ (gastrointestinal, cardiovascular, cutaneous, ocular, neurologic, etc), or a combination of 2 or more organs. The ‘combination’ pattern can be identified by connecting the dots on the bottom of the figure. GI, gastrointestinal; CV, cardiovascular; ENT, ear, nose & throat.

A

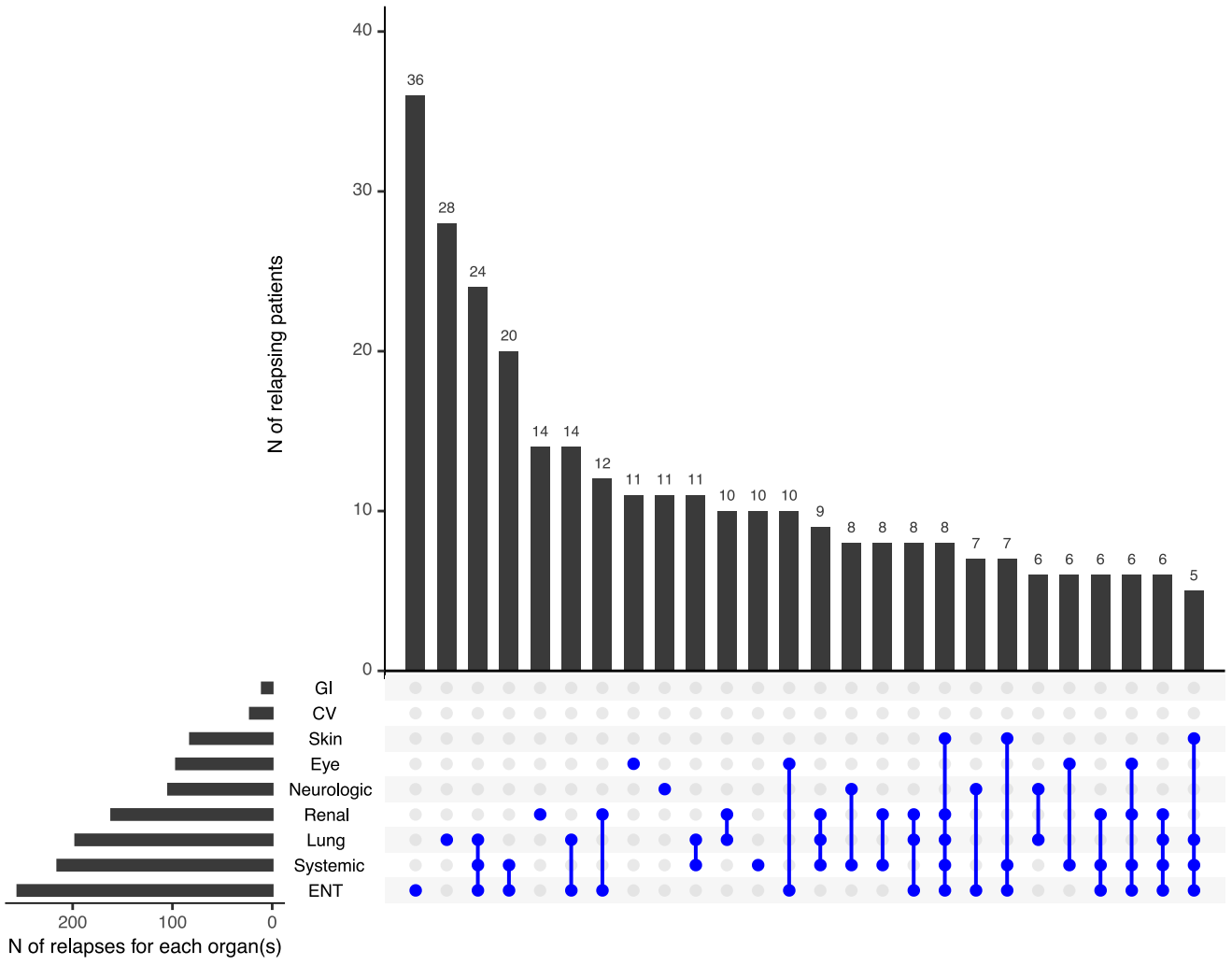
N at risk

	0	1	2	3	4	5	6	7	8	9	10
before 2000	135	95	60	42	27	19	16	13	12	7	6
after 2000	660	514	366	240	155	118	74	43	29	22	17

B

N at risk

	0	1	2	3	4	5	6	7	8	9	10
before 2000	135	108	82	68	61	52	48	43	37	28	27
after 2000	660	579	474	377	307	258	185	140	109	84	65

A**B**