Review

Unsolved questions and concerns about treatment of anti-neutrophil cytoplasm antibody-associated vasculitides

B. Chaigne, L. Guillevin

Department of Internal Medicine, National Referral Center for Rare Autoimmune and Systemic Diseases, INSERM U1016, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, University of Paris Descartes, France.

Benjamin Chaigne, MD
Loïc Guillevin, MD

Please address correspondence to:
Prof. Loïc Guillevin,
Department of Internal Medicine, National Referral Center for Rare Autoimmune and Systemic Diseases, INSERM U1016, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, University of Paris Descartes, 27, rue du faubourg Saint-Jacques, 75679 Paris, Cedex 14, France.
E-mail: loic.guillevin@cch.aphp.fr

Received on March 8, 2016; accepted in revised form on April 5, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 97): S121-S128.

Key words: ANCA, vasculitis, treatment, rituximab, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis

Competing interests: none declared.

ABSTRACT

The treatment strategy for vasculitis has changed dramatically over the last few years, but some major questions remain. Herein, after reviewing the literature, we provide answers to, or at least an analysis of, available evidence on 10 specific and practical questions concerning ANCA-associated vasculitis management.

Introduction

Despite controlled trials and case series on the treatment of ANCA-associated vasculitides (AAVs), several major questions have not yet been answered and therapeutic strategies concerning some essential points remain unclear. Herein, after analysing the literature, we attempt to answer specific questions or at least synthesise the current state of the art of treating AAVs. Ten questions were chosen to highlight the recent findings of major investigations and specify therapeutic priorities.

General AAV patients

Should we consider rituximab (RTX) for every AAV patient?

Following the publication of the results of three randomised-controlled trials (RCTs) evaluating RTX efficacy against AAVs, the AAV standard-of-care has changed dramatically and, clearly, RTX is considered a valid therapeutic option for every AAV patient (1-3). However, despite a strong level of evidence for its use as an induction agent, according to the RAVE and RITUXVAS RCT results, it is still unclear that every AAV patient would benefit from its use (4, 5).

First, depleting immunosuppressants, *e.g.* cyclophosphamide (CYC) or RTX, can be considered for induction. Indeed, in terms of mortality, patients with a Five-Factor Score (FFS) ≥1 with granulomatosis with polyangiitis (GPA) definitely require such an immunosuppressant in their induction regimens. For other patients, *i.e.* those with microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis (EGPA) and an FFS score of <1, those first-line agents are unnecessary because 5-year overall mortality is 9% (6-8).

Second, evidence supporting RTX induction for every patient is still lacking. Indeed, EGPA patients were not included in either of those two trials and the RAVE trial excluded patients with severe renal involvement and/or severe lung haemorrhage (1, 2). Therefore, the standard-of-care for such patients still relies on CYC. *Post-hoc* analysis of data from the non-inferiority RAVE trial also revealed that relapsing patients and/or those with antineutrophil cytoplasm antibodies to proteinase-3 (PR3-ANCA) patients benefitted even more from RTX than CYC. Thus, those findings highlighted subsets of patients for whom RTX should be preferred. On the same line, the efficacy of RTX was proved in randomised clinical trials in which patients with GPA or MPA were included based on specific inclusion criteria, which should be applied to patients for which RTX is considered. When comparing characteristics and outcomes of patients with GPA and/or MPA enrolled in observational cohorts to patients with GPA and/or MPA enrolled in randomised clinical trials, Pagnoux *et al.* highlighted differences in the age of the patients, the activity of the disease, the renal function, the frequency of ear, nose and throat symptoms, and the mortality and relapse rates. The authors concluded that these differences should be remembered when interpreting the results of these studies (9).

For AAV patients with ANCA to myeloperoxidase (MPO) and those with

newly diagnosed disease, it is now certain that RTX is non-inferior to CYC. Therefore, RTX represents an alternative to CYC for them. Hence, the benefit of RTX over CYC must be sought in the rates and types of adverse events (AEs). In the RAVE and RITUXVAS RCTs, the AE rates were similar (1, 2). The RAVE trial AE rate was 22% for the RTX group compared to 32% for the controls ($p<0.01$) (1, 2). That difference was no longer found at the 18-month evaluation, with nearly every patient in both groups experiencing at least one AE (10), and serious AEs (SAEs) in 42% of RTX-treated patients and 38% for the CYC–azathioprine (AZA) controls. Infections and leukopenia were the two most frequent SAEs but they were significantly less frequent than for the controls (10). Only the short-term evaluation of the RITUXVAS study is available; with 36% SAEs, mostly infections, for the 33 RTX-treated patients and 11 CYC-treated controls (1).

Notably, the safety of long-term (exceeding 5 and 10 years) RTX administration to AAV patients remains to be elucidated, with possible concerns regarding the risk of malignancies. As a newer therapeutic agent, RTX is more expensive and, thus, the cost-effectiveness of its use should also be evaluated in each country.

Third, Holle *et al*. gave RTX to 59 patients with refractory GPA, and highlighted factors that could be associated with poor response to it (11). They differentiated patients with vasculitis symptoms from those with granulomatosis lesions. Interestingly, they found that complete remission or disease attenuation percentages were lower for patients with granulomatosis lesions (mainly orbital masses, pachymeningitis or pulmonary masses) than those with vasculitis manifestations (58.2% *vs*. 90.4%, respectively). To explain this poorer response, the authors argued for a different inflammatory environment and/or more difficult treatment diffusion to the lesions. Those observations make us question the use of RTX as a first-line therapy for patients with severe granulomatosis lesions.

Regarding maintenance therapy, needed because relapse rates are close to 40%, the MAINRITSAN trial results clearly showed that GPA or MPA patients with FFS ≥1 benefit from it (3). That being said, in the MAINRITSAN study, patients' remissions were obtained with CYC, raising the questions of when to start RTX maintenance and its tolerance when patients received RTX as an induction. Moreover, using iterative RTX infusions can also raises doubts because of delayed B-cell reconstitution in AAV patients. Venhoff *et al*. examined peripheral B-cell reconstitution in 37 AAV patients after repeated RTX-induction infusions followed by maintenance with a conventional immunosuppressant (12). Notably, every patient's B cells were completely depleted 2 months after RTX induction, only one patient's reconstitution had started within 9 months after the last dose, and, after 21 months, repopulation had started in only 41% of the patients. Moreover, at month 21, the 14 reconstituted patients had a median 17 B cells/μL. Pertinently, this depletion is only peripheral and does not necessarily account for the presence or absence of B cells in pathological tissues. Indeed Ferraro *et al*. described an RTX-treated GPA patient who relapsed 30 months after two 1-g RTX infusions (13). At relapse, the patient had no peripheral B cells but immunohistochemical analysis of the granulomatosis lesion biopsy revealed the presence of $CD20^+$ cells; it was impossible to know whether the $CD20^+$ cells were newly formed or if they had persisted despite RTX treatment (13). Nonetheless, it supports that sanctuary lesions can resist RTX action and/or that full peripheral B-cell depletion does not mean full B-cell depletion. Thus, it remains difficult to argue for or against RTX reutilisation when peripheral B-cell depletion is complete. Hopefully, the MAINRITSAN 2 (NCT01731561) and 3 (NCT02433522) studies will provide information to improve the timing of RTX administration as maintenance therapy.

To conclude, RTX is being prescribed more and more, treating two out of three AAVs (*i.e*. MPA and GPA), but evidence is still lacking concerning its superiority or non-inferiority for patient subsets, including those with severe disease and/or localised vasculitis. To date, long-term evaluations of the RAVE and RITUXVAS trial results are reassuring concerning long-term AEs but follow-up must be pursued (14). MAINRITSAN study extension should also provide additional information. Improving our knowledge on the RTX effect on specific patient subsets and over the long-term will improve AAV-patients' care and our global understanding of these diseases.

Should we treat EGPA as other AAVs?

EGPA belongs to the AAV family of diseases (15). As such, its management is similar to that of MPA and GPA, and that includes achieving and maintaining remission. For decades, EGPA treatment has included corticosteroids (CS) and CYC for patients with severe disease.

However, EGPA clearly stands apart from MPA and GPA in every definition of the disease, including classification criteria, pathogenesis and symptoms (15-17). Therefore, EGPA patients were not included in recent RCTs on AAVs (1-3). As a result, it could even be argued that EGPA could be individualised from the other two AAVs. Thus, in our opinion this question should be answered negatively, in agreement with the Consensus Task Force evaluation and management of EGPA (18). Indeed, using CS (prednisone, 1 mg/kg/day) to achieve EGPA remission for patients with organ- or life-threatening manifestations is the only A-level evidence. However, their role has never been formally demonstrated.

Obviously, RTX is a tempting alternative to CYC for EGPA patients. Despite promising results in retrospective studies and one open-label pilot study, its efficacy needs to be fully demonstrated (19). In seven retrospective studies based on a total of 64 RTX-treated EGPA patients, 36 (56%) achieved remission. In their open-label pilot study, Cartin-Ceba *et al*. described three patients achieving remission within 3 months and remaining in remission 12 months after the first of 4 RTX infusions (20). Notably, three severe bronchospasms occurred during infusions

and nine infections were reported raising safety concerns (19).

Interestingly, Mohammad *et al*. retrospectively studied the difference between remissions of ANCA$^+$ and ANCA$^-$ EGPA patients (21) after RTX administration. At month 12, 80% (n=13) of the former group *vs*. 38% of the latter group were in remission. This observation recalls EGPA patients' pathophysiological and phenotypic differences; those findings seem to suggest that EGPA-patient subgroups exist and that they should be treated differently (15, 16, 21).

Finally, EGPA stands apart from MPA and GPA, and the REOVAS trial, assessing the role of RTX and CS as induction therapy for EGPA *vs*. conventional treatment, should elucidate differences among the three AAVs. Based on the findings of Mohammad *et al*., we anticipate that, two EGPA-patient categories will be defined: those who could be treated like MPA/GPA and the others, for whom finding steroid-sparing treatment will be a challenge.

Last but not least, because asthma is a major symptom of the disease, other treatment options, such as mepolizumab, omalizumab of lebrikizumab, could also be part of an EGPA regimen. To date, promising results with anti-interleukin (IL)-5 agents and conflicting data concerning anti-IgE therapy are available (19). The Consensus Task Force for EGPA evaluation and management has recommended further research to optimise treatment of patients with persistent asthma (18).

After RTX, what else?

This is a challenging issue because it questions our understanding of the disease's pathophysiology and how to more effectively treat patients. As discussed above, RTX has emerged as a new effective treatment for AAVs. Therefore, it is highly probable that other B-cell-depletion therapies or B-cell-targeting agents will be tested on AAV patients or found to be at least non-inferior. For example, belimumab combined with AZA will soon be evaluated to maintain remissions in GPA or MPA patients (NCT01663623).

Depleting B cells has proven to be effective but is it sufficient? What risk of relapse is acceptable under maintenance therapy? Statistically speaking, it must be recognised that proving to be more effective than RTX is going to be very difficult. Indeed, for new therapies, more patients will have to be included – more than for induction and more than for maintenance.

Targets other than B cells in AAVs could be investigated. Among them, complement is very attractive and relies on a translational success story, whose clinical results should soon be published (23). MPO-ANCA vasculitis induced in a mouse model revealed a major role for the alternative complement pathway and complement-system activation. Following the demonstration that the alternative pathway through factor B was required to develop glomerulonephritis (24), C5a receptor (C5aR) was shown to be activated on inflammatory cells involved in the murine anti-MPO inflammatory response. As a result, C5 inhibition was first studied in mice. To inhibit C5, mice were given a C5-blocking monoclonal antibody to attenuate glomerulonephritis development after anti-MPO-IgG transfer. Furthermore, in anti-MPO-IgG-mediated glomerulonephritis, especially in C5aR–knocked-in mice, C5aR was targeted with the C5aR antagonist, CCX168, that limited the development of the glomerulonephritis (25).

Gou *et al*. confirmed the increased C5a levels in plasma and urine of AAV patients with active disease or in remission compared to healthy controls (26, 27). A phase-II trial assessed CCX168 safety and tolerance in AAV patients (NCT01363388). Findings based on the first 16 patients enrolled and treated with CCX168 in adjunction with CYC were presented during the 2014 EUropean League Against Rheumatic diseases (EULAR) meeting. Tolerance was reported to be good and that CCX168 regiment does not seem to be less effective than CYC and high-dose CS.

Our group also uncovered a pathway that could lead to novel approaches for treating GPA patients. Millet *et al*. showed that apoptotic cells expressing phosphatidylserine-associated PR3 induced a macrophage pro-inflammatory response that involves the IL-1R/MyD88 pathway and perpetuates disease-associated inflammation with NO release (28). A possible translational opportunity of those observations would be to add an anti-IL-1R, *e.g*. anakinra, to the regimens of patients with refractory EGPA. Indeed, anakinra is known to competitively block the IL-1R and inhibit IL-1α and IL-1β functions (29), which include NO production. However, IL-1 antagonists require daily or weekly infusions and their price may be an obstacle. Nonetheless, it could be hypothesised that an IL-1 antagonist would be useful to treat disease refractory to RTX.

Better RTX use and better patient-monitoring will most likely contribute to improving the current standard-of-care.

Should ANCA or another biological marker be monitored for treatment adaptation?

ANCA as a biomarker of relapse remains an ongoing matter of debate that, unfortunately, has not yet been resolved. This question can be subdivided: Are ANCA predictive of relapses? Should we preemptively treat patients with increasing ANCA titers?

It is now well-demonstrated that anti-PR3-ANCA are associated with a higher risk of relapses (30–32) and that ANCA-positivity at maintenance-therapy onset doubles the risk of relapse (30, 31). Thus, assessing ANCA at least once at maintenance onset could be recommended. According to the meta-analysis by Tomasson *et al*., ANCA persistence during remission had a likelihood ratio for relapse of 1.97 (95% CI 1.43-2.7) (34). Therefore, it would seem logical to monitor ANCA status at least with immunofluorescence (IF) assays.

For patients with persistent IF ANCA-positivity, the role of ELISA-assessed ANCA titers and subsequent ANCA rise could contribute to clarifying this unresolved question. Rising anti-PR3-ANCA titers have been reported to be associated with GPA relapse. A current limitation of such studies is that the patients had received CYC for induction and maintenance (33, 34), thereby nar-

rowing the type of patients for whom ANCA-monitoring will be recommended. Indeed, that association was not found for patients prescribed AZA or methotrexate (MTX) maintenance therapy.

Terrier *et al*. showed that relapse within 1 year was associated with an increased anti-MPO-ANCA titer in >90% of AAV patients (37). This heightened risk was also found in other studies (34, 36).

In their meta-analysis, Tomasson *et al*. found the ANCA rise during remission to be associated with a 2.84 (95% CI 1.65-4.90) risk of relapse (34). To lower the cost of ANCA-monitoring, it could be recommended that ANCA status be assessed only by IF, if it had been negative at the beginning of maintenance therapy, and by ELISA, if it had been positive at that time.

Lastly and obviously, relapses may occur without prior ANCA appearance or rise, forbidding basing AAV management solely on the ANCA level.

To date, the authors of one study observed that anti-PR3-ANCA or ANCA switch from negative to positive were risk factors for relapse in AAV 69 patients given RTX for induction and maintenance (39), with risk of relapse odd ratios of 7.04 for the 13 patients whose ANCA-status switched. In that study, B-cell restoration within 12 months of the last RTX infusion was also a risk factor for future relapse but the authors stressed that data were not always consistently available for all patients. The possible usefulness of ANCA- and CD19-monitoring during maintenance therapy is being explored in the MAINRITSAN 2 trial (NCT01731561).

Notably, Walsh *et al*. observed that creatinine >200 µmol/L at diagnosis was associated with a lower risk of relapse (30).

The evolution of RTX use as standard AVV care and the absence of total certainty regarding the relapse risk assessed by ANCA level prevent recommending preemptive treatment.

What are the optimal dose and duration of CS treatment?

CS are a part of AAV treatment and, independently of the other drugs that can be prescribed concomitantly, expert consensus is to give CS. However, no consensus has been reached concerning optimal CS duration and different regimens have been tested in several prospective therapeutic trials. It should be also underlined that the optimal CS duration has never been an RCT objective, nor has the CS-dosing schedule been considered a priority. In the RAVE study (2), treatment at onset comprised, one to three methylprednisolone pulses (1000 mg each), followed by oral prednisone at 1 mg/kg/day. That dose was gradually tapered so that, by 5 months, all patients who achieved remission without disease flares had discontinued CS. That regimen effectively induced remission and had the major advantage of limiting the number and severity of AEs, frequently seen in patients on long-term CS. In the RAVE trial (1), remission likelihood at 6 months was affected by whether or not CS had been tapered to complete discontinuation. That trial compared RTX, a weekly RTX infusion for 4 weeks, without maintenance treatment to oral CYC (2 to 3 months) followed by AZA maintenance. Different remission rates in the RAVE and other trials showing better outcomes than in other vasculitis trials might be explained by patients usually continuing to take CS for at least 1 year (40-45). More than the remission rate, the major concern is long-term remission maintenance. The same RAVE authors more recently published the 12- and 18-month trial results (10), which showed comparable remission rates in both arms. At 12 and 18 months, respectively, 48% and 39% of the RTX-treated patients, and 39% and 33% of CYC-AZA recipients maintained their complete remissions. Those results demonstrated the non-inferiority of RTX *vs*. CYC-AZA but also higher relapse rates at 12 and 18 months. The RAVE trial 18-month relapse rate was 29%, twice that observed in other RCTs. Of course several limitations compromise such a comparison: different induction treatments, patient heterogeneity, non-standardised CS treatment. However, the question of the ability of CS alone to maintain remission persists. The results of a retrospective study showed that longer CS use was associated with fewer relapses (46). Based on that finding, long-term low-dose CS, independently of other treatments, could be recommended. A prospective trial to determine the optimal CS dose and duration is urgently needed to know, once and for all, the contribution of keeping AAV patients on CS. The prospective TAPIR trial to investigate the effect on disease flare and/or relapse rates of low-dose CS *vs*. CS discontinuation in GPA patients in remission, is currently recruiting patients in the US. At present, our strategy is to keep AAV patients on low-dose CS, gradually diminished to 5 mg at 12 months, then further progressively tapering, mg by mg, until complete withdrawal during the second year of treatment.

Long-term low-dose CS (5-8 mg/day oral and/or inhaled) is usually prescribed to control residual asthma in EGPA patients, most of whom are in vasculitis remission. This context explains why it is not possible to analyse the preventive role of CS on EGPA relapses.

(How) Can we stop immunosuppression /immunomodulation?

Although the early period of induction-remission for AAV is now better codified and maintenance-treatment modalities are better understood, its optimal treatment duration remains a matter of discussion among specialists. Recent publications on the more extensive use of biotherapies, especially RTX, raise new questions about maintenance therapy.

Considering conventional AAV treatments, comprising induction with CYC and CS followed by AZA or MTX maintenance, most physicians treat patients for 18 months to 2 years but, because of high relapse rates in all published studies, it is obvious that optimal long-term therapy remains elusive. Springer *et al*. suggested keeping patients on long-term AZA to reduce the relapse risk (47) and Hoffman urged our group to "advocate for long-term indefinite maintenance therapy in all patients with GPA" (48). The demonstration of RTX non-inferiority to CYC for induction-remission (1, 2) and its superiority to AZA to maintain remission brought new hope (3). However,

the demonstrated RTX superiority to AZA after 28 months of follow-up was tempered by some later relapses, especially in anti-PR3-ANCA-positive patients (personal observation). This warning of relapses must be confirmed but, in our opinion, could underscore that 1) RTX does not cure AAVs; 2) long-term maintenance therapy might help prevent relapses; and 3) Hoffman's suggestion to maintain decades-long immunosuppression could be applicable to RTX.

The decision to keep patients on long-term immunosuppressants or biotherapy could be responsible for SAEs, mainly infections and malignancies, and such a decision can only be made after taking the relapse-prevention/AE-development-risk ratio into account. Infections have occurred frequently in all trials with conventional treatments but biotherapies can also cause AEs (49, 50). Among conventional treatment AEs, infections, sterility and malignancies have been reported (49-52). However, prescribing CYC for only a few months markedly limits the risks of malignancy or sterility. The short-term infectious risk is lower but late infectious complications occur and might be increased when RTX is prescribed because it induces prolonged, very low immunoglobulin levels. Therefore, the infectious risk should be evaluated for months or years after its administration. Late infectious complications could compromise the choice to infuse RTX over several years. If such a decision were made, a preventive anti-infectious policy would have to be organised and codified, including preventive detection of JC virus, as is now proposed for multiple sclerosis patients exposed to natalizumab and other treatments (53).

Special conditions

Does end-stage renal disease (ESRD) modify treatment?

We frequently observed that ESRD implicated discontinuation of CS and immunosuppressants. It has been shown in some other autoimmune diseases, like systemic lupus erythematosus (SLE), that ESRD onset coincided with prolonged SLE remission or at least very low disease activity. AAV-evolution profiles differ among entities, especially anti-PR3 AAVs, that sometimes relapse very late, even decades after the first disease manifestations. No available proof or observation suggests that ESRD is linked to a remission or cure of the causal disease, *i.e.* vasculitis. On the other hand, we have observed that the AAV remains active and may express new clinical manifestations, *e.g.* alveolar haemorrhage. That is why we treat ESRD AAV patients according to the usual recommendations to adapt drug doses to renal function, as appropriate.

How to manage a pregnant patient with AAV?

Although very limited data are available regarding pregnancy of AAV patients, these pregnancies are considered to be high-risk (54). Most reports concerned GPA patients. The mother's condition at conception is critical for the outcome of pregnancy. While complications or flares occur in 25% of pregnant AAV patients in remission at conception, 40-100% of those pregnancies end in miscarriage or therapeutic abortion or even the mother's death, when conception occurred during active GPA (55-58). Obstetric and vasculitic complications are diverse including, respectively, preeclampsia, placenta praevia, premature membrane rupture, intrauterine growth retardation, preterm birth, caesarian section, fetal death and postpartum complications, and AAV flares, renal deterioration or subglottic stenosis and/or cranial bleeding that can lead to maternal and fetal deaths (55, 57-59).

CS and AZA can be used during pregnancy. MTX is contraindicated, as it is highly teratogenic. Although CYC is cytotoxic and known to be teratogenic as well, it has been used and was apparently safe during the second and third trimesters (56, 60).

A few pregnancies in RTX-treated AAV patients have been reported. Pagnoux *et al*. described the first case of an RTX-treated woman whose pregnancy ended well (57). Sangle *et al*. also reported the favorable outcome of an RTX-treated GPA patient's pregnancy (63).

More recently, Sangle *et al*. reported nine GPA patients' and six EGPA patients' pregnancies: one EGPA patient developed preeclampsia complicated by premature delivery and newborn death; another had a flare during pregnancy; and six GPA patients experienced flares during pregnancy or the postpartum period. None had been prescribed CYC (64). Similarly, Fredi *et al*. also recently reported on 16 pregnancies in four GPA and nine EGPA patients. Six pregnancies were complicated by flares and three by flares during the year after delivery (65). Taken together, the observations of these two studies suggest a risk of flares during pregnancy and the year thereafter.

As for other patients with any chronic autoimmune disease, a few rules should be applied to pregnancy and AAV patients: it should be planned only when the vasculitis has been in remission for at least >6-months; medical counseling and multidisciplinary follow-up of the pregnancy are mandatory; and teratogenic immunosuppressant drugs (including CYC, mycophenolate mofetil and MTX) should be stopped 3-6 months before conception for both men and women (61).

How should elderly AAV patients be treated?

AAV also occurs after 65 years old and it is not uncommon to see patients with AAV, mainly MPA, after 90 years old. An elderly population has rarely been described (66) but, in addition to the risk of death related to AAV severity (as assessed by the FFS) (6), patients' general condition at older ages may add risk factors jeopardising their outcomes. Increased risk of infections, denutrition and modified drug metabolism are well-known and, until recently, recommendations to adapt therapeutic agents for the elderly were limited to arbitrary CS- and CYC-dose reductions for remission induction. Based on a series of 150 elderly patients from Sweden and the Czech Republic (67) (mean age 79 years), 30% died and 25% required dialysis 1 year after diagnosis.

Our group previously showed that simultaneously lowering the CS and CYC doses achieved the same remis-

sion rate as high-dose CS and higher conventional CYC dose, but fewer and less severe AEs (68). The 3-year analysis of the 108 patients randomised in that trial included 53 patients (21 GPA, 21 MPA, 8 EGPA, and 3 polyarteritis nodosa (PAN)) in the arm with lower CS and CYC doses and 51 patients (15 GPA, 23 MPA, 6 EGPA, and 7 PAN) in the conventional arm found, respectively: 32 (60%) *vs*. 40 (78%) had >1 SAEs (p=0.04), most frequently infections; six (11%) *vs*. seven (14%) failed to achieve remission; and nine (17%) *vs*. 12 (24%) died. Those results showed, for first time, the negative impact of intensive treatment with no survival benefit.

Based on that RCT's findings and a reasonable approach to caring for elderly patients, it seems logical to 1) treat patients with active AAV because we can expect a satisfactory survival rate; 2) choose the therapeutic regimen based on known drug AEs; 3) evaluate treatment strategies based on life expectancy and quality of life.

When should renal transplantation be proposed/authorised for AAV patients?

When AAV patients develop ESRD, kidney transplantation may be an option. It is not contraindicated and should be proposed to all AAV patients with ESRD not limited by their general condition and accepting subsequent therapeutic constraints. Outcomes are good and do not differ from those of patients without vasculitis, except that AAV patients who are anti-PR3-ANCA-positive at transplantation have a greater risk of poorer outcomes (69). No formal recommendation has been established to organise renal transplantation in AAV patients. However, common sense and case-series outcomes can help the clinician adopt some elementary rules to indicate renal transplantation. First of all, a remission, defined as the absence of clinical symptoms and stable biological parameters under maintenance, without considering ANCA status, should be obtained before transplantation.

Based on our experience, we recommend waiting at least 2 years after starting treatment and 12 months after obtaining remission. For patients satisfying transplantation indications after a relapse, the interval should be longer before such an undertaking. The minor clinical symptoms that could precede relapse should be sought when possible: arthralgias, asthenia, crusting in GPA patients, new anti-PR3-ANCA–titer rise or detectability if they had previously disappeared. It was shown that ANCA-positive patients, especially anti-PR3 at the time of transplantation, relapsed more than those with anti-MPO-ANCA (OR 2.19) (69). According to the Dutch survey patients, vasculitis-relapse risk was 2.8%/patient-year and was independently associated with subsequent graft loss (70, 71.

How to use ANCA-test results as a marker of relapse and contraindication to renal transplantation remains a major concern. Patients can be transplanted despite ANCA-positivity but perhaps not all of them. We know now that the relapse risk is lower in anti-MPO- than anti-PR3-ANCA–positive patients (10).

Results regarding ANCA titer as a predictor of relapse are controversial. Many patient series failed to show any clear contribution of the ANCA titer to predicting an oncoming flare (32) and, thus, to postpone transplantation because of increased anti-PR3-ANCA titer. We do not have the answer but, it seems reasonable that, for a rapidly rising ANCA titer or ANCA reappearance, the patient should be followed for several months before reconsidering transplantation. In the absence of clinical manifestations, transplantation should be authorised and the patient's name should be put back on the transplantation-waiting list.

References

1. JONES RB, TERVAERT JWC, HAUSER T *et al*.: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20.
2. STONE JH, MERKEL PA, SPIERA R *et al*.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221-32.
3. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771-80.
4. SPECKS U: Pro: Should all patients with anti-neutrophil cytoplasmic antibody-associated vasculitis be primarily treated with rituximab? *Nephrol Dial Transplant* 2015; 30: 1083-7.
5. KRONBICHLER A, JAYNE DRW: Con: Should all patients with anti-neutrophil cytoplasmic antibody-associated vasculitis be primarily treated with rituximab? *Nephrol Dial Transplant* 2015; 30: 1075-81.
6. GUILLEVIN L, PAGNOUX C, SEROR R *et al*.: The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* (Baltimore) 2011; 90: 19-27.
7. SAMSON M, PUECHAL X, DEVILLIERS H *et al*.: Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) enrolled in two prospective trials. *J Autoimmun* 2013; 43: 60-9.
8. SAMSON M, PUECHAL X, DEVILLIERS H *et al*.: Long-term follow-up of a randomized trial on 118 patients with polyarteritis nodosa or microscopic polyangiitis without poor-prognosis factors. *Autoimmun Rev* 2014; 13: 197-205.
9. PAGNOUX C, CARETTE S, KHALIDI NA *et al*.: Comparability of patients with ANCA-associated vasculitis enrolled in clinical trials or in observational cohorts. *Clin Exp Rheumatol* 2015; 33 (Suppl. 89): S77-83.
10. SPECKS U, MERKEL PA, SEO P *et al*.: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369: 417-27.
11. HOLLE JU, DUBRAU C, HERLYN K *et al*.: Rituximab for refractory granulomatosis with polyangiitis (Wegener's granulomatosis): comparison of efficacy in granulomatous versus vasculitic manifestations. *Ann Rheum Dis* 2012; 71: 327-33.
12. VENHOFF N, NIESSEN L, KREUALER M *et al*.: Reconstitution of the peripheral B lymphocyte compartment in patients with ANCA-associated vasculitides treated with rituximab for relapsing or refractory disease. *Autoimmunity* 2014; 47: 401-8.
13. FERRARO AJ, SMITH SW, NEIL D, SAVAGE COS: Relapsed Wegener's granulomatosis after rituximab therapy – B cells are present in new pathological lesions despite persistent "depletion" of peripheral blood. *Nephrol Dial Transplant* 2008; 23: 3030-2.
14. GUILLEVIN L: Rituximab for ANCA-associated vasculitides. *Clin Exp Rheumatol* 2014; 32 (Suppl. 82): S118-21
15. JENNETTE JC: Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. *Clin Exp Nephrol* 2013; 17: 603-6.
16. COMARMOND C, PAGNOUX C, KHELLAF M *et al*.: Eosinophilic granulomatosis with polyangiitis (Churg–Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum* 2013; 65: 270-81.
17. CHAIGNE B, TERRIER B, THIEBLEMONT N, WITKO-SARSAT V, MOUTHON L: Dividing the Janus vasculitis? Pathophysiology of eosinophilic granulomatosis with polyangitis. *Autoimmun Rev* 2016; 15: 139-45.

18. GROH M, PAGNOUX C, BALDINI C *et al*.: Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015; 26: 545-53.
19. PUECHAL X: Therapeutic immunomodulation in eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Joint Bone Spine* 2016; 83: 7-10.
20. CARTIN-CEBA R, KEOGH KA, SPECKS U, SETHI S, FERVENZA FC: Rituximab for the treatment of Churg-Strauss syndrome with renal involvement. *Nephrol Dial Transplant* 2011; 26: 2865-71.
21. MOHAMMAD AJ, HOT A, ARNDT F *et al*.: Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg–Strauss). *Ann Rheum Dis* 2016; 75: 396-401.
22. SABLE-FOURTASSOU R, COHEN P, MAHR A *et al*.: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005; 143: 632-8.
23. KALLENBERG CGM, HEERINGA P: Complement system activation in ANCA vasculitis: a translational success story? *Mol Immunol* 2015; 68: 53-6.
24. XIAO H, SCHREIBER A, HEERINGA P, FALK RJ, JENNETTE JC: Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. *Am J Pathol* 2007; 170: 52-64.
25. XIAO H, DAIRAGHI DJ, POWERS JP *et al*.: C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J Am Soc Nephrol* 2014; 25: 225-31.
26. GOU S-J, YUAN J, WANG C, ZHAO M-H, CHEN M: Alternative complement pathway activation products in urine and kidneys of patients with ANCA-associated GN. *Clin J Am Soc Nephrol* 2013; 8: 1884-91.
27. GOU S-J, YUAN J, CHEN M, YU F, ZHAO M-H: Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int* 2013; 83: 129-37.
28. MILLET A, MARTIN KR, BONNEFOY F *et al*.: Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis. *J Clin Invest* 2015; 125: 4107-21.
29. CVETKOVIC RS, KEATING G: Anakinra. *BioDrugs Clin Immunother Biopharm Gene Ther* 2002; 16: 303-11.
30. WALSH M, FLOSSMANN O, BERDEN A *et al*.: Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2012; 64: 542-8.
31. SLOT MC, TERVAERT JWC, BOOMSMA MM, STEGEMAN CA: Positive classic antineutrophil cytoplasmic antibody (C-ANCA) titer at switch to azathioprine therapy associated with relapse in proteinase 3-related vasculitis. *Arthritis Rheum* 2004; 51: 269-73.
32. THAI L-H, CHARLES P, RESCHE-RIGON M, DESSEAUX K, GUILLEVIN L: Are anti-proteinase-3 ANCA a useful marker of granulomatosis with polyangiitis (Wegener's) relapses? Results of a retrospective study on 126 patients. *Autoimmun Rev* 2014; 13: 313-8.
33. SANDERS J-SF, HUITMA MG, KALLENBERG CGM, STEGEMAN CA: Prediction of relapses in PR3-ANCA-associated vasculitis by assessing responses of ANCA titres to treatment. *Rheumatolgy* (Oxford) 2006; 45: 724-9.
34. TOMASSON G, GRAYSON PC, MAHR AD, LAVALLEY M, MERKEL PA: Value of ANCA measurements during remission to predict a relapse of ANCA-associated vasculitis - a meta-analysis. *Rheumatolgy* (Oxford) 2012; 51: 100-9.
35. TERVAERT JW, VAN DER WOUDE FJ, FAUCI AS *et al*.: Association between active Wegener's granulomatosis and anticytoplasmic antibodies. *Arch Intern Med* 1989; 149: 2461-5.
36. TERVAERT JW, HUITEMA MG, HENE RJ *et al*.: Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. *Lancet* 1990; 336: 709-11.
37. TERRIER B, SAADOUN D, SENE D *et al*.: Antimyeloperoxidase antibodies are a useful marker of disease activity in antineutrophil cytoplasmic antibody-associated vasculitides. *Ann Rheum Dis* 2009; 68: 1564-71.
38. BOOMSMA MM, STEGEMAN CA, VAN DER LEIJ MJ *et al*.: Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study. *Arthritis Rheum* 2000; 43: 2025-33.
39. ALBERICI F, SMITH RM, JONES RB *et al*.: Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. *Rheumatolgy* (Oxford) 2015; 54: 1153-60.
40. JAYNE D, RASMUSSEN N, ANDRASSY K *et al*.: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349: 36-44.
41. WEGENER'S GRANULOMATOSIS ETANERCEPT TRIAL (WGET) RESEARCH GROUP: Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; 352: 351-61.
42. GOEK ON, STONE JH: Randomized controlled trials in vasculitis associated with anti-neutrophil cytoplasmic antibodies. *Curr Opin Rheumatol* 2005; 17: 257-64.
43. PAGNOUX C, MAHR A, HAMIDOU MA *et al*.: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359: 2790-803.
44. DE GROOT K, RASMUSSEN N, BACON PA *et al*.: Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; 52: 2461-9.
45. DE GROOT K, HARPER L, JAYNE DRW *et al*.: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670-80.
46. WALSH M, MERKEL PA, MAHR A, JAYNE D: Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: a meta-analysis. *Arthritis Care Res* 2010; 62: 1166-73.
47. SPRINGER J, NUTTER B, LANGFORD CA, HOFFMAN GS, VILLA-FORTE A: Granulomatosis with polyangiitis (Wegener's): impact of maintenance therapy duration. *Medicine* (Baltimore) 2014; 93: 82-90.
48. HOFFMAN GS: L52. Vasculitis treatment: is it time to change the standard of care for ANCA-associated vasculitis? *Presse Méd* 2013; 42: 643-50.
49. TALAR-WILLIAMS C, HIJAZI YM, WALTHER MM *et al*.: Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 1996; 124: 477–84.
50. LE GUENNO G, MAHR A, PAGNOUX C, DHOTE R, GUILLEVIN L, FRENCH VASCULITIS STUDY GROUP: Incidence and predictors of urotoxic adverse events in cyclophosphamide-treated patients with systemic necrotizing vasculitides. *Arthritis Rheum* 2011; 63: 1435-45.
51. GAYRAUD M, GUILLEVIN L, LE TOUMELIN P *et al*.: Long-term follow-up of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001; 44: 666-75.
52. BOURGARIT A, LE TOUMELIN P, PAGNOUX C *et al*.: Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: a retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine* (Baltimore) 2005; 84: 323-30.
53. HUNT D, GIOVANNONI G: Natalizumab-associated progressive multifocal leucoencephalopathy: a practical approach to risk profiling and monitoring. *Pract Neurol* 2012; 12: 25-35.
54. SOH MC, NELSON-PIERCY C: High-risk pregnancy and the rheumatologist. *Rheumatolgy* (Oxford) 2015; 54: 572-87.
55. KOUKOURA O, MANTAS N, LINARDAKIS H, HAJIIOANNOU J, SIFAKIS S: Successful term pregnancy in a patient with Wegener's granulomatosis: case report and literature review. *Fertil Steril* 2008; 89: 1-5.
56. AUZARY C, HUONG DT, WECHSLER B, VAUTHIER-BROUZES D, PIETTE JC: Pregnancy in patients with Wegener's granulomatosis: report of five cases in three women. *Ann Rheum Dis* 2000; 59: 800-4.
57. PAGNOUX C, LE GUERN V, GOFFINET F *et al*.: Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. *Rheumatolgy* (Oxford) 2011; 50: 953-61.
58. GRYGIEL-GORNIAK B, PUSZCZEWICZ M: Granulomatosis with polyangiitis in pregnancy - clinical implications and treatment possibilities. *Eur Rev Med Pharmacol Sci* 2015; 19: 2331-5.
59. MILFORD CA, BELLINI M: Wegener's granulomatosis arising in pregnancy. *J Laryngol Otol* 1986; 100: 475-6.
60. BLAIVAS AJ, STRAUSS W, YUDD M: Subglottic stenosis as a complication of Wegener's granulomatosis. *Prim Care Respir J* 2008; 17: 114-6.
61. PAGNOUX C, MAHENDIRA D, LASKIN CA: Fertility and pregnancy in vasculitis. *Best Pract Res Clin Rheumatol* 2013; 27: 79-94.
62. HUONG DLT, AMOURA Z, DUHAUT P *et al*.: Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. *J Rheumatol* 2002; 29: 2571-6.
63. SANGLE SR, LUTALO PMK, DAVIES RJ, KHAMASHTA MA, D'CRUZ DP: B-cell depletion

therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. *J Autoimmun* 2013; 43: 55-9.

64. SANGLE SR, VOUNOTRYPIDIS P, BRILEY A*et al*.: Pregnancy outcome in patients with systemic vasculitis: a single-centre matched case–control study. *Rheumatolgy* (Oxford) 2015; 54: 1582-6.
65. FREDI M, LAZZARONI MG, TANI C *et al*.: Systemic vasculitis and pregnancy: a multicenter study on maternal and neonatal outcome of 65 prospectively followed pregnancies. *Autoimmun Rev* 2015; 14: 686-91.
66. MOUTHON L, LE TOUMELIN P, ANDRE MH, GAYRAUD M, CASASSUS P, GUILLEVIN L: Polyarteritis nodosa and Churg-Strauss angiitis: characteristics and outcome in 38 patients over 65 years. *Medicine* (Baltimore) 2002; 81: 27-40.
67. WEINER M, GOH SM, MOHAMMAD A *et al*.: Outcome and prognostic factors in elderly patients with ANCA-associated vasculitis. *Presse Méd* 2013; 42: 674.
68. PAGNOUX C, QUEMENEUR T, NINET J *et al*.: Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. *Arthritis Rheumatol* 2015; 67: 1117-27.
69. GEETHA D, LEE SM, SHAH S, RAHMAN HM: Relevance of ANCA positivity at the time of renal transplantation in ANCA associated vasculitis. *J Nephrol* 2015, [Epub ahead of print].
70. GOCEROGLU A, RAHMATTULLA C, BERDEN AE *et al*.: The Dutch Transplantation in Vasculitis (DUTRAVAS) Study: outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Transplantation* 2016; 100: 916-24.
71. FLOSSMANN O: Risks of treatments and long-term outcomes of systemic ANCA-associated vasculitis. *Presse Méd* 2015; 44: 251-7.