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Treatment of systemic necrotizing vasculitides: The 40-year experience of the French Vasculitis Study Group

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ABSTRACT

Treatment of vasculitides has benefited from the results of several prospective clinical trials focusing on the evaluation of new drugs, therapeutic strategies and adjuvant treatments. In the field of autoimmunity, vasculitides are the group of diseases for which the most important medical progress has been made, combining advances in understanding the pathogenetic mechanisms, classification of the various entities and willingness to evaluate treatments. Several international groups have been actively involved in these tasks. The French Vasculitis Study Group was the first to design and organize prospective trials in the field and to contribute to these medical advances. In this review, we analyze the different treatments and therapeutic strategies evaluated over the last few decades and, more precisely, the last 39 years by the French Vasculitis Study Group.

Better understanding of the pathogenetic mechanisms of vasculitides, the discovery of antineutrophil cytoplasm antibodies (ANCA), a more comprehensible classification system, new therapeutic strategies and novel therapeutic agents have contributed to the remarkable improvement made in their treatment over the last 40 years. The major progress made in terms of survival and outcomes was due, in part, to coordinated efforts of groups-of-interest from different countries and continents. The French Vasculitis Study Group (FVSG) was the first to initiate prospective trials in the world and has contributed over the last 39 years to these medical advances. This review presents an overview of treatment strategies based on the results of prospective clinical trials and case-series studies, and emphasizes the contributions of cooperative trials in the field.

1. Methods

We analyzed the results of all prospective therapeutic trials organized on systemic necrotizing vasculitides (SNVs) over the last decades along with the major case-series, ancillary studies of prospective trials and major research papers that had notable impact on understanding the pathogenesis of vasculitides and fostered the organization of clinical trials. We mainly address primary and secondary SNVs, not taking non-necrotizing vasculitides into consideration.

The FVSG was established before ANCA were discovered and new classification systems devised, which can explain why some of the early prospective trials were not designed around present classifications and definitions that were published several years after the first FVSG prospective trials (Table 1). However, the FVSG's objectives were based on top-priority questions for vasculitis care, with continuity and structured connections between the different protocols organized over time.

2. How to treat?

2.1. Corticosteroids (CS)

CS are the cornerstone of vasculitis therapy. They have documented efficacy but are also responsible for adverse events (AEs). However, CS alone are not sufficient to treat several vasculitides, like granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), but can suffice for others. Leib et al. [1] demonstrated that CS were indeed able to induce remission in approximatively half of their patients. Fauci et al. [2] showed the benefit of cyclophosphamide (CYC) to obtain sustained SNV

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remission in patients who had received CS for a mean duration of 22 months before starting CYC. In our first prospective trial [3], in accordance with the 1970s therapeutic consensus in France, the CS-induction regimen was 1 mg/kg/day for 8 weeks, before being gradually tapered to reach low dose and were stopped at 18 months.

CS are quickly effective and, for the most severely ill patients, 1–3 methylprednisolone pulse(s) (at 7.5–15 mg/kg/day) can markedly attenuate symptoms and life-threatening manifestations, and improve renal function.

However, CS can cause some AEs, which could shorten life expectancy. The decade-after-decade efforts to reduce CS doses positively impacted event-free survival. CS doses have now been lowered worldwide to the benefit of all patients. Notably, one of our prospective trials (CORTAGE) was devoted to decreasing CS doses for elderly patients [4], and its results demonstrated that lower CS doses were not only possible but also limited AEs.

An ongoing trial on eosinophilic granulomatosis with polyangiitis (EGPA; formerly Churg–Strauss syndrome) (REOVAS) [5] is comparing remission-induction treatment with rituximab + CS vs CYC + CS, with the following CS regimen: 1 mg/kg/day (maximum 80 mg/day) for 3 weeks, 35 mg at 1 month, 10 mg at 3 months and steroid discontinuation before the end of the first year. This trial not only evaluates rituximab for remission-induction but promotes CS discontinuation.

In our routine practice, we now usually recommend starting CS at 1 mg/kg/day for 2–3 weeks, then initiating tapering with the objective of reaching 20 mg at 3 months, 10 mg at 6 months and 5 mg at 12 months. However, CS-administration duration is still not consensual among groups. In the US, CS are frequently stopped 6 months after induction [6]. In Europe, and especially France, we prolong their use for 18 months to 2 years, with progressive tapering to under 5 mg/day. Pertinently, Walsh et al. [7] underlined the advantage of long-term CS to prevent relapses based on their retrospective analysis. The recent published prospective study (PEXIVAS) [8] compared 2 regimens of CS + immunosuppressants or rituximab to induce vasculitis remission. Over the 6 first months, one treatment arm received half the CS dose prescribed to the other group. Findings at 1 year showed no disease-control difference between the 2 arms but less infections with the reduced CS-dose arm.

Ongoing prospective trials are targeting CS discontinuation at different treatment durations [9,10] and one aims to stop treatment (not only CS but also immunosuppressants or rituximab) [11] in patients with end-stage renal disease, supposing that disease activity might become quiescent once the patient starts chronic dialysis.

However, for EGPA patients, it remains difficult to follow the CS regimen adopted for other ANCA-associated vasculitides (AAVs) because residual asthma control requires CS (inhaled and/or oral). In our patient-series [12], the majority of subjects took long-term CS (mean: 8 mg/day), often in combination with bronchodilators. Attempted CS-sparing efforts were unsuccessful. Immunosuppressants, like azathioprine (AZA) are unable to spare CS [13]. In contrast, mepolizumab, an anti-interleukin-5 (IL5) monoclonal antibody, has demonstrated efficacy at reducing CS doses for asthmatic EGPA patients, along with fewer relapses and flares [14]. That effectiveness seems more prominent on the respiratory manifestations than the extrapulmonary vasculitis symptoms. Those results are promising and mepolizumab is also expected to lower the CS dose during EGPA remission-induction. It is crucial to reduce severe AE (SAE) numbers and severity when CS are prescribed for months.

2.2. Cyclophosphamide

In 1979 [15], Fauci et al. published an open study, based on 22 patients, whose SNVs did not respond to CS or who had experienced treatment AE(s), and were successfully treated with oral CYC adjunction. That major study, despite having been conducted on a small number of patients, demonstrated that oral CYC, combined with CS, was the best treatment to control SNVs.

To evaluate the indication of oral CYC as first-line SNV therapy, we designed the first prospective trial comparing CS + CYC vs CS alone [3]. Because, in the 1980s, plasma exchanges (PEs) were considered an integral SNV therapeutic intervention, we decided to prescribe PEs for all patients in both groups. We will return later to PE indications in light of more recent findings. Seventy-one patients with polyarteritis nodosa (PAN) or EGPA were included. The CYC + CS + PE regimen was beneficial in preventing relapses during long-term follow-up but 19 patients died. The 10-year cumulative survival rates for the 2 groups were comparable (respectively, 72% and 75%). We concluded that the CYC–CS–PE combination achieved a lower relapse rate and better quality clinical responses to therapy but did not improve survival. Oral CYC was prescribed for 12 months, a dose considered acceptable at that time, but it caused SAEs.

Several prospective trials organized in the 1990s were designed to shorten the CYC-administration duration and lower the total dose. In 1990, the FVSG launched a prospective trial comparing, in addition to CS, oral vs intravenous pulse (IV) CYC for patients with GPA [16]. Its results demonstrated, for the first time, the absence of difference between oral and IV CYC to achieve initial GPA remission and pulses were associated with fewer side effects. Paul Bacon's group also advocated for more extensive prescription of IV—rather than oral—CYC [17]. Now, clinicians in France and many other countries most often opt for IV CYC to induce vasculitis remission. Pulses are administered IV at the dose of 600 mg/m^2 every 2 weeks for 4 weeks, then 700 mg/m^2 every 3 weeks usually for 3 additional pulses.

The EUVAS group organized a prospective trial, published in 2003, comparing 12 months of oral CYC to 3–6 months of oral CYC, both followed by AZA [18]. Survival and relapse rates were comparable for the 2 groups, definitively demonstrating that long-term oral CYC intake is not needed to treat vasculitis. EUVAS organized another prospective trial on AAVs, published in 2009, comparing oral vs IV CYC [19]. That study was larger than our earlier one (148 vs 50 patients, respectively) but the conclusions were the same. The IV CYC regimen induced AAV remission as well as daily oral intake with a smaller cumulative CYC dose and fewer cases of leukopenia. Although IV CYC treatment was shown to be as effective as oral intake to induce AAV remission, it was also found that, after a median follow-up of 4 years, relapses occurred more frequently when IV CYC had been prescribed [20]: 20 (20.8%) of the patients treated orally vs 30 (39.5%) pulse recipients had at least 1 relapse. However, that analysis was post hoc and the conclusions could have been biased, mainly because of missing data for 10% of patients.

One reason to recommend IV CYC is that it lowers the cumulative dose of the drug and, consequently, fewer and less severe AEs occur. Severe CYC-induced AEs have been extensively described in the past, including infections, infertility and malignancies [21,22]. Using monoclonal antibodies (mainly rituximab) to treat AAVs has a clear benefit on preventing AEs, especially sterility and malignancies. However, many vasculitides are not associated with ANCA and CYC is often indicated to treat them. Lowering the total CYC dose (by shortening its administration time to only 3–6 months) since 2003 has also positively impacted its AE numbers but CYC's persistently "bad reputation" comes from events arising when the "old" therapeutic strategies, i.e. high cumulative CYC dose, were applied.

For clinicians choosing to treat patients with CYC, its dose—not only the administration route and cumulative dose—also has a major effect on the AE rate. If oral CYC is chosen, 2 mg/kg/day, limited to 150 mg/day, seems adequate, except when previously prescribed immunosuppressants failed. When CYC pulses are

Table 1
Prospective clinical trials organized by the French Vasculitis Study Group.

Disease(s) targeted: treatment(s)	Acronym	1st inclusion	Patients, *N*	1st author	Reference		
					No.	Year	*Journal* volume: 1st page
PAN and CSS/EGPA: comparing CS, PEs + CYC vs CS + PEs	–	1980	71	L. Guillevin	[3]	1991	*J Rheum* 18:567
HBV–PAN: vidarabine + PEs	–	1981	33	L. Guillevin	[68]	1993	*J Rheumatol* 20:289
PAN and CSS/EGPA without poor-prognosis factors: CS + PE vs CS	–	1983	78	L. Guillevin	[64]	1992	*Arthritis Rheum* 35:208
HBV–PAN: interferon-α + PEs	–	1988	6	L. Guillevin	[69]	1994	*Ann Rheum Dis* 53:334
PAN and CSS/EGPA with poor-prognosis factors: CS + CYC + PE vs CS + CYC	–	1989	62	L. Guillevin	[65]	1995	*Arthritis Rheum* 38:1638
PAN and CSS/EGPA without poor-prognosis factors: CS + oral or IV CYC	–	1989	25	M. Gayraud	[76]	1997	*Br J Rheumatol* 361290
WG/GPA: CS + oral CYC vs CS + IV CYC	–	1990	50	L. Guillevin	[16]	1997	*Arthritis Rheum* 40:2187
PAN and MPA without poor-prognosis factors: CS then AZA or IV CYC then AZA	CHUSPAN	1993	124	C. Ribi	[77]	2010	*Arthritis Rheum* 62:686
CSS/EGPA without poor-prognosis factors: CS then AZA or IV CYC then AZA	CHUSPAN	1994	72	C. Ribi	[78]	2008	*Arthritis Rheum* 58:586
CSS with poor-prognosis factors: CS + 6 vs 12 IV CYC	CHUSPAN	1994	48	P. Cohen	[82]	2007	*Arthritis Rheum* 57:686
PAN and MPA with poor-prognosis factors: CS + 6 vs 12 IV CYC pulses	CHUSPAN	1994	65	L. Guillevin	[81]	2003	*Arthritis Rheum* 49:93
AAV-remission maintenance: CS + MTX vs CS + AZA	WEGENT	1998	126	C. Pagnoux	[30]	2008	*N Engl J Med* 359:2790
HBV–PAN: lamivudine and PE	LAMIPAN	1999	10	L. Guillevin	[70]	2004	*Arthritis Rheum* 51:482
AAV relapses: IVIg	IGANCA	2001	22	V. Martinez	[41]	2008	*Arthritis Rheum* 58:308
IgA vasculitis: CS vs CS + CYC[a]	CESAR	2002	54	E. Pillebout	[26]	2010	*Kidney Inter* 78:495
Refractory/relapsing AAVs: infliximab	RELANCA	2004	17	M. de Menthon	[37]	2011	*Clin Exp Rheumatol* 29:S63
Vasculitis in patients ≥ 65 years old: lower CS dose	CORTAGE	2005	108	C. Pagnoux	[4]	2015	*Arthritis Rheum* 67:1117
AAV-remission maintenance: CS + AZA vs CS + rituximab	MAINRITSAN	2008	115	L. Guillevin	[44]	2014	*N Engl J Med* 371:1771
PAN, MPA and EGPA without poor-prognosis factors: CS vs CS + AZA	CHUSPAN2	2008	101	X. Puéchal	[13]	2017	*Arthritis Rheum* 69:2175
Autoimmune diseases: seasonal pandemic A/H1N1 flu vaccination	MAIVAX	2009	199	A. Kostianovsky	[89]	2012	*Clin Exp Rheum* 30:S83
Individually tailored rituximab for AAV maintenance	MAINRITSAN2	2012	162	P. Charles	[47]	2018	*Ann Rheum Dis* 77:1143
Long term vs conventional maintenance rituximab treatment	MAINRITSAN3	2015	97		–	–	Not yet published
Total No. of patients included			1645				

PAN: polyarteritis nodosa; CSS/EGPA: eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome); CS: corticosteroids; PEs: plasma exchanges, CYC: oral or intravenous pulse (IV) cyclophosphamide; HBV–PAN: hepatitis B virus-related PAN; WG/GPA: granulomatosis with polyangiitis (formerly Wegener's granulomatosis); AZA: azathioprine; MTX: methotrexate; IVIg: intravenous immunoglobulins.
[a] With the participation of the FVSG.

prescribed, we recommended 600 mg/m^2 every 2 weeks for 4 weeks, then 700 mg/m^2 every 3 weeks for 3 additional pulses maximum dose of 1200 mg/pulse. In the case of renal insufficiency (creatininemia clearance < 30 mL/min), severe denutrition or age > 65 years, we recommended reducing each pulse to 500 mg/m^2 in our first trials and, more recently, to a fixed 500-mg dose. Another group [19] recommends 15 mg/kg/pulse, which is grossly comparable to the dose calculated in m^2. In a prospective trial dedicated to elderly patients, comparing two CS schemes, we chose to limit the CYC pulse dose to 500 mg [4] for patients with a 1996 Five-Factor Score (FFS) ≥ 0 [23]. That strategy was effective and survival was better when low-dose rather than conventional CS was prescribed, respectively: 32 (60%) vs 40 (78%) patients had > 1 SAEs ($P = 0.04$), most frequently infections; 6 (11%) vs 7 (14%) failed to achieve remission ($P = 0.71$); 9 (17%) vs 12 (24%) died ($P = 0.41$); and 20/45 (44%) vs 12/41 (29%) survivors in remission relapsed ($P = 0.15$).

For most FVSG trials on PAN, microscopic polyangiitis (MPA), GPA and EGPA, we chose therapeutic strategies for vasculitides according to disease severity, in order to adapt treatment to it and the expected prognosis [23,24]. Our therapeutic strategies are detailed below.

2.3. Azathioprine, methotrexate and mycophenolate mofetil

These three immunosuppressive agents are considered effective at maintaining remission but do not induce it, except some rare data on methotrexate [25].

2.3.1. Azathioprine (AZA)

Azathioprine (AZA) has been evaluated mainly as maintenance therapy [18]. After stopping CYC for SNVs, maintenance is needed to prevent relapses.

For other vasculitides, the indications of immunosuppressants are not so clear, e.g., for IgA vasculitis. Most juvenile patients with IgA vasculitis should not be treated like adults, because the indication of immunosuppressants together with CS has not yet been clearly demonstrated. Many patients are not treated and recover in a few weeks but some with severe gastrointestinal manifestations and/or glomerulonephritis are prescribed CS and immunosuppressants. For severe IgA vasculitis, induction therapy usually comprises CYC + CS but the indication of an immunosuppressant has not been fully documented. A prospective trial, organized in conjunction with the FVSG, did not conclude an

advantage of CYC + CS over CS alone [26]. Unfortunately, that study-sample size was underpowered and the debate on immunosuppressant indication continues. For adult IgA vasculitis, although induction with an immunosuppressant can sometimes be prescribed, maintenance therapy does not seem useful for most patients.

On the other hand, for AAVs and PAN, the CS + AZA combination is recommended for maintenance. The results of a EUVAS-organized prospective trial showed that AZA was as effective as CYC for MPA- and GPA-remission maintenance, and that CYC should be prescribed only for remission-induction and for approximately 3 months [18]. At 18 months, 13.7% of the CYC-treated group and 15.5% of the AZA recipients had relapsed. AZA-administration duration is not consensual. Although most authors treat SNVs for 18–24 months, some patients are kept under treatment for several years and sometimes for life, mainly GPA, depending on their clinical evolution and phenotype.

Another EUVAS-organized prospective trial, in which FVSG members participated, found the relapse rate to be lower when patients received 48, rather than 24, months of AZA maintenance [27]. That latter trial showed that AZA had some efficacy as vasculitis-remission-maintenance therapy but its indications have been changing since the advent of rituximab and its prescription for remission-induction. A trial comparing oral CYC followed by AZA to a weekly rituximab infusion for 4 weeks followed by a placebo did not demonstrate any difference between the 2 groups after 18 months of follow-up [28]. However, although those results indicated no between-group difference, they highlighted the high risk of relapse independently of the maintenance regimen or its absence, suggesting that maintenance therapy could be recommended, but AZA, like other immunosuppressants, should no longer be the first choice to maintain remission.

However, because CYC is still part of the induction regimen, AZA still has a place in maintenance regimens. The optimal AZA dose is 2–3 mg/kg/day. A few patients experienced liver toxicity. That toxicity is favored by interindividual differences, attributable to potentially defective thiopurine *S*-methyltransferase metabolism. Some authors recommended looking for such a deficiency before selecting treatment, with the objective of adapting the daily AZA dose [29]. In practice, we did not test for the enzyme but replaced it by careful and frequent monitoring of transaminases and other liver parameters to detect potential toxicity.

AZA has also been tried as the remission-induction agent for vasculitis in patients without FFS-defined poor-prognosis factors (FFS = 0) [13]. In a prospective trial, MPA, EGPA or PAN patients with FFS = 0 received a combination of CS + AZA vs CS + placebo. That study's results did not demonstrate that AZA had any benefit in terms of preventing relapses, controlling the disease evolution or CS-sparing. However, they clearly demonstrated that AZA is not indicated for vasculitis-remission induction.

2.3.2. Methotrexate

Methotrexate is mostly prescribed as maintenance therapy at a weekly dose of 0.3 mg/kg, respecting its clinical contraindications and the treating physician's choice, as for AZA. The results of an FVSG prospective randomized–controlled trial comparing methotrexate vs AZA demonstrated that tolerance and efficacy to prevent relapses were the same for both drugs [30]. In practice, clinicians frequently prescribed methotrexate as induction therapy for minor AAV forms, despite the fact that their relapse rate is higher than that observed when CYC is used for induction [25]. Methotrexate is frequently chosen to treat granulomatous forms of GPA with mainly ear, nose & throat (ENT) manifestations and without visceral involvement, like the kidney. After 10 years of follow-up [31], methotrexate effectiveness and AEs were comparable to those observed with AZA, prescribed for an initial period of 18 months, but that its efficacy at preventing relapses was also poor, as with other immunosuppressants like AZA or mycophenolate mofetil (MMF). It must be also underlined that methotrexate is not recommended for patients with severe renal insufficiency or those with liver disease. Methotrexate can sometimes, albeit rarely, be responsible for interstitial pneumonia and, although it has not been demonstrated that it could worsen vasculitis-related interstitial pneumonia, it is reasonable to avoid this drug in patients with preexisting interstitial pneumonia or lung fibrosis.

2.3.3. Mycophenolate mofetil (MMF)

Since MMF has been widely used to treat systemic lupus, it has also been tried in systemic vasculitis patients. A EUVAS randomized–controlled trial compared AZA vs MMF for remission-maintenance [32]. That study's results showed that MMF was inferior to AZA to prevent relapses. The same group also prospectively evaluated MMF for remission-induction in non-renal or in non-severe renal MPA or GPA, compared to CYC [33]. Those authors considered MMF to be non-inferior to CYC for induction, but the subsequent relapse rate was higher in patients induced by MMF. Based on the results showing that MMF was less effective than AZA to maintain remission, it seems unlikely that MMF has a role as a CYC or rituximab competitor to induce AAV remission. In our practice, we consider MMF for maintenance only in case of failures or contraindications to all other drugs.

2.4. Targeted monoclonal antibodies and biotherapies

2.4.1. Anti-tumor necrosis factor (TNF)

Many autoimmune and systemic diseases have been successfully treated with targeted monoclonal antibodies, especially anti-TNF. Notably, it has been evaluated as an AAV-remission–maintenance agent. A prospective trial [34] comparing etanercept, targeting the TNF receptor, to an immunosuppressant, mainly methotrexate, failed to show any benefit of the anti-TNF but the etanercept group had more frequent AEs. Etanercept is a fusion protein with no activity against granulomatous manifestations, which could explain the poor results observed in that trial.

The FVSG evaluated infliximab, an antibody with a direct effect on granuloma, in an open pilot study [35]. That study's results showed infliximab efficacy but also its suspensive effect [36], as improvement disappeared during the months after its discontinuation. We also compared infliximab to rituximab in a prospective randomized–controlled trial on GPA patients who did not respond or flared, despite optimal CS + immunosuppressant treatment [37]. Based on the 17 patients included in that trial, rituximab was superior to infliximab, with 4/8 vs 2/9 complete remissions obtained, respectively. In addition, among the 5 patients whose disease did not respond to infliximab, 4 were subsequently treated successfully with rituximab. That trial's results confirmed that anti-TNFα monoclonal antibodies have only a limited effect and should not be prescribed to treat GPA. However, they can exert some efficacy against granulomatous forms of GPA that failed to respond to CS, immunosuppressant and rituximab.

2.4.2. IV Immunoglobulins (IVIg)

IVIg have been prescribed to treat ANCA vasculitis for decades [38,39]. Their effectiveness was based on antibody neutralization and anti-idiotype activity but also probable cellular mechanisms. The results of a prospective trial conducted by Jayne et al. [40] showed some IVIg efficacy but also highlighted the limited duration of their action, which lasted only 3 months. It is not recommended to treat AAVs with IVIg alone but sometimes, in combination with other agents. The results of an FVSG prospective

trial [41] showed that IVIg, when added to CS and immunosuppressants, which had previously failed to obtain AAV remission, could be successful. Twenty-two patients received, in addition to their previous ineffective CS + immunosuppressant, monthly IVIg infusions, at a dose of 2 g/kg/session, for 6 months. When evaluated at 9 months (3 months after the last IVIg infusion), all 22 had obtained remission. Effectiveness duration exceeded 9 months for most patients, showing that combining IVIg with conventional treatments had beneficial effects and could be included in therapeutic strategies. One major advantage of IVIg is that they do not induce an immunosuppression syndrome and can be given to severely immunocompromised individuals. IVIg contraindications should be respected; notably, IVIg should not be prescribed to patients with renal insufficiency.

IVIg are also the standard-of-care for patients with Kawasaki disease [42]. This vasculitis, which affects medium-sized vessels, mainly occurs in newborn and very young children; it is rare in adults. Among several systemic symptoms, Kawasaki disease is responsible for cardiac symptoms with coronary vessel involvement, microaneurysms and sometimes cardiac-insufficiency. Because of its potential severity, a rapidly active treatment is needed and IVIg have documented efficacy. For most patients, one cycle (2 g/kg) suffices to treat the disease [42].

IVIg can also be prescribed as a replacement therapy in the case of immune deficiency.

2.4.3. Rituximab

Rituximab, an anti-CD20 monoclonal antibody, has revolutionized the treatment of AAVs. Rituximab targets B-lymphocytes. Two pivotal studies [6,43] demonstrated the non-inferiority of rituximab to CYC to induce AAV remission. Those prospective trials focused on GPA and MPA, excluding EGPA. In one trial [6], one arm of patients took oral CYC + CS for 3–6 months followed by AZA, while the other arm-received rituximab (375 mg/m^2, every week for 3 weeks for 4 infusions) without any subsequent maintenance immunosuppressant. Among the 197 patients included, 63 (64%) rituximab recipients reached the primary endpoint of remission at 6 months without CS, compared to 52 (53%) control-group patients ($P < 0.001$ for non-inferiority). The rituximab-based regimen was more effective than the CYC-AZA based regimen at inducing sustained remission of relapsing disease. Rituximab was also as effective as CYC in patients with major renal disease or alveolar hemorrhage. The number of AEs was comparable in the 2 groups.

The continuation study [27] on the same patients showed that, after 18 months, the relapse rate was comparable for both groups. The authors concluded that AZA was not useful to maintain remission when rituximab had been chosen to induce remission. However, the relapse rate was high in both groups: at 12 and 18 months, respectively, 48% and 39% of the rituximab recipients had sustained complete remissions, compared with 39% and 33%, of the controls.

The second study [43] also compared rituximab vs CYC but the rituximab recipients initially received 1 CYC pulse. The trial enrolled 44 patients, with 3/1 randomization (11 patients were included in the CYC arm). Twenty-five (76%) rituximab recipients and 9 (82%) controls had sustained remissions. More AEs occurred than in the trial previously cited [6]. SAEs occurred in 14 (42%) rituximab recipients and 4 (36%) controls ($P = 0.77$).

Rituximab has now been approved by the Federal Drug Administration and European Medical Agencies to induce and maintain AAV remissions. The extremely high relapse rates for both groups during the 18 months of follow-up in Specks et al.'s [28] study served as an incentive for the FVSG to look for a more effective AAV-remission–maintenance therapy. The poor AZA efficacy, regardless of the induction regimen, incited us to seek a new standard-of-care.

We therefore designed a prospective, randomized–controlled trial (MAINRITSAN 1) that compared, after stopping the remission-induction CYC + CS regimen for all participants, conventional AZA (2 mg/kg/day) for 12 months, then tapered to stopping at 22 months, vs five 500-mg rituximab infusions scheduled to start 2 weeks post-induction, then at 5.5 months and every 6 months until month 18. The numbers of relapses and event-free survival were determined at 28 months. At that time, 28% of the patients had experienced a major relapse on AZA and 5% on rituximab ($P < 0.001$) [44]. Survival was good, with no deaths among rituximab recipients and 2 in the AZA group (septicemia or pancreas cancer). The 5-year follow-up of the same study [45] showed that patients in both groups relapsed but more frequently for those initially randomized to the AZA group. At month 60, for the AZA and rituximab arms, respectively, the major relapse-free survival rates were 71.9% and 49.4% ($P = 0.003$). Quality-adjusted time without symptoms and toxicity analysis showed that rituximab-treated patients had 12.6 months more without relapse or toxicity than those given AZA ($P < 0.001$). Like Specks et al. [27], we also observed that relapses occurred more frequently in patients who were anti-proteinase-3 (PR3) ANCA-positive at diagnosis and at 12 months or when anti-PR3 did not disappear under treatment, than patients with anti-myeloperoxidase (MPO) ANCA or who had no ANCA at diagnosis or during follow-up. The multivariate analysis hazard ratios for relapse for PR3-ANCA–positive and AZA-treated patients, respectively, were 2 and 2.72.

The FVSG also reported the results of retrospective analyses of 80 AAV patients [46]. Albeit uncontrolled, that study's findings confirmed rituximab efficacy for remission-induction and its maintenance.

Demonstration of rituximab efficacy also has to be completed by answering other questions concerning predictive criteria for dose adaptation, relapse and optimal treatment duration. The FVSG has organized a prospective trial aiming to evaluate the contribution of ANCA titer and/or the presence of circulating CD19+ B cells to patient-centered therapy (MAINRITSAN 2) [47]. In that trial, we compared, after randomization, the fixed rituximab-infusion schedule, as applied in the previous MAINRITSAN 1 trial, vs an "on-demand" arm, meaning rituximab was infused only when the ANCA titer increased, or circulating CD19+ B cells remained present or reappeared. The trial results showed that it was possible to maintain remission with less rituximab than in the MAINRITSAN 1 study (1.5 g instead of 2.5 g), and that ANCA titer and CD19+ presence were not associated with relapses. Indication for rituximab reinfusion should be based more on the presence of enzyme-linked immunosorbent assay-detected ANCA than their titer. No association has been found with CD19-positivity, a marker considered to reflect rituximab activity on B cells, but those lymphocytes have been detected in peripheral blood and further studies are needed to look at the relationship between memory cells and clinical response. That study is ongoing.

MAINRITSAN 3, a follow up study of MAINRITSAN 2, compared, post-randomization, 4 additional semestrial rituximab infusions in 1 arm vs placebo in the other. This study showed that long-term rituximab-maintenance therapy significantly reduced AAV-relapse rates and did not seem to increase the SAE rate or severity.

Among AAVs, EGPA has a special place. It almost always occurs in previously asthmatic patients and its pathogenesis is heterogeneous, involving ANCA in a minority of patients and more complex mechanisms, including eosinophil toxicity through IL5.

The positive effect of rituximab on EGPA is currently restricted to low-evidence–based open-label, uncontrolled studies [48,49] and case reports. Those results support rituximab use for severe refractory/relapsing EGPA. In the largest retrospective series [48], clinical improvement had been obtained at 12 months by 36/41 (88%) patients: 49% in remission and 39% with partial responses.

Pertinently, rituximab appeared more effective for ANCA-positive patients, but ANCA-negativity did not preclude potential benefit.

Those observations indicate potential rituximab benefit for EGPA patients but controlled study confirmation is needed. An ongoing FVSG phase-III randomized–controlled trial (REOVAS) is assessing rituximab induction [5], another is being prepared to evaluate mepolizumab [50] and third is planned for maintenance therapy (MAINRITSEG) [51].

2.4.4. Omalizumab (anti-IgE)

Omalizumab (Xolair®), a humanized IgG monoclonal antibody, targets the Fc fragment of free-circulating, but not membrane-bound, IgE. Its binding prevents interaction with specific FcεRI receptors on basophils and mast cells, thereby inhibiting their degranulation in response to allergen exposure and blocking the allergic cascade. Omalizumab was proven effective and safe as add-on therapy for severe persistent allergic asthma and chronic sinusitis. Omalizumab's impact on allergic asthma and eosinophilia has suggested its potential activity against EGPA, particularly for patients with uncontrolled asthma. Omalizumab treatment of EGPA remains limited to a case-series of 17 patients or a case report [52,53].

Although anti-IgE omalizumab effectively controlled the asthma-exacerbation rate and airway obstruction for most patients, a few developed EGPA flares [52,54]. Even though omalizumab responsibility for EGPA flare has never been demonstrated, the clinical extension of omalizumab use to EGPA has been stopped and no randomized–controlled trial in this context is currently planned.

2.4.5. Mepolizumab (anti-IL5)

Mepolizumab (Nucala®), a humanized IgG1 monoclonal antibody, inhibits IL5 signaling in eosinophils, thereby preventing their activation, recruitment and tissue accumulation, as demonstrated in asthma patients with fewer blood and sputum eosinophils.

Mepolizumab has been investigated in several eosinophilic disorders, like asthma [55], rhinosinusitis, hypereosinophilic syndrome and atopic dermatitis. Mepolizumab better controlled disease (exacerbations), slightly improved lung-function–test results and had a CS-sparing effect [55,56]. The recommended mepolizumab dose for this indication is 100 mg injected subcutaneously once every 4 weeks.

Potential mepolizumab efficacy was evaluated in a large, multinational, randomized–controlled trial on relapsing/refractory EGPA [14], in which patients received subcutaneous mepolizumab (300 mg) injections every 4 weeks or placebo (68/group) for 1 year. EGPA patients were representative of those requiring new therapeutic options, with previous relapses/difficult-to-treat disease, all taking CS and about half on immunosuppressants. The protocol-defined primary efficacy endpoints reached significance: comparing mepolizumab vs placebo, respectively, 28% vs 3% had $>$ 24 weeks of accrued remission; 32% vs 3% were in remission at weeks 36 and 48, with 44% vs 7% of the patients benefiting from CS-dose tapering taking $<$ 5 mg/day prednisone or equivalent. Although the mepolizumab-group's 1-year relapse rate was 50% lower, 56% of them still relapsed, with asthma and/or ENT-symptom exacerbation, and/or vasculitis manifestations.

Mepolizumab efficacy against specific vasculitis-related symptoms and not only asthma/sinusitis manifestations deserve to be investigated to determine the respective effects on those two aspects of this vasculitis.

The ability of anti-IL5 to induce EGPA remission was investigated on a small series of patients [57]. The results were encouraging and vasculitis control was obtained in 8/10 patients and it was possible to quickly taper CS in most patients. A randomized-controlled study is needed to evaluate this indication.

2.4.6. Interferon-alpha (IFNα)

IFNα, a cytokine with pleiotropic effects on immune cells, can decrease blood eosinophilia, block IL5 secretion in vitro and attenuate a skewed Th2 profile. In light of those properties, IFNα was tested on a small number of patients in a small prospective open-label study [58], and an uncontrolled retrospective analysis of 30 patients followed $>$ 24 months [59]. Although some remission-induction success was reported, long-term follow-up indicated high relapse rates and numerous AEs, e.g., depression and neuropathy. Therefore, in 2015, the EGPA Consensus Task Force advocated its use only as second- or third-line therapy for relapsing/resistant cases [60].

2.5. Therapeutic plasma exchanges

Therapeutic PEs have been proposed to treat vasculitis since the 1970s. At that time, clinicians were so convinced of their efficacy that PEs were prescribed for all severely ill patients and, in our first trial evaluating CYC as first-line therapy, they were included in both arms [3]. Its notable benefit was shown for patients with rapidly progressive crescentic glomerulonephritis but the series was retrospective and small [61,62]. Results of the first controlled trials [63–65], designed to treat all vasculitis forms, failed to find any improved survival advantage. Indeed, two FVSG prospective, randomized–controlled trials [64,65] showed the absence of between-group differences for survival, disease control and relapse prevention. Those studies focused on PAN and EGPA, aiming to demonstrate efficacy on disease control, relapses and survival.

In the first trial [64], 78 patients included in 2 arms were prescribed immunosuppressants only when CS ± PEs failed. The treatment-failure, relapse and survival rates did not differ significantly between the 2 groups. At 7 years of follow-up, 56 patients had completely recovered (27 in group CS + PEs, 29 in group CS), 7 were in clinical remission and 15 had died (6 group CS + PEs patients and 9 group CS). PE adjunction was no more beneficial than CS alone at preventing relapses over the long term. The 7-year cumulative survival rates were comparable for arms CS + PE and CS (83% and 79%, respectively).

The second randomized–controlled trial [65] evaluated PE adjunction to CS + IV CYC, for patients with poor-prognosis factors (severe disease; FFS $\geq$ 1). Seven patients relapsed: 3 assigned to receive CS + CYC + PEs and 4 given CS + CYC. At 5 years of follow-up, 38 patients (61.3%) were in complete remission (16 in group CS + CYC and 22 in group CS + CYC + PEs) and 5-year cumulative survival rates did not differ significantly (88% of the CS + CYC + PE arm and 75% of CS + CYC recipients).

However, according to EUVAS randomized-trial results, PEs did not prolong survival but improved renal function [66]. PEXIVAS, is a more recent trial [67] on AAV patients that compared PE adjunction or not, to CS + CYC or rituximab. The study had a dual objective: evaluate PE impact on AAV patients' mortality and morbidity and the CS doses (high vs low) required to control their diseases. The composite judgment criterion comprised mortality and other clinical and biological parameters; results were negative for all of them. The discrepancies between that study [67] and the previous one [66] can be explained by the fact that in the study randomized initial PEs vs IV methylprednisolone (3 boluses), then all received CYC + oral CS. In the recent study [67] also randomizing PEs, patients in both trial arms received initial IV pulse methylprednisolone then oral CS + CYC or rituximab. Initial methylprednisolone could explain the disease-control difference

and PEs might have been unnecessary for many patients already controlled by oral and IV steroids and immunosuppressant or rituximab.

Severe alveolar hemorrhage is usually one of the indications for PEs. No prospective trial has substantiated that indication but, based on good clinical results obtained for patients with severe anti-glomerular basement membrane (GBM) vasculitis (Goodpasture's syndrome), PEs are widely prescribed for severe alveolar hemorrhage and good clinical results have been obtained.

Another well-recognized PE indication was PAN associated with hepatitis B virus (HBV) infection, for which we devised several prospective trials [68–70] to assess a novel therapeutic strategy at that time: combining PEs and antiviral agents, after short-term and abruptly withdrawn CS + immunosuppressants. When developing that approach with Christian Trepo [71,72], we hypothesized for the first time that treating the underlying PAN etiology might facilitate recovery from the vasculitis and perhaps even cure it. Notably, CS + immunosuppressants are able to successfully treat HBV-related PAN (HBV–PAN), achieving short-term outcomes comparable to those obtained with PEs + antiviral agents. However, immunosuppressants are not innocuous agents: they enhance HBV replication, perpetuate chronic HBV infection and facilitate progression towards cirrhosis, which may later progress to hepatocellular carcinoma.

Antiviral efficacy against chronic hepatitis and the PE contribution to PAN therapy led us to combine the two to treat HBV–PAN. The following therapeutic sequence was defined: initial CS, to control the severe life-threatening PAN manifestations, common during the first weeks of the vasculitis; followed by abrupt CS discontinuation to improve immunological clearance of HBV-infected hepatocytes and favor HBe-antigen-to-anti-HBe-antibody seroconversion, all with concomitant PEs to control PAN.

Obtained within a few weeks, the therapeutic outcomes of combining an antiviral (vidarabine, interferon-alpha-2b, lamivudine or, more recently, entecavir or other more effective drugs) and PE were globally excellent [73]. Notably, the seroconversion rate rose from 14.7% with conventional treatment to 49.4% for patients given the antiviral + PE strategy.

That approach has also been applied to other SNVs, e.g., HCV-associated cryoglobulinemic vasculitis [74], for which antiviral agents, like inhibitors of non-structural protein 5B (NS5B) polymerase, alone or combined with PE or, more recently, rituximab, have been shown to be able to cure the vasculitis.

Our analysis of HBV–PAN clinical characteristics and outcomes revealed that the antivirals, rather than immunosuppressants, revolutionized patients' outcomes [73].

2.6. Drugs under evaluation

New drugs, like avacopan [75], or old drugs in search of new uses and extended indications can be prescribed to treat AAVs.

2.6.1. Abatacept

Abatacept can play a role, albeit limited. Anecdotically, it obtained some good clinical responses of non-severe GPA. Abatacept was usually combined with CS + immunosuppressant [76]. A prospective study is ongoing for non-severe relapsing GPA.

2.6.2. Avacopan

Avacopan (CCX168) is an oral, selective C5a-receptor inhibitor that might replace oral CS [75]. In a randomized, placebo-controlled trial, 67 patients with newly diagnosed or relapsing AAVs were assigned to receive—placebo + prednisone (60 mg/day), i.e., served as controls; avacopan (30 mg, twice daily) + prednisone (20 mg/day); or avacopan (30 mg, twice daily) without prednisone. All patients received cyclophosphamide or rituximab. At week 12, clinical responses were observed in 14/20 (70%) controls, 19/22 (86.4%) patients taking avacopan + reduced-dose CS and 17/21 (81%) taking avacopan alone ($P = 0.01$ for non-inferiority). The authors considered that C5a-receptor–inhibition by avacopan could successfully replace high-dose CS to treat AAVs [75]. A larger prospective study for a longer time is ongoing.

3. Therapeutic strategies

The FVSG's main role was to evaluate the optimal vasculitis treatment with the aim to evaluate drugs, codify therapeutic strategies and, especially, to choose treatments according to the disease etiology (e.g., HBV–PAN), and adapt them to the entity diagnosed and its severity.

3.1. Five-Factor Score

The initial FFS was published in 1996 [23] and the revisited version in 2011 [24]. The main objective of these scores was to determine, at diagnosis, which clinical and biological manifestations are associated with higher mortality. The 1996 FFS considered only PAN, including HBV–PAN, and EGPA—not MPA, GPA or other vasculitides. Only adults < 75 years old were included, among those enrolled in the first 4 FVSG-organized prospective trials [3,64,65,68,69,77].

Because the FFS revealed different evolutionary profiles according to clinical symptoms associated with vasculitis severity, we decided to design prospective trials tailoring treatment according to that criterion. Those trials explored the hypothesis that disease severity should guide treatment adaptation and minimization, and that some SNVs could be treated without an immunosuppressant. PAN, MPA [78] and EGPA [79] were the first to be subjected to that strategy.

For PAN and MPA without poor-prognosis factors (FFS = 0), CS alone were able to obtain remission in 98/124 (79%) patients; among them, 40% had sustained remissions and 37% relapsed [78]. In that prospective trial (CHUSPAN), patients whose disease relapsed or failed to respond to initial CS were randomized to receive 6 CYC pulses or AZA. Those two drugs were equally effective, with respective 1- and 5-year survival rates of 99% and 92%.

Then, among 72 EGPA patients enrolled in a prospective trial using the same protocol [79], 93% of them entered remission and 35% relapsed. The patients who were randomized to receive immunosuppressants for relapse responded equally to AZA or CYC. At the end of follow-up, 79% were on low-dose CS, mainly to control asthma.

Those studies benefitted from long-term follow-up [80,81]. For PAN and MPA [80], follow-up lasted 98 ± 41 months. At 8 years, 86% of the patients survived, with no difference between relapsers and non-relapsers or the 2 entities. Disease sequelae included peripheral neuropathy, arterial hypertension and osteoporosis. The long-term EGPA follow-up study combined patients independently of baseline severity factors [81]. Its mean follow-up lasted 81 ± 40 months, during which 41% of the patients suffered 1 relapse, with 57% of those events occurring when CS-tapering reached < 10 mg/day. Treatment achieved new remissions in $> 90\%$, but 38% of them relapsed again. Overall survival reached 90% at 7 years and was good, regardless of baseline vasculitis severity; the only parameter associated with a higher risk of death during follow-up was age ≥ 65 years.

For PAN, MPA or EGPA patients with poor-prognosis factors of (FFS ≥ 1), we also designed prospective trials [82,83]. For these patients, combined CS + CYC was compulsory and we focused the trials on optimal treatment duration, comparing 6 to 12 CYC pulses without maintenance treatment. The 12 CYC-pulse, PAN, MPA [82]

and EGPA [83] recipients had significantly lower relapse probabilities and higher event-free survival rates, but mortality rates did not differ significantly. The 10-year follow-up of those studies showed that the early 12-pulse–CYC benefit disappeared over time, and that clinical responses and survival rates were comparable [84]. Based on those results, we consider that the therapeutic regimen should be chosen according to vasculitis severity and not prescribed independently of such factors. This parameter is only one among others to guide treatment choice.

3.2. Diagnostic criteria

Criteria for diagnosing vasculitis do not exist for most of the entities, whose diagnoses are made based on histology and clusters of clinical symptoms. Classification and diagnostic criteria have frequently been inappropriately confounded. Diagnostic criteria have only been developed for PAN combining the presence and absence of clinical-biological items [85]. Criteria need to be established for all vasculitides to help diagnose them more rapidly, choose the most appropriate treatment and thereby prevent sequelae.

3.3. Biological and immunological markers

Inflammation (C-reactive protein and erythrocyte sedimentation rate) and immunological markers are useful parameters to help physicians classify and diagnose the entity, prescribe optimal therapeutic regimens and follow patients. Most patients have inflammation markers that become normalized under treatment. Creatinine is another parameter that reflects disease activity and sequelae. Transaminase levels are also extremely helpful in diagnosing HBV–PAN, as they can be moderately elevated. Under treatment, transaminase levels can rise, reflecting the onset of acute hepatitis, which usually precedes HBe–anti-HBe seroconversion. In other patients, transaminases return to within the normal range with or without the appearance of anti-HBe or -HBs antibodies. However, highly elevated transaminases can also signal fulminant hepatitis.

Immunological markers are also of major interest in AAVs and anti-GBM vasculitis. Around 25% of the patients have detectable anti-MPO ANCA and anti-GBM antibodies [86]. The anti-GBM–vasculitis prognosis is mainly linked to renal failure and dialysis—not antibody titers. In contrast, AAV relapses are clearly linked to ANCA-positivity. It has been shown that anti-PR3–positive patients relapse more than those anti-MPO-positive [27]. The long-term follow-up results of our MAINRITSAN 1 trial [45] also showed that patients without ANCA at diagnosis or those who were anti-MPO-positive relapsed less that those with the following criteria: anti-PR3-postivity at diagnosis, anti-PR3 persistence at 12 months of follow-up and thereafter. However, the ANCA titer was not associated with relapses [46]. Relapse-free survival was longer for patients who remained anti-PR3–negative [87]. Hence, ANCA can be considered useful markers that could guide treatment duration to prevent relapses.

3.4. Additional measures

Parameters other than vasculitis entity, its severity or biological markers are implicated in choosing the optimal therapy. The patient's age, other chronic comorbidities (e.g., diabetes, hypertension, osteoporosis) influence treatment choices. We designed the only prospective trial (CORTAGE) evaluating therapeutic strategies for elderly patients [4]. Treatment of juvenile vasculitis follows the therapeutic strategies adopted for adult patients and specific studies are needed to establish whether children should be treated differently than adults.

Treatments are responsible for AEs or SAEs, some of which can be prevented. *Pneumocystis jirovecii* pneumonia (PJP) is one of them; it can be prevented by prophylactic co–trimoxazole. The FVSG has investigated PJP frequency in vasculitis and highlighted the impact of CS + CYC on T lymphocytes [88]. Since the introduction of systematic co–trimoxazole (400/80 mg/day) prophylaxis, the PJP rate has declined. Although rituximab has often taken the place of cytotoxic agents, PJP pneumonia has continued to occur, despite the fact that rituximab depletes mainly B lymphocytes. PJP is diagnosed in 1%–3% of vasculitis patients [44,46]. Co–trimoxazole should be taken prophylactically until immune reconstitution has been documented, which can take several months or years.

Other prophylactic measures are needed, depending on the identified risk factors, such as tuberculosis or other mycobacterial infections.

Vasculitis patients are often in poor general condition, with notable recent weight loss. Maintaining normal nutritional status or compensating for hypoprotidemia can help prevent infectious AEs.

When CYC is prescribed, adequate hydration is essential to prevent cystitis and bladder cancer [21]. Lowering the total CYC dose and predominant IV administration are the most effective measures to counter bladder toxicity.

Vaccination can prevent infections and should be encouraged. To be effective, vaccines should be administered as soon as possible after vasculitis diagnosis. Use of CS, immunosuppressants and/or biotherapies impairs the body's ability to produce specific antibodies, as shown by an FVSG prospective trial [89] and others [90]. According to a recent systematic review [91] focusing on anti-pneumococcal vaccination, the initial serological responses to pneumococcal conjugate and pneumococcal polysaccharide vaccines are impaired. The defective response was more severe after pneumococcal conjugate than pneumococcal polysaccharide vaccine. The FVSG has launched a prospective study (PNEUMOVAS) on immune responses to pneumococcal vaccination of AAV patients [92]. Despite some EGPA patients' flares after desensitization or vaccinations [93], immunizations against influenza and pneumococci are strongly recommended. The risk/benefit ratio favors immunization, except during an EGPA flare.

Disclosure of interest

The author declares that he has no competing interest.

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