Review

One year in review 2021: systemic vasculitis

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ABSTRACT

Large- and small-vessel vasculitis are complex potentially life-threatening systemic autoimmune diseases that have recently been subjected to considerable immunologic and clinical research.

Following the other reviews of this series, here we aim to summarise some of the most significant studies that have been recently published on the pathogenesis, clinical features and novel treatments of systemic vasculitis.

Introduction

Systemic vasculitis are complex and heterogeneous diseases potentially leading to severe morbidity and mortality. Following the previous annual reviews (1-3) of this publishing series, we will here provide a critical digest of the most relevant literature on epidemiology, classification, pathogenesis, clinical features and novel treatments of small- and large-vessel (LVV) systemic vasculitis. All the articles were critically analysed in order to select the most relevant contributions on theese topics.

Cryoglobulinaemic vasculitis

Pathophysiology advances in hepatitis C virus-cryoglobulinaemic vasculitis

Mixed cryoglobulinaemia (MC) syndrome is the prototype of hepatitis C virus (HCV)-driven autoimmune and lymphoproliferative disorders. The HCV trigger effect leads to permanent clones of B-lymphocytes producing oligoclonal or monoclonal IgM with rheumatoid factor (RF) activity, encoded by the VH1-69 heavy chain gene paired with VK3-20 light chain variable gene, thus representing the common link for inflammatory and lymphoproliferative alterations. Indeed, HCV-MC patients display a 35-fold higher risk of developing lymphoma than the general population, therefore current clinical research is focusing on searching for a biomarker "signature" able to reveal the complex sequence of events leading from inflammation to lymphoma.

From this perspective, it is widely recognised that genetic background can influence the phenotype and outcome of HCV-related diseases. De Re *et al*. (4) lately highlighted an epistatic contribution of IFNL4 and PDCD1 genes in patients with MC. Particularly, PD-1[ACG]-IFNL4[C] is positively associated with MC (OR=4.237), and the opposite haplotype PD-1[GTA]-IFNL4[T] (OR=0.458) is negatively associated with MC. The association between PDCD1 polymorphisms and the risk of HCV-related lymphoproliferative disorders should be further investigated.

Besides genetics, several biological biomarkers have been also investigated. Basile *et al*. (5) confirmed that serum levels of IgG3 subclass were higher in HCV-MC patients compared with rheumatoid arthritis (RA)-patients, reinforcing the key role of IgG3 as the initial trigger of cryoglobulins formation and, in turn, in the vasculitic process underlying cryoglobulinaemic vasculitis (CV). Another Italian study (6), demonstrated that levels of soluble (s) CD138, k-free and λ-free chains were significantly higher in HCV-non Hodgkin lymphoma (NHL) patients than in healthy controls. However, free k and λ and the k/λ ratio were inversely related with sCD138; the authors suggest that sCD138 may reflect more closely the lymphoma risk of the disease while the prognostic value of the free light chains (FLC) remain uncertain being altered by the presence of a monoclonal IgM component.

Regarding epigenetic biomarkers, it was observed a downregulation of miR-26b in HCV-CV and HCV-NHL

patients, and a restoration of microRNAs (miRNAs) miR-26b levels in CV patients after treatment-induced clinical remission of vasculitis. The functional effectors of miR-26b are the lymphoid enhancer-binding factor 1, overexpressed in pre-lymphomatous conditions, therefore the downregulation of miR-26b could be an indicator of a molecular mechanism of tumor progression (7). The first miRNA with an accepted oncogenetic role was miR 17-92, known as oncomiR-1. Lorini *et al*. (7) analysed the expression levels of miR 17-92 in 20 CV patients pre- and post-antiviral therapy. A significant reduction in the expression levels of miR 17-92 following viral eradication was observed, even if they did not reach levels comparable to those pre-therapy in the control group (HCV patients without CV) (7).

New insights in hepatitis C virus-negative cryoglobulinaemic vasculitis

Concerning HCV-negative cryoglobulinemia, the vast majority of HCV-negative CV cases has been described in primary Sjögren's syndrome (pSS) (8) being the presence of cryoglobulinemia a well recognised risk factor for lymphoma development. Lately, a multicentre study on 1997 consecutive pSS patients explored lymphoma incidence and risk factors in individuals with early disease-onset (young ≤35years) in comparison with patients with late disease-onset (old ≥65years). Cryoglobulinaemia remains an independent lymphoma-associated factor in younger pSS patients in addition to other traditional lymphoma risk factors such as: low C4, lymphadenopathy, and SGE. By contrast, in older pSS patients SGE, low C4 and male gender but not cryoglobulinaemia were identified as independent lymphoma-associated factors. Moreover, young pSS lymphoma patients presented two different peaks of incidence for lymphoma: the first one within 3 years from pSS onset and the second one after 10 years of disease duration. The first peak was explained by a strong B cell response along with classical risk factor for lymphoma, while the second one was assigned to a longstanding stimulation of B-cells and a strong immunoregulatory mechanism that delay the lymphomagenesis process (9). On the contrary, old pSS lymphoma patients presented very early lymphoma, suggesting an immunosenescence incapable to contrast the lymphomagenesis (9).

Finally, among recent literature contributions on non-infectious MC cases classified as idiopathic or essential MC (EMC), the study by Del Padre M *et al*. (10) is worth to be quoted. The authors (10) showed that when compared to HCV-MC patients, EMC patients had lower circulating CD21low B-cells, mainly naïve-like CD21lowCD27- cells. CD21low B-cells of EMC and HCV-MC shared functional features of exhaustion and had defective proliferative responses to ligation of Toll-like receptor 9 (TLR9), supporting a common pathogenetic mechanism with autoantigen-driven clonal expansion and exhaustion of selected RF producing B-cells (10).

New insights in HCV-cryoglobulinaemic vasculitis therapy

The introduction of DAAs has radically transformed the management of HCV-CV and has changed the epidemiology of MC. A large observational longitudinal French cohort study (11) has shown a 1.5 fold decrease in incident MC cases between 2011-2014 and 2015-2018 periods. Furthermore, in the 2016-2018 period, HCV was no longer the leading cause of MC whereas systemic autoimmune disease (*i.e*. systemic lupus erythematosus (SLE) and pSS) represent the main causes of MC and CV (11).

Lately, DAAs have confirmed their efficacy in virological response achievement (sustained virological response [SVR] rates greater than 95%) and in the reduction of the mean cryocrit level and RF level in MC patients at the end of treatment (EOT) (12). Importantly, results from the RENALCRYOGLOBULINEMIC study indicated that DAA treatment improves also kidney survival and reduces mortality in HCV-MC compared with control patients treated with pegylated interferon-ribavirin (IFN±RBV), regardless of the initial glomerular filtration rate (GFR), proteinuria and age (13).

Despite these comforting results, we know that cryoglobulins and RF can be detected in most cases after DAAs therapy, reflecting the persistence of B-cells autoreactive clones. These "dormant" cells may be reactivated by events that perturb B-cell homeostasis, therefore, even in the DAA era, relapses of MC or cases refractory to treatment are described. In these patients, rituximab (RTX) might be used as additional therapy (14). The timing of anti-CD20 treatment and dosages are still debated in MC patients, and the identification of serological biomarkers of minimal residual disease (MRD) in RTX-treated MC patients could improve the MC-management. High levels of FLCs, heavy/light chains (HLCs), and vascular growth factor (VEGF) allow to recognise a MRD in RTX-treated patients, representing a possible signature of "dormant" B cell clones' activity (14), and the re-treatment of these patients could prevent a relapse. Despite the safety and effectiveness of RTX (15), a retrospective French study revealed a low risk (3.4%) of CV exacerbation within two weeks after RTX. These CV-flares have been reported more frequently in patients with renal involvement, B-cell lymphoproliferation, a higher level of cryoglobulin and lower level of C4 (16).

Lastly, non-infectious RTX-refractory CV showed usually an overexpression of BAFF levels. Thus, several case series have further supported the efficacy of sequential therapy by anti CD20 treatment and belimumab in the case of pSS-refractory CV (17-19).

In the upcoming years, we speculate that the incidence of HCV-MC will continue to decline along with its mortality, thus major interest could move on different clinical phenotypes of non-infectious MC and their risk of NHL development and mortality (20), establishing an era of precision medicine.

Take home messages

- Novel genetic and epigenetic biomarkers that can be useful to predict lymphoma risk in HCV-CV have been identified;

- The value of cryoglobulinaemia as an independent lymphoma risk factor has been demonstrated in younger pSS patients with HCV-negative CV but not in the older ones;
- Important progresses have been made to speculate on the positioning of DAA and RTX, alone or in combination, in therapeutic algorithms in HCV-CV.

Large-vessel vasculitis

Pathophysiology advances in large-vessel vasculitis

During the last twelve months, interesting efforts have been made towards the identification of molecular biomarkers involved in the pathogenesis of LVV. In particular, both angiogenic inducers (VEGF, FGF-2, angiopoietin 1, -2, soluble VCAM-1) and inhibitors (angiostatin, endostatin, pentraxin-3) have been implied in LVV angiogenesis dysregulation. When analysed in peripheral blood samples, only VEGF was significantly higher in Takayasu's arteritis (TAK) patients compared to healthy controls (no difference was found in giant cell arteritis (GCA) patients), while angiostatin, endostatin and PTX3 were significantly higher in both GCA and TAK patients. These biomarkers also correlated with disease activity evaluated by using PET scan and clinical indices (21).

In addition to angiogenic biomarkes, the role of inflammatory cells in pathogenesis of TAK has been also the objective of several studies (22, 23). TAK patients showed a decreased number of peripheral blood natural killer (NK) cells, as well as a reduced production of granzyme B and perforin compared to control group. More specifically, granzyme B-expressing NK cells were lower in active TAK compared to inactive TAK. On the other hand, T helper-like Treg cells were lower in peripheral blood of TAK patients with respect to healthy controls, suggesting these cells might play a role in TAK pathogenesis.

New insights in LVV clinical features

The guidelines on diagnosis and treatment of GCA from the British Society for Rheumatology have lately represented an important step forward in improving the early diagnosis and treatment of GCA. These guidelines recommends either temporal artery biopsy (TAB) or ultrasound of temporal artery as confirmatory diagnostic test for cranial GCA. Indeed, a diagnostic approach has been proposed to perform either one or both these tests, depending on the estimated probability of GCA diagnosis. In the absence of clinical features of cranial GCA, imaging of the extracranial vessels should be considered in order to evaluate the involvement of aorta and its proximal branches (24).

Moreover, the recognition of GCA has been further improved by highlighting possible unusual manifestation at the onset of the disease such as concomitant pericardial disease (25). Patients developing pericardial effusion as initial disease manifestation might represent a clinical phenotype of GCA with less cranial symptoms and a better prognosis, but more studies are required to confirm this hypothesis. In the framework of outcome for GCA, Hočevar *et al*. identified jaw claudication, smoking and increasing age as factors most significantly predictive of cranial ischaemic complications in GCA (26).

New insights in LVV imaging

Temporal artery biopsy (TAB) represents the gold standard for GCA diagnosis. Recently, however, ultrasonography (US) has been recognised at least equivalent to histology in confirming the diagnosis of LVV (27). Moreover, the sensitivity and specificity of color duplex ultrasonography (CDU) highly increases when considering also axillary artery (28). Notably, even not well predictive of future ischaemic events, US findings seems to strongly correlate to the clinical features, final diagnosis and outcome of GCA (29). Ultrasound may also be important during follow-up to evaluate the effect of steroids treatment; major findings displayed a change along temporal circulation with reduction of the hyperechoic wall thickening than in axillary arteries (30). Specifically, ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography (CT) demonstrate a concentric thickening of the arterial wall whereas positron emission tomography (PET) shows an increased uptake of fluorodeoxyglucose (FDG) in active vasculitis. A whole-body examination is suggested with particular attention to aorta and aortic main branches and extracranial cephalic arteries. The homogeneous segmental FDG uptake of those vessels higher than liver uptake indicates LVV; but lower uptake intensity and non-homogeneous distribution patterns should be suspicious of an alternative diagnosis (31). High-resolution ultrasound is important to identify smaller arteries while MRI and PET/CT display better extracranial arteries. Unfortunately, imaging sensitivity decreases with treatment so an important issue affecting all these tools is represented by a corrected timing (32).

As well known, another main issue, particularly related to CDU is the inter-operator reproducibility; nevertheless, the introduction of artificial intelligence algorithms improved the detection of the halo sign on CDU images. Data from 137 patients were retrospectively collected and analysed using the VIA software. A sensitivity of 60% and a specificity of 95% was reached after the definition of an image positivity threshold. The main confounding factors identified were the presence of a thrombus and the acquisition modalities and even if further validation is needed, the approach seems promising (33).

Other imaging techniques have been evaluated for diagnosis of GCA such as 3T-MRI with 2D sequences and full-field optical coherence tomography (FF-OCT). Rodriguez-Régent *et al*. evaluated the diagnostic performance of fat-suppressed 3D T1-weighted black-blood MRI (CUBE T1) with 3D TOF coregistration. The examination was performed in 32 patients with clinically suspected GCA and 10 patients with diagnosis of GCA. CUBE showed a sensitivity of 80% and a specificity of 100%, suggesting a reproducible use of MRI along the diagnostic process of GCA (34).

FF-OCT uses white light interference microscopy to obtain high resolution images of biological structures and also of subcellular metabolic contrast in the

tissue depth. Maldiney *et al*. reported their experience applying high definition interference microscopy for pathological diagnosis of GCA. FF-OCT revealed its potential for qualitative and quantitative evaluation of arterial wall identifying architectural change and fibrous tissue formation. This preliminary report encourages further researches to confirm the role of this device, especially using a handheld acquisition probe to image the artery directly (transcutaneous approach), rapidly and with a non-invasive examination (35).

The role of imaging in Takayasu arteritis (TAK) has been widely recognised especially regarding management, nevertheless diagnosis remains difficult and delayed. In this regard, Kenar *et al*. defined disease activity according to vascular imaging (Rad-Active) and verified its agreement with other disease activity indexes; 76% of agreement was observed with physician global assessment and 83% with with Kerr's criteria, confirming the key role of imaging in TAK to detect disease activity (36).

Finally, Goel *et al*. explored the possibility of an angiographic-based disease classification, potentially helpful in identifying three novel cluster of patients based on arterial damage. Patients in cluster one presented more disease in the abdominal aorta, renal and mesenteric arteries; patients in cluster two had more bilateral disease and the carotids and subclavian arteries are more involved. Finally, patients in cluster three had asymmetric disease with less territories involved. These three clusters still require validation and their aetiological and prognostic value need to be confirmed through further research but it is surely an interesting topic to be explored (37). Globally, all these data further confirmed how the role of imaging in LVV is of undoubtful importance in order to confirm the diagnosis and avoid important delay in their management.

New insights in LVV treatment

In 2020, the publication of the 2018 update of the EULAR recommendations for the management of LVV (38), has been followed by the release of the British Society for Rheumatology guidelines on diagnosis and treatment of GCA (24) confirming the important evidence-based advances to support the management of LVV.

In a recent meta-analysis of 34 studies (8 RCTs), including 2505 GCA patients treated with glucocorticoids (GC) alone, about half of the patients experienced one or more than one relapses during follow-up. Notably, relapse rate was significantly higher for patients enrolled in RCTs compared to patients from observational studies (65.8% *vs*. 41.7%), mainly due to a shorter duration of GC therapy (39).

In order to decrease the risk of relapse during GC tapering and minimise chronic GC exposure, several studies have focused on maintenance treatment strategies and GC-sparing regimens in GCA. Song *et al*. performed a meta-analysis of 6 RCTs assessing the efficacy and safety of tocilizumab, tumor necrosis factor (TNF)-inhibitors and abatacept for the treatment of GCA (40). Relapse rate and risk of serious adverse events (AE) was significantly lower with tocilizumab than with placebo, whereas no significant benefit in terms of remission rate was observed between groups receiving TNF-inhibitors, abatacept, and placebo.

To determine if the results of the GiACTA study (41) could be rationally extended to real-world clinical practice, Calderón-Goercke *et al*. conducted a comparative study between the GiACTA trial (251 patients) and a multicentre series of GCA patients treated with tocilizumab in a real-world scenario (134 patients)(42). Sustained remission rate did not differ between the two groups (54.6% in the GiACTA trial *vs*. 70.4% in clinical practice group). Nevertheless, a higher cumulative GC dose and a higher proportion of patients treated with a conventional immunosuppressive agent was observed in the clinical practice group, contributing to a higher risk of serious infections.

In order to mitigate GC-related AE, tocilizumab monotherapy, administered for 1 year without concomitant GC, was tested in an open-label study including 12 patients with newly diagnosed LVV (8 GCA, 4 TAK), followed for 2 years (43). Complete responses were observed in 75% and 66% of GCA and TAK patients, respectively. No significant increase of relapse risk in the year following tocilizumab discontinuation was observed.

Given the suppression of inflammatory markers provoked by the inhibition of the interleukin (IL)-6 pathway, imaging modalities, such as CDU of temporal arteries/large vessels and 18FDG PET-CT, may play a crucial role in the follow-up of patients receiving tocilizumab. In a recent study enrolling 22 consecutive GCA patients, tocilizumab induced remission in 91% of patients, confirming its effective GC-sparing role, as well as a significant reduction of quantitative assessment of both CDU halo thickness of TA/large vessels and 18FDG PET-CT vascular uptake (44).

A recent multicentre, randomised, double-blind, placebo-controlled trial evaluated the efficacy of different therapeutic schedules of sirukumab, a selective, high-affinity human anti-IL-6 monoclonal antibody, in patients with active GCA (45). Despite early study termination resulting in short treatment duration, the proportion of patients with relapses at 52 weeks was significantly lower with sirukumab than with placebo.

Despite some initial promising results on the effectiveness of ustekinumab (46), a recent open-label trial was prematurely interrupted, as 7 out of the initial 10 patients relapsed soon after GC discontinuation (47).

In a multicentre retrospective case-control study, Quartuccio *et al*. analysed the rate of GC-related AE in 114 GCA patients treated with an immunosuppressant within 3 months from diagnosis, compared to 51 GCA patients who received GC monotherapy or an immunosuppressant after at least 3 months highlighting the significantly higher rate of GC-related AE and relapses in patients treated with monotherapy (48).

A recent case series of 14 GCA patients suggested some benefits from adjunctive treatment with leflunomide, with 64% of patients achieving remission at 6 month (49). In a retrospective study including 37 patients with LV-GCA followed for ≥2 years, the introduction of mycophenolate mofetil at diagnosis yielded a GC-sparing effect, with rela-

tively low relapse rates (16.2 and 27% at 1 year and 2 years, respectively) (50). These promising results require confirmation in larger cohorts or clinical trials.
The evidence published during the last 12 months regarding TAK confirmed the long-term efficacy and safety of tocilizumab. A 96-week extension of the TAK treated with tocilizumab (TAKT) trial including 28 patients treated with weekly tocilizumab showed a steroid-sparing effect, improvement in imaging findings (17.9% of patients) or stable imaging findings (67.9% of patients) compared to baseline (51). A French open-label trial in naïve patients with TAK assessed the chances of glucocorticoids discontinuation after 7 infusions of tocilizumab which was achieved by 54% of patients. However, after discontinuation of tocilizumab, approximately half of the patients relapsed suggesting that long-term maintenance treatment is necessary (52).
Newer therapeutic options are desirable in the treatment of TAK. Indeed, the drug retention rate in patients with TAK is relatively low, with 43% of treatment courses being stopped by 24 months. In this scenario, TNF inhibitors have been reported to have a longer retention rate compared to tocilizumab (53). Infliximab has been confirmed to ensure a glucocorticoid sparing effect in an open-label study including 23 patients with TAK (54).
Recently, small case reports are reporting the potential effectiveness of tofacitinib in the management of TAK. These interesting findings warrant further confirmation in larger studies (55, 56). A number of studies published in the past 12 months have assessed the role of conventional immunosuppressants, especially leflunomide in the management of TAK. In a case series of 56 patients with TAK, leflunomide treatment was associated with complete remission in approximately 70% of patients at 12 months, including a good response rate in patients refractory to previous lines of treatment, including cyclophosphamide (57). Two observational studies conducted in China compared the effectiveness of leflunomide *versus* cyclophosphamide in patients with TAK reporting significantly higher rates of remission at 12 months in patients treated with leflunomide (ranging 77.4–84.6% *vs*. 38.2–53.5%) (58, 59).
Finally, an observational study enrolling 68 patients with TAK compared the effectiveness of leflunomide (40 patients) *versus* methotrexate (28 patients). Prevalence of complete remission at 6 months was achieved by a significantly higher proportion of patients treated with leflunomide compared to methotrexate (72.5% *vs*. 53.6%). However, the benefit was not confirmed during longer follow-up, despite a lower frequency of relapses in patients treated with leflunomide (60).

Take home messages

- Angiogenic inducers (VEGF, FGF-2, angiopoietin 1, -2, soluble VCAM-1) and inhibitors (angiostatin, endostatin, pentraxin-3) have been implied in LVV angiogenesis dysregulation opening new avenues for targeted therapies;
- Ultrasonography (US) has been recognised at least equivalent to histology in confirming the diagnosis of LVV and crucial in the follow-up to monitor disease activity; moreover, other imaging techniques such as 3T-MRI with 2D sequences and full-field optical coherence tomography (FF-OCT) have been evaluated for diagnosis of GCA;
- Therapeutic goals have shifted from symptom control towards GC-sparing regimens in GCA.

ANCA vasculitis

Pathophysiology advances in AAV vasculitis

ANCA vasculitis (AAV) are complex potentially life-threatening systemic autoimmune diseases that have recently been subject of considerable immunologic and clinical research (61-64).
New insights into AAV pathogenesis are on the rise, paving new avenues for targeted therapies. As highlighted in a comprehensive review by Kronbichler *et al*. (65) a variety of different genetic and environmental factors have been implicated in the pathogenesis of AAV. Lately, the importance of recognising the specific pathogenetic role of different ANCA serotypes (*i.e*. proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA) has been further underlined by two recent original papers. The first one by Lee *et al*. (66) showed that PR3 antibody production may even precede the development of vasculitis. The second one by van Dam *et al*. (67) demonstrated that the increased production of PR3 antibodies also predicts relapses in patients treated with rituximab pin pointing the crucial role of ANCA serotypes in the pathogenesis of ANCA and also their potential usefulness as therapeutic biomarkers in the management of AAV patients. Besides ANCA, great attention has been paid to neutrophils and to the alternative complement pathway. Moiseev *et al*. (68) evaluated complement components in 59 AAV patients and performed a meta-analysis on the topic highlighting that plasma MAC, C5a and factor B were increased in patients with active AAV compared to patients in remission thus supporting the role of the alternative pathway of the complement system in AAV patients. Activation of the alternative complement pathway results in generation of C5a, which in turn can prime neutrophils through the C5a receptor. The potential of C5aR antagonism as a therapeutic option for vasculitis has been largely explored recently with the avacopan, an orally administered C5a receptor inhibitor (69). Noteworthy, novel therapies may also be identified exploring neutrophils and other immune cells immunemetabolisms. According to the study by Leacy *et al*. (70) priming events may alter the metabolism of immune cells (*i.e*. increased glycolysis), fostering the inflammatory immune response and the interaction between ANCA and neutrophils; preliminary data suggest that inflammation can be therefore modulated through a metabolic inhibition.

New insights into AAV clinical features and treatment

Recent literature widely underlines that AAV are disabling disorders leading to severe disease-related and treatment related organ-damage with important long term sequelae (71). During the past few months it has been generally em-

phasised that the clinical presentation and the outcome of the patients more closely reflect the ANCA serotype rather than the traditional definition GPA or MPA (72). Still, there is an unmet need for phenotype identification in order to ameliorate the management of AAV. From this perspective, this year great efforts have been made and two studies specifically deserve to be mentioned. Wojcik *et al*. (62) applied latent class analysis (LCA) to subcategorise GPA and MPA AAV patients included in the multicentre POLVAS registry. The authors identified four different subgroups of patients potentially candidate to different therapeutic approaches: a group presenting anti-MPO autoantibodies positivity (defined as severe MPO AAV) and three different subgroups among anti-PR3 positive patients that differ in renal involvement severity (no renal, mild renal and severe renal involvement) and number of organs involved (less or more than 3). Particularly the authors identified a subgroup of young GPA patients characterised by multiorgan involvement, high relapse rate, relatively high risk of death, but no end-stage kidney disease that may require prompt diagnosis and aggressive treatment. Similarly, Matsumoto *et al*. (73) investigated the association between AAV patients' clinical characteristics and immune cell profiles in AAV. Cluster analysis according to peripheral immune cell populations (*i.e*. plasma cells, plasmablasts, activated T cells, $CD14^{++}$ $CD16^{+}$ monocytes, eosinophils and neutrophils) indicated three subgroups: antibody production-related, cytotoxic activity-related and neutrocytosis/lymphocytopenia-related. The antibody production-related or cytotoxic activity-related group was associated with CNS involvement, and the neutrocytosis/lymphocytopenia-related group was associated with high incidence of kidney involvement and severe infections. Incidence of disease relapse was comparable among the three groups. The authors concluded that immunoprofiles may help to stratify homogeneous subsets of AAV patients useful to select more appropriate treatment.

Indeed, one of the most relevant unmet need in AAV is represented by the improvement of current therapeutic strategies to optimise remission induction and maintenance therapeutic strategies. In this regard, during the last few months, a number of important studies have been carried out (74, 75) to pave new ways for lesser toxic induction regimens based on low-dose glucocorticoids (Table I).

a. PEXIVAS (76). A recent large multicentre study primarily aimed at defining the role of plasmapheresis in patients with severe AAV, has recently shown that plasma exchange do not benefit in patients with glomerulonephritis or pulmonary haemorrhage. However, indeed PEXIVAS has addressed the question of glucocorticoid dose for induction of remission in AAV. Patients were randomly assigned or to a standard or to an accelerated prednisone-tapering schedule defined as around 50% of standard dose over 3 months and around 60% over 6 months. The authors observed a significative reduction in severe infections in the low-dose glucocorticoid group during the first year. Noteworthy, lower doses of prednisone were as effective as the higher dose regimens in preventing death or end stage renal disease in AAV patients.
b. ADVOCATE (69). Activation of the alternative complement pathway has been identified as a key mechanism in the pathogenesis of AAV vasculitis; preclinical data as well as CLEAR and CLASSIC phase II trial data have shown that AVACOPAN (68) a selective oral inhibitor of C5a receptor may replace glucocorticoids in the control of AAV-related renal involvement thus reducing glucocorticoid toxicity. The ADVOCATE trial, a randomised, double-blind, phase 3 trial has evaluated the efficacy of Avacopan in patients with AAV treated with rituximab or cyclophosphamide. Patients were randomised to receive Avacopan or standard glucocorticoids in addition to standard immunosuppression. The authors demonstrated that Avacopan was not inferior to glucocorticoids in obtaining remission at week 26 and superior to glucocorticoids for sustained remission at week 52. Avacopan improved eGFR and albuminuria in vasculitis probably by preventing the chemoattraction, activation of neutrophils and the consequent damaging of the glomeruli. A better quality of life was observed in both treatment groups. The mean daily glucocorticoid dose in the Avacopan group was one third of that in the prednisone and Avacopan reduced the incidence of glucocorticoid-related toxicities from 80.5% to 63.5%.
c. RITAZAREM (77). In this trial patients with relapsing GPA and MPA were prospectively randomised to receive remission-induction therapy with rituximab and a higher or lower dose of glucocorticoids. A proportion of patients around 90% achieved remission at the fourth month. Notably, 71% of them received the lower dose of glucocorticoids regimen. Smith *et al*. concluded that rituximab, in conjunction with relatively lower doses of glucocorticoids, was effective at reinducing remission also in patients with AAV relapsing disease.

Overall, these data encourage the use of lower doses of prednisone to foster better long-term outcomes for patients.

Likewise, during the last few months less toxic drugs such as mycophenolate mofetil (MMF) have been evaluated as alternative options to CYC as remission-inducing therapy. From this perspective Kuzuya *et al*. (78) performed a meta-analysis of four randomised controlled trials (RCTs) with mycophenolate mofetil (MMF). In these studies patients with a newly diagnosed disease (79), relapsing disease(80) and an early onset of disease (81) were enrolled. Patients with life-threatening AAV were excluded MMF was compared with intravenous (79, 81) and oral CYC (80). Data showed that remission rates were similar between CYC and MMF groups. However, Jones *et al*. (79) found that patients in the MMF treatment group, particularly PR3-ANCA-positive patients, were more likely to relapse than ones in the CYC. In conclusion, according to this meta-analysis, MMF was suggested as an alternative drug for non-life-threatening MPO positive

Table I. Low-dose glucocorticoids regimes in clinical trials.

Trial	Eligibility criteria	Study design	First outcome: results	Second outcome: results
Pexivas	704 patients ANCA vasculitis (new or relapse) eGFR <50 ml/min / Lung involvement	*All: CYC or RTX plus*: PLEX + standard GC PLEX + reduced GC No PLEX + standard GC No PLEX + reduced GC	Death/ESKD	Death from any cause ESKD Sustained remission Serious adverse events (SAEs) Serious infections at 1 year
			1) PLEX did not reduce death or ESKD 2) reduced GC not inferior to a standard GC 3) Severe infections: GC standard > GC reduce	
Advocate	331 patients ANCA vasculitis eGFR ≥15 ml/min	*All: CYC or RTX plus* Avacopan (30 mg twice daily) + PDN-matching PBO PDN + avacopan-matching PBO	Remission (week 26): Avacopan = PDN Sustained remission (week 52) Avacopan >PDN	GC-induced toxic effects: Avacopan < PDN GC Toxicity index aggregate Improvement score: Avacopan < PDN Effects on eGFR (change from baseline): Avacopan > PDN
Ritazarem (induction phase)	188 patients ANCA vasculitis (relapse)	*All: RTX* Schedule 1A: GC starting dose: 1 mg/kg/day GC cumulative dose: 3010 mg Schedule 1B: GC starting dose: 0.5 mg/kg/day GC cumulative dose: 1960 mg	Remission (month 4th): GC cumulative dose (patients remission) = GC cumulative dose (patients not remission)	• *SAEs:* Schedule IA:18,5%; IB: 12,7% • *Serious infections:* Schedule IA:0%; IB:3,7% • *Non-serious infections:* Schedule IA: 22%; IB:35.1% • *IgG <5 g/L:* Schedule IA: 50.0%; IB: 25.4%

CYC: cyclophosphamide, RTX: rituximab, PLEX: plasma exchange, GC: glucocorticoids, AE: adverse event; SAE: serious adverse event; PDN prednisone; eGFR: glomerular filtration rate; ESKD: end-stage kidney disease; PBO: placebo.

AAV patients, and particularly in young women to avoid gonadal toxicity.

Despite the identification of novel drugs such as Avacopan and less toxic strategies, RTX still retains a central role within the AAV therapeutic armamentarium (77, 82, 83). A significant effort has been made during the past twelve months in order to better define RTX regimens for induction and maintenance of AAV. Indeed, RTX indications have been addressed by the most recently published recommendations on AAV management (84-87), which take into account the experience of the last trials and are briefly summarised in Table II. Nevertheless, despite the most recent advances, several issues about RTX use remain a matter of debate.

The first open question is related to how long clinicians should push maintenance immunosuppressive treatment with RTX.

Long-term follow-up data from the MAINRITSAN trial showed a progressive reduction in relapse-free survival after RTX cessation, with around 60% relapse-free survival rate 32 months after the last rituximab infusion. In the MAINRITSAN3 trial (88), patients who were in complete remission after receiving standard RTX maintenance treatment for 18 months, were randomly assigned to receive an extra 18 months RTX maintenance course with the MAINRITSAN regimen (fixed 500 mg dose on D0, D14, M6, M12, M18) or placebo. Relapse-free survival at 28 months (the primary endpoint) was significantly higher in the extended treatment group, moving the authors to propose extending maintenance duration in patients at high risk for relapses (*i.e.* with PR3 ANCAs, and patients with previous relapse).

These results have been acknowledged by the main study groups on AAV, who unanimously suggest prolonging the maintenance treatment with RTX in patients considered at high risk for relapse (Table II) (84-87). From this perspective, McClure *et al*. (89) generated a risk prediction models to identify those patients who were at higher risk of relapses when stopping maintenance immunosuppression, taking into account at the same time their risk for infections. The following predictors were retained in the final risk model for relapse: male sex, age >60 years, ANCA positivity, previous relapse, ENT involvement, lower prednisolone dose and absence of concomitant immunosuppression. For infection risk, five predictors were retained in the model: male sex, presence of structural lung disease, diabetes mellitus, occurrence of infections during rituximab treatment and lower IgG level. These models could guide the clinician decision making, by separating patients into low- and high- risk groups for relapse and infection respectively.

The second open question is related to the most appropriate dosing intervals for RTX.

The MAINRITSAN2 trial explored the potentialities of an individually tailored RTX-infusion schedule based on ANCA positivity and $CD19^+$B-cell levels, suggesting that in the near future a single-patient individualised treatment approach could be guided by serum biomarkers (90). In a recent *post hoc* analysis of the MAINRITSAN2, Charles *et*

Table II. Recommendations for the use of rituximab (RTX) in ANCA-associated vasculitis.

Recommendations	RTX for induction	RTX for maintenance	RTX duration
BSR consensus guidelines (84)	No specific regimen	500 mg or 1000 mg every 6 months for 2 years	5 yrs
French recommendations (85)	375 mg/m^2/week (4 infusions 1-week intervals).	500 mg D0, D14, M6, M12, M18 (MAINRITSAN regimen)	4 years (PR3-AAV severe or relapsing MPO-AAV) 2 years (newly severe MPO-AAV)
CanVasc 2020 (86)]	No specific regimen	no specific dose recommended every 4-6 months	2 years 2 years (plus additional 18 months): (patients with previous relapse(s), pre-existing organ damage, PR3-ANCA and/or persistent ANCA)
FVSG recommendations (87)	375 mg/m^2/week (4 infusions 1-week intervals).	500 mg D0, D14, M6, M12, M18 (MAINRITSAN regimen)	18 months: patients in first remission. Beyond 18 months: patients with previous relapse(s)

al. (91) suggested that omitting the D14 rituximab remission-maintenance dose may not modify the short-term relapse-free rate of ANCA vasculitis.

However, a clear and solid correlation between ANCA titres, circulating CD19$^+$ B-cell and relapse risk has not been proved yet. As a result of this, the last recommendations do not support the use of tailored-administration strategy as a first-line maintenance treatment, suggesting that more data on this field are needed.

On this respect, van Dam *et al*. employed highly-sensitive flow cytometry (HSFC), traditionally used to detect minimal residual disease in haematologic neoplasia, to perform a phenotypic analysis of the B-cell compartment in patients undergoing RTX treatment for either induction or remission maintenance (92). They showed that RTX induced strong reductions in circulating B-cells, but never resulted in complete B-cell depletion when the serum samples were analysed by HSFC, in contrast to conventional low-sensitive flow cytometry. This "minimal residual autoimmunity", driven mainly by memory B-cells and plasma cells, may explain some instances of relapse where conventional flow cytometry would mistakenly indicate a complete B-cell depletion.

Another study that is worth mentioning was performed by Springer *et al*., who measured RTX concentrations in the sera of 30 AAV patients treated for induction or remission maintenance (93). The authors noticed that RTX concentrations were significantly associated with the depth of B cells depletion. More in detail, they individuated a cut-off value of 550 ng/mL above which 100% of patients displayed B-cell depletion in contrast with 51% of patients with RTX levels below 550 ng/mL.

The third open question is related to the use of RTX in EGPA. Currently there are no available prospective controlled trial on RTX use for induction or remission maintenance in EGPA patients.

After performing a systematic literature review, Akiyama *et al*. analysed the results of seven studies (mainly retrospective) for a total of 171 EGPA patients treated with RTX (94). Patients were mostly refractory to the standard therapy or had relapsing disease, although 14 of them had newly diagnosed EGPA. RTX was used for induction of remission with the RAVE trial regimen (375 mg/m2 x 4/weekly), or the RA regimen (1000 mg x 2 biweekly). The remission rates were 36 to 100%, a result that is similar to that observed for the use of RTX in GPA and MPO patients induction. A trend for higher remission rates in ANCA positive patients was noted, a difference that reached statistical significance in one of the studies included in the review. Moreover all the studies reported a successful reduction of the GC dose, namely from a median dose of 12.5–60 mg/day to a median dose of 0–8.5 mg after RTX treatment. In spite of these results the French Vasculitis Study Group does not recommend to use RTX as a first line agent for neither induction nor remission maintenance of EGPA patients, because of the weakness of the available data. On the other hand the BSR GL for maintenance of remission with RTX recommend employing B-cells ablation therapy with the same modalities as in GPA and MPA.Currently there are two ongoing RCTs on the use of RTX respectively for induction (REOVAS) and remission maintenance (MAINRITSEG) of EGPA. Their results are impatiently awaited to better define the role of anti-CD20 therapy in such a complex disease.

Take home messages

- PR3-ANCA and MPO-ANCA have different roles in the pathogenesis of AAV;
- C5aR antagonism represents a valid therapeutic option for AAV;
- Induction regimens based on low-dose glucocorticoids seem to be associate with a significative reduction in severe infections and adverse events;
- Plasma exchange do not benefit in patients with glomerulonephritis or pulmonary haemorrhage;
- RTX regimens for induction and maintenance of AAV should be better defined in the near future in terms of maintenance duration, dosing intervals, and use in EGPA.

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