Review

Systemic vasculitis: one year in review 2023

M. Moretti[1], E. Treppo[2], S. Monti[3], G. La Rocca[1], G. Del Frate[2], P. Delvino[3], N. Italiano[1], F. Di Cianni[1], F. D'Alessandro[1], R. Talarico[1], F. Ferro[1], L. Quartuccio[2], C. Baldini[1]

[1]*Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;*
[2]*Clinic of Rheumatology, Department of Medical and Biological Sciences, University Hospital Santa Maria della Misericordia, Udine;*
[3]*Department of Rheumatology, University of Pavia, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy.*

Michele Moretti, MD
Elena Treppo, MD
Sara Monti, MD
Gaetano La Rocca, MD
Giulia Del Frate, MD
Paolo Delvino, MD
Nazzareno Italiano, MD
Federica Di Cianni, MD, PhD
Francesco D'Alessandro, MD
Rosaria Talarico, MD, PhD
Francesco Ferro, MD
Luca Quartuccio, MD, PhD
Chiara Baldini, MD, PhD

Please address correspondence to:
Chiara Baldini
U.O. di Reumatologia,
Dipartimento di Medicina
Clinical e Sperimentale,
Università di Pisa,
via Roma 67,
56126 Pisa, Italy.
E-mail: chiara.baldini74@gmail.com

Received on April 10, 2023; accepted on April 12, 2023.

Clin Exp Rheumatol 2023; 41: 765-773.

Key words: systemic vasculitis, giant cell arteritis, Takayasu's arteritis, antineutrophil cytoplasmic antibody associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, cryoglobulinaemic vasculitis

Competing interests: none declared.

ABSTRACT

Systemic vasculitides are heterogeneous disabling diseases characterised by chronic inflammation of the blood vessels potentially leading to tissue destruction and organ failure. The recent COVID-19 pandemic has had a significant impact on the epidemiology and management of patients with systemic vasculitis. In parallel, new insights have been provided on systemic vasculitis pathogenetic mechanisms, possible new therapeutic targets, and newer glucocorticoid-sparing treatments with better safety profiles. As in the previous annual reviews of this series, in this review we will provide a critical digest of the most recent literature regarding pathophysiology, clinical manifestations, diagnostic tools and treatment options in small- and large-vessel vasculitis focusing on precision medicine in vasculitis.

Introduction

Systemic vasculitides are rare and complex disorders considerably affecting patients' long-term outcomes and quality of life. In the era of precision medicine, a considerably international effort has been recently made to facilitate individualised medical approaches based on novel insights into systemic vasculitis pathogenetic mechanisms, -omics biomarkers and innovative target therapies. Following the other reviews of this series (1, 2), here we aim to summarise the most relevant literature contributions on this topic published in 2022. We performed a Medline search of English language articles published in the PubMed database from 1st January 2022 to 31st December 2022. The following key words formed the data sources: vasculitis, giant cell arteritis (GCA), Takayasu's arteritis (TAK), antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV), microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly Wegener's), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss) and cryoglobulinaemic vasculitis (MC).

Systemic vasculitis: new 2022 ACR/EULAR classification criteria

One of the most relevant contributions of the 2022 literature on vasculitis is represented by the publication of the new ACR/EULAR classification criteria for large and medium-small vessel vasculitis. Indeed, in the era of precision medicine these classification criteria represent a crucial prerequisite to include homogeneous subsets of patients in novel clinical trials, thus paving the avenues for individualised therapeutic approaches. The ACR/EULAR criteria were developed based on real-world cases enrolled in the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study and validated on a separate set of patients. The items included are weighted and a point-system is applied to reach the minimum cumulative classification score. Regarding GCA (3) a confirmed diagnosis of vasculitis, and age ≥50 years at diagnosis are absolute requirements to apply the criteria. Noteworthy, great attention has been paid to imaging biomarkers. In fact, temporal artery halo sign on ultrasound, temporal artery abnormality on vascular examination, bilateral axillary involvement on imaging, and fluorodeoxyglucose-positron emission tomography activity throughout the aorta have been now included in the criteria. Similarly, the 2022 ACR/EULAR classification criteria for TAK (4) included three imaging criteria as absolute entry criteria. Namely these items

include: the number of affected arterial territories, the symmetric involvement of paired artery and the involvement of abdominal aorta with renal or mesenteric imaging abnormalities. Overall, these criteria have the advantage to provide a higher sensitivity compared to the previous ACR 1990 criteria when applied to either the DCVAS cohort or external cohort as confirmed by Cao *et al*. who applied the new criteria to their Chinese cohort (5). Regarding AAV, the 2022 ACR and EULAR new classification criteria for GPA (6), MPA (7) and EGPA (8) showed a relatively good concordance with the 1990 ACR criteria, the 2007 EMA algorithm and the 2012 CHCC definitions; however, the concordance rate was highest in patients with MPA (96.6%), and lower in those with EGPA (86.3%) and GPA (73.8%) (9).These results highlight from one side the good sensitivity and specificity of the novel criteria and from the other the need for further studies aimed at addressing specific "classification" issues in the most difficult and controversial cases (*i.e*. patients classified as having two AAVs at the same time, patients reclassified as having unclassifiable vasculitis etc).

Systemic vasculitis following either infection or vaccination against COVID-19

Since the onset of the COVID-19 pandemic, several reports have highlighted the link between the SARS-CoV-2 infection and autoimmunity, resulting in the production of multiple autoantibodies and the occurrence of autoimmune diseases (10). It remains controversial whether SARS-CoV-2 infection or vaccination may have had an impact on epidemiology of systemic vasculitis.

Several case reports of *de novo* vasculitis, affecting medium, or small vessels, following either infection or vaccination against COVID-19, during the pandemic outbreak (11).

One retrospective study conducted in Australia compared the frequency of new cases of GCA during the period April 2020-August 2021 to the pre-pandemic period, finding a reduction in the incidence of GCA of 55%. Nevertheless, these findings should be interpreted cautiously given the reduced accessibility to hospital facilities and routine visits registered during the first phases of the pandemic (12). On the other hand, a large, global pharmacovigilance study revealed an association with increased reporting of GCA and polymyalgia rheumatica (PMR) diagnoses. The frequency was higher with mRNA vaccines (61.9% of cases) compared to viral vector vaccines (37.4%). The median time from vaccination to first symptoms was 4 (1-14) days. Although the study raises a potential safety signal, the relative risk of GCA or PMR following COVID-19 vaccination seems to be lower than that reported with influenza vaccination (13).

Recently published evidence has confirmed the safety of vaccination against SARS-CoV-2 also in MC patients (14). A multicenter Italian population study (14) included a total of 416 MC patients, of whom 92.3% had received SARS-CoV-2 vaccination and 7.7% refused to be vaccinated, mainly because of fear of the vaccine side-effects. Overall, short-term, mild, and self-limiting, adverse effects (AEs) were recorded in 21.4% of patients: asthenia (13.7%), arthralgia (10.6%) and fever (7%) were the most frequent AEs reported. Disease relapses were observed in 5.3% of patients and were mostly characterised by exacerbation of previous manifestations of the MC syndrome and improved rapidly with a temporary increase in ongoing treatment. Disease relapses were reported primarily in patients on ongoing glucocorticoid therapy (p=0.04), and relapse of purpura was reported in 25% of patients with active vasculitis at the time of vaccination (p=0.004). Similarly, 17.5% of patients with peripheral neuropathy experienced symptomatic neurological worsening after vaccination (p=0.029) and 7.5% of patients with peripheral neuropathy experienced a vasculitis flare (p=0.45) (14). These data are quite comparable to another prospective multicenter study that had recruited HCV-related MC (complicated or uncomplicated by low grade non-Hodgkin's lymphoma (NHL)) and essential MC (EMC) (15). MC vasculitis relapses were reported in 12.7% of patients and were more common in EMC patients than HCV-related MC (p=0.023). Anti-SARS-CoV-2 IgG responses were measured 8-14 days after the second vaccine dose, with seronegative detected in 71% and in 11.6% of rituximab (RTX)-treated and RTX-free patients, respectively (p=0.002). The seronegative rate in RTX-treated was correlated with B cell count, whereas unknown disease-related factors may impair vaccine immunogenicity in treatment-free patients (15). Overall, the serum levels of IgG-neutralising antibodies (NAb) were lower in patients with ADs compared to general population (16); and over one-quarter of AD patients had none or suboptimal production of NAb after the first vaccine cycle. These findings indicate the usefulness of booster vaccine administration in AD patients.

New insights into GCA

Imaging biomarkers and clinical unmet needs

In the last decades algorithms and procedures used to make the diagnosis of LVV have considerably changed. As shown by a Spanish study (17) examining their nationwide register, temporal artery biopsy (TAB) underwent a slow decline of its application going from being the leading test in 2013 to being used in only a third of cases in 2019. On the other hand, in 2019 more than half diagnoses were established by ultrasound (US) and another 20% by FDG-PET.

Imaging biomarkers may indeed be specifically useful to identify subclinical GCA in patients with PMR which is one of the unmet needs in GCA. A recent meta-analysis including 566 patients reported a pooled prevalence of subclinical GCA of 23% (95% CI 14%-36%, I2=84%). The highest frequency was reported when PET-CT was used as a screening method (29%), followed by TAB (20%), and ultrasound (15%). The clinical predictors of subclinical GCA were inflammatory back pain, absence of lower limb pain, female sex, fever, weight loss, thrombocyte count, and haemoglobin level. The study suggests the need to further studying the cost-effectiveness of implementing imaging studies in newly diagnosed patients with PMR (18-21).

Novel biomarkers from translational may increase the probability to identify GCA among patients with new onset PMR. Among them angiopoietin-2/1 ratios and metalloproteinase-3 levels (22) as well as interferon-γ levels and T-cell activation (23) were identified and proposed.

Another clinical challenge in GCA is represented by the possibility of distinguishing active from inactive disease. [18F] FDG-PET/CT is one of the most used techniques to detect active vascular inflammation, but there is still lack of uniformity in its interpretation. In a study by Espitia *et al*. (24) semiquantitative interpretation using a threshold SUV max of 3.45 gives sensitivity and specificity around 90%, while in the study by Dashora *et al*. (25) SUV-metric interpretation shows poorer performance when compared to semiquantitative metric based on liver tissue-to-background ratio (TBR Liver) and qualitative PETVAS scoring approaches. A Brazilian study (26) indicates that to enhance the accuracy of detecting vascular inflammation with of ^{18}F-FDG PET/CT also in treated patients, it is preferrable to perform late image acquisition at 180 minutes.

In this regard, one of the most intriguing future perspectives is assessing LVV-patient using macrophage-targeting PET tracers. Many molecules have been proposed to replace ^{18}F-FDG (27), but still none of them found use in clinical practice. Another imaging technique that may find application in the future is [^{18}F]F-FDG-PET/MRI (28, 29), even though at present there is still need to improve its interpretation parameters.

Magnetic resonance angiography is an alternative technique already largely employed in clinical practice to assess vascular wall inflammation. It is not considered a first-line test since it is characterised by non-excellent sensitivity and specificity, as illustrated in the study by Zhang *et al*. (30). As also suggested by EULAR recommendations, MRI accuracy can be enhanced adopting imaging multimodal algorithms. Namely, MRI combined with retinal angiography (RA) appears to be the association with the best performance (31, 32).

Contrast-enhanced ultrasonography (CEUS) is another test that still has not found widespread use in clinical practice but could prove effectiveness in disease follow-up, mainly to evaluate subclinical relapses and therapy response (33).

Therapy of LVV

According to the international recommendations, GCs remain the cornerstone of LVV induction therapy. Adjunctive therapies with methotrexate (MTX) or tocilizumab (TCZ) represent the first choice to treat refractory or relapsing disease in GCA or for patients at high risk for GCs-related AEs. A large, multi-centre, prospective, observational study in Japan evaluated effectiveness of weekly subcutaneous TCZ in 120 patients for 52 weeks. Relapses were observed in 20% of patients. At the last observation, 83% of relapse-free patients were assuming a dose of prednisone/prednisone equivalent lower than 10 mg/day. These results are consistent with the TCZ efficacy and GC-sparing effect observed in TAKT trial (34). Another study from Japan retrospectively compared effectiveness and safety of *i.v.* TCZ with CTX (35) at 3 and 6 months, showing higher and faster response in the TCZ group in terms of lower activity scores and decreased axillary mural thickness at ultrasound. Also, cumulative incidence of AEs and dose of GCs at last evaluation were significantly lower in the TCZ group. Intriguingly, patients with GCA displayed an ineffective induction of glycoprotein A repetitions predominant (GARP) and CD25, together with reduced T cell receptor-induced calcium influx that would be recovered in patients treated with tocilizumab who achieved remission (36).

Recent literature also explored further biological therapeutic options for LVV. IL-6–IL-17 axis and IL-12–IFN-γ axis play critical roles in the disease pathogenesis, and activation of IL-17 signature was associated with higher relapse frequency in LVV (37). This observation indicates IL-17 as a promising target for precision medicine in LVV therapy, as it is potentially suppressed by JAK inhibitors. A systematic review reported that current evidence regarding the use of JAK inhibitors in LVV is derived mostly from case reports of moderate quality (38). However, a recent transcriptomic study demonstrates a clear type I interferon signature upregulation in aortas of 43 patients with active large-vessel GCA (LV-GCA). Dysregulated molecular pathways were also demonstrated in circulating CD4$^+$ and CD8$^+$ T cells in GCA. STAT3 was significantly upregulated in both aorta and T cells and appeared as a potential therapeutical targeting (39).

Regarding TAK, vascular wall fibrosis represents a therapeutic issue since most immunosuppressive treatments frequently fail to prevent its development or progression. In a recent study, heart-type fatty acid binding protein 3 (FABP3), a molecule involved in the fatty acid oxidation (FAO) process, was significantly overexpressed in the fibrotic adventitia of patients with active TAK (n=12) as compared with healthy controls (n=8) (40). Notably, the administration of curcumin (60 g/day), a polyphenolic compound with anti-fibrotic properties, led to a reduction a of serum level of FABP3, as well as an inhibition of vascular fibrosis through a down-regulation of FAO in the fibroblasts of the aortic adventitia. In contrast to other systemic autoimmune diseases, the impact of gut microbiome in pathogenesis of TAK is not fully understood. In a recent study integrating multi-omics approaches, the authors identified an increased representation of specific bacterial species, such as unclassified *Escherichia, Veillonella parvula, Streptococcus parasanguinis, Dorea formicigenerans, Bifidobacterium adolescentis, Lachnospiraceae bacterium 7 1 58FAA, Escherichia coli, Streptococcus salivarius, Klebsiella pneumoniae, Bifidobacterium longum, and Lachnospiraceae Bacterium 5 1 63FAA* in patients with TAK compared to healthy controls (41). Interestingly, a significant correlation between microbial metabolites and disease phenotypes, vascular involvement, systemic inflammation, and prognosis was observed, highlighting a potential role for the gut microbiome in the pathogenesis of the disease and providing insights for future research in this field.

Take home messages

- Fatty acid oxidation in fibrotic adventitia in TAK play a fundamental role in LVV pathogenesis (40).
- The 2022 ACR/EULAR classification criteria have established the importance of imaging in the assessment of LVV. Distinguishing between active and inactive disease remains an issue, with multimodal imaging algorithms and macrophage-targeting PET tracers representing interesting possible future options (18-21).
- Data from real-world settings favour TCZ in GCA treatment for effectiveness, GC-sparing effects, safety, and radiographic response (34-36).

New insights into cryoglobulinaemic vasculitis: from epidemiology to novel therapeutic approaches

Changes in the epidemiology of cryoglobulinaemia before and after the introduction of direct-acting antivirals (DAAs) have been studied in different cohorts of MC patients. A recent US study (42) compared the proportionate mortality ratio (PMR) of cryoglobulinaemia cases with HCV and those with AD to assess the impact of the introduction of DAAs in 2014. The authors identified 1299 individuals aged ≥20 years who died of cryoglobulinaemia in the United States between 1999 and 2018 and reported a decrease in HCV-related MC mortality in 2014-2018 (26%) compared with 2009-2013 (39%), with a PMR of 0.67 (95% CI 0.50-0.89) (42). In contrast, the proportion of deceased with cryoglobulinaemia and AD increased from 2.6% in 2009-2013 to 4.2% in 2014-2018, with a PMR of 1.58 (95% CI 0.66-3.82) (42). These results are consistent with the epidemiological changes found in previous studies, *i.e.* AD are currently the main causes of MC and CV (43, 44).

Regarding cryoglobulinaemia in primary Sjögren's syndrome (pSS), persistent salivary gland enlargement (SGE) and MC remain the best validated biomarkers for lymphoma development (45). A recent retrospective analysis (46) demonstrated that MC, focus score and the total EULAR SS Disease Activity Index (ESSDAI) at pSS diagnosis were independent mucosa-associates lymphoid tissue (MALT) lymphoma predictors. Besides pSS, SLE is one of the most common autoimmune diseases associated with cryoglobulinaemia. In a French retrospective study (47) performed on 213 SLE patients, 142 (66%) had at least one cryoglobulinaemic finding in their history and 67% of them had persistent cryoglobulinaemia at follow-up. Of the 142 patients with cryoglobulinaemia, 15% developed vasculitis: (48): main manifestations were skin and joint involvement, whereas neurological and renal involvement were rare. Surprisingly, in contrast to other case series, the central (19%) nervous system was more affected than the peripheral (10% of patients). In addition, serum protein electrophoresis for the analysis of paraproteinaemia and rheumatoid factor (RF) was recently shown to also have high sensitivity for the detection of clinically relevant cryoglobulinaemia, even when samples were not collected under ideal preanalytical conditions and may provide a rapid and effective screening strategy (49). Of 586 eligible cryoglobulinaemia positive samples collected over an 11-year period, 91% had either detectable paraprotein of RF activity, with the highest sensitivity for type I and type II cryoglobulinaemia (97% and 98%, respectively) (49).

Although interferon (INF)-free DAA regimens have been widely shown to be safe and effective in HCV-related MC, enabling clinical and immunological response in the majority of patients, it is well known that symptom maintenance and recurrence may occur during the follow-up after a transitory remission (50, 51).

Recently, Quartuccio *et al.* (52) published the evidence- and consensus-based recommendations of the Italian Study Group of Cryoglobulinaemia (GISC) on RTX in MC. It was widely accepted that RTX is effective and safe in both severe and non-severe clinical manifestation of MC. Moreover, low-dose treatment is as effective as high-dose RTX treatment, although for life-threatening manifestations, high-dose treatment may be required even in combination with cyclophosphamide or plasma exchange (53). As for subsequent cycles of RTX, retreatment with RTX appears to be successful and safe in patients with major relapse. In the last year, an Italian retrospective study (54) showed further evidence in favor of the efficacy of RTX in the renal involvement of HCV-unrelated MC.

A European collaborative retrospective multicentre study with Belimumab was conducted in patients with HCV-unrelated and RTX-refractory MC (55). Of 33 patients, 14 (42%) were primary refractory to RTX, whereas 19 (58%) had an initial clinical response to RTX before immune scape to treatment. The active clinical manifestation after RTX failure were cutaneous involvement (72%), peripheral neuropathy (56%), renal (41%), articular (31%) and gastrointestinal involvement (6%). Anti-CD20 plus belimumab, alkylating agent alone, and anti-CD20 plus alkylating agent resulted in the highest rates of clinical response in 100%, 82% and 73%, respectively; contrasting with a poor immunological response observed in 50%, 30% and 38%, respectively (55). However, an increased risk of infections with anti-CD20 plus belimumab was reported (55).

Recently, Gragnani *et al.* (56) investigated the association of allelic variants of the BAFF/BAFF-R system in HCV patients with and without lymphoproliferative disorders and suggested that anti-BAFF therapy might not be effective in patients carrying the mutated BAFF-R (rs61756766), as this receptor variant is able to recruit TRAF2/3 and induces hyperactive signaling even in the absence of BAFF binding. These results pave the way for further studies aimed at tailoring treatment. Finally, regarding new therapeutic approaches the possibility of targeting cholesterol biosynthesis has also been proposed. In fact, a recent study based on tandem mass tag (TMT)-labelled mass spectrometry (MS) technology has shown that the levels of APOA1 and PCSK9 were significantly increased in MC patients, suggesting that proteins involved in cholesterol metabolism are also involved in the development of cryoglobulinaemia (57). In addition, B lymphocyte activation and antibody

production processes derive their capacity mainly from oxidised fatty acids (58). These results suggest that lipid metabolism and the cholesterol biosynthesis pathway also play an essential role in lymphocyte proliferation. Whether drugs targeting APOA1 and PCSK9 or the cholesterol biosynthesis pathway can actually represent new approaches to cryoglobulinaemia and lymphoma deserves further research.

Take home messages:

- Cholesterol metabolism pathway is involved in lymphocyte proliferation and in the development of cryoglobulinaemia. New therapeutic approaches could target cholesterol biosynthesis (56-57).
- After the introduction of direct-acting antivirals (DAAs), AD are currently the main causes of MC and CV (42-44).
- After HCV eradication, around 50% of MC patients do not show any clinical improvement in the long term (50-51).
- Belimumab has been studied as an add-on therapy in RTX-refractory MC. Specific genotypic features could predict its effectiveness (55).

New insights into AAV: from epidemiology to novel therapeutic approaches

ANCA associated vasculitides (AAVs) are rare and heterogenous diseases, whose clinical phenotypes are complex and often difficult to be identified. In a systematic review including studies published from 1995 to 2020 (59), Redondo-Rodgriguez *et al*. confirmed an important update on AAV epidemiology. Granulomatosis with polyangiitis (GPA) was the most frequent type of AAVs with a pooled incidence of 9 per million person-years, while microscopic polyangiitis (MPA) pooled incidence was 5.9 and eosinophilic granulomatosis with polyangiitis (EGPA) incidence was 1,7. GPA and MPA adult pooled prevalence were 96.8 per million and 39.2 per million, while EGPA prevalence was 15.6.

Treatment strategies for both induction and maintenance of AAV have been consolidating in the last few years and were corroborated by observational studies and meta-analysis published in 2022. Moreover, the COVID-19 pandemic has pinpointed the risk of increasing AE numbers and severity with new biological drugs that have demonstrated efficacy against AAVs thus opening important questions on how to optimise AAV therapeutic management (60).

Last year, Bellos *et al*. (61) performed a meta-analysis of clinical trials comparing immunosuppressive treatment regimens for remission maintenance of AAV patients. As expected, a RTX-based maintenance treatment was found to provide longer relapse-free survival compared to traditional immunosuppressants. Among the latter mycophenolate mofetil resulted the least effective when compared to CYC, AZA and leflunomide (61). Increasing evidence pointing at the efficacy of RTX in the management of AAV have progressively shaped the current therapeutic algorithm, with the most recent guidelines from the ACR recommending employment of RTX over cyclophosphamide (CYC) for remission induction of severe GPA and MPA cases. However, this statement is primarily based on the RAVE trial (62), demonstrating the *non-inferiority* of RTX compared to CYC for remission induction of severe GPA and MPA, combined with the less toxic profile of RTX treatment. Remarkably, last year RTX *superiority* over CYC in inducing remission of both PR3- and MPO-positive GPA patients was shown in an observational study conducted on a large cohort of patients enrolled in the French Vasculitis Study Group Registry (63).

Of note, both the RAVE trial (62) and the aforementioned study (63) excluded AAV patients with severe renal involvement and rapidly progressive kidney failure. In this clinical scenario the choice between RTX and CYC regimens for remission induction is still hardly debated and the 2020 French recommendations (64) considered IV CYC the first line therapy for severe AAV cases with glomerular filtration rate (GFR) <15 ml/min. Recently, Roccatello and colleagues (65) reported that an "Intensified B Cell Depletion Therapy protocol" (IBCDT) based on combined RTX and low dose CYC was able to induce complete remission in the vast majority of AAV patients with biopsy proven crescentic glomerulonephritis and GFR<15 ml/min. Compared to matched historical controls treated with oral CYC and Azathioprine (AZA) maintenance, the IBCDT regimen resulted in comparable overall survival, 6 months remission rate and functional kidney improvement, with an impressive sparing of CYC exposure (65). In line with the investigation of optimal treatment strategies for difficult to treat phenotypic groups, last year an observational study confirmed RTX efficacy in AAV patients older than 75 years, though raising serious concerns for the high rate of serious infections observed in the induction, but not in the maintenance phase (66). This was probably related to the high doses of steroids administered during remission induction and underlines one of the greatest unmet needs in AAV management: minimising glucocorticoid doses and therefore infective risk during remission induction of active severe patients. Indeed, a recent retrospective study on a large Chinese cohort confirmed that infections occurring in the early phase of the induction treatment, and more specifically respiratory, Gram-bacterial and fungal infections represent independent risk factors for short term mortality, while prophylactic treatment with Trimethoprim-sulfamethoxazole resulted protective for 1-year mortality (67), This appears particularly relevant for elderly patients that are indeed more fragile. Indeed, in elderly patients, the Birmingham vasculitis score 3, eGFR, methylprednisolone pulse use, and cyclophosphamide use were significantly associated with infectious complications (68).

Besides immunosuppressive treatment with RTX or CYC, Plasma exchange (PEX) has long been considered an option in the management of AAV with life-threatening presentations, until the PEXIVAS trial (69) recently demonstrated that the addition of PEX to either CYC or RTX provided no benefits in terms of death and End Stage Kidney Disease (ESKD). However, according

to an updated meta-analysis published last year by Walsh and colleagues, PEX probably does not influence all-cause mortality, while it possibly reduces 1-year ESKD risk, at the cost of increased risk of serious infections (70). Based on these findings a panel of experts has recently expressed a weak recommendation in favour of PEX employment in patients at moderate-high risk of ESKD (71).

Regarding other novelties in AAV armamentarium some additional important contributions have been published in 2022. A randomised clinical trial (NCT05376319) will compare Obinutuzumab (OBI) to RTX for remission induction of PR3+ AAV patients and in the near future OBI may represent a safe alternative to RTX in allergic patients and perhaps even provide more efficient and persistent B-cell depletion. On the same line, Alemtuzumab, a pan-lymphocyte depleting agent has been employed for the compassionate treatment of refractory AAV (72). However, an open-label phase IIb trial including a small cohort of AAV patient's refractory to conventional therapy has shown only a partial and transient efficacy of Alemtuzumab, at the cost of a significant incidence of AEs (73).

The C5aR inhibitor Avacopan will probably be a gamechanger as an add-on, steroid-sparing agent and last year the first real-world data on non-refractory AAV patients treated with Avacopan were published, confirming its great effectiveness and steroid-sparing capacity (74). Moreover, a sub-analysis of the ADVOCATE trial (75) (76) recently confirmed the main efficacy and safety endpoints on a subpopulation of Japanese patients included in the trial. This is especially interesting since these patients were older and included a greater proportion of MPA and MPO+ subjects compared to the general population enrolled in the trial, accounting for a phenotype with poor prognostic factors.

The new ACR recommendations on EGPA treatment published in 2021 (77) highlighted the role of anti-IL5/anti-IL5R therapies, especially mepolizumab. Indeed, several reports have been recently published pinpointing the effectiveness of mepolizumab on EGPA respiratory symptoms. In a European retrospective study (78), mepolizumab showed safety and effectiveness in EGPA treatment at both doses commonly used in clinical practice (100 mg every 4 weeks in severe eosinophilic asthma or 300 mg every 4 weeks in EGPA). Nakamura *et al*. (79) also found symptoms improvement in a retrospective study involving patients with peripheral neuropathy treated with 12-months of low-dose mepolizumab therapy. An important unmet need remains the use of mepolizumab in severe EGPA induction treatment and interesting reports have been recently presented that require further validation. In a retrospective study Ueno *et al*. (80) compared induction treatment with corticosteroids plus cyclophosphamide with therapy with corticosteroids plus mepolizumab. They found similar values of VDI, BVAS and eosinophil counts at 6 months in both groups, with use of lower doses of corticosteroids, higher retention rate and lower number of adverse events in mepolizumab group compared to cyclophosphamide. However, in specific organ manifestations such as myocarditis, targeting IL-5 might leave uncovered the Th1 and Th17 arms of the immune system (81).

As outlined by Berti *et al*. (82), data are still lacking about some critical points, such as use of mepolizumab in severe vasculitis phenotypes and tailored dose regimens. Future randomised controlled trials are necessary to provide stronger data about possible broader indications of mepolizumab and the other IL-5/IL-5R-targeted therapies.

Take home messages

- RTX showed superiority over CYC for remission induction of severe PR3+ and MPO+ GPA (63).
- Combination of RTX and low-dose CYC is effective for remission induction of AAV with very severe renal involvement and allows CYC sparing (65).
- Infections during remission induction are common, especially in older patients treated with RTX. Early infections drive mortality risk, therefore steroid sparing strategies (Avacopan), systematic screening of infections and prophylaxis with TMP-SMZ become key. (67-68)
- Preliminary data suggest the use of mepolizumab also in systemic manifestations of EGPA (78-82).

References

1. LA ROCCA G, DEL FRATE G, DELVINO P *et al*.: Systemic vasculitis: one year in review 2022. *Clin Exp Rheumatol* 2022; 40(4): 673-87. https://doi.org/10.55563/clinexprheumatol/ozhc85
2. FERRO F, QUARTUCCIO L, MONTI S *et al*.: One year in review 2021: systemic vasculitis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 129): S3-12. https://doi.org/10.55563/clinexprheumatol/v1tpfo
3. PONTE C, GRAYSON PC, ROBSON JC *et al*.: 2022 American College of Rheumatology/EULAR Classification Criteria for Giant Cell Arteritis. *Arthritis Rheumatol* 2022; 74(12): 1881-9. https://doi.org/10.1002/art.42325
4. GRAYSON PC, PONTE C, SUPPIAH R *et al*.: 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. *Ann Rheum Dis* 2022; 81(12): 1654-60. https://doi.org/10.1136/ard-2022-223482
5. CAO RJ, YAO ZQ, JIAO PQ, CUI LG: Comparison of diagnostic efficacy of different classification criteria for Takayasu arteritis in Chinese patients. [Article in Chinese] *Beijing Da Xue Xue Bao Yi Xue Ban* 2022; 54(6): 1128-33. https://doi.org/10.19723/j.issn.1671-167X.2022.06.012
6. ROBSON JC, GRAYSON PC, PONTE C *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. *Ann Rheum Dis* 2022; 81(3): 315-20. https://doi.org/10.1136/annrheumdis-2021-221795
7. SUPPIAH R, ROBSON JC, GRAYSON PC *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. *Ann Rheum Dis* 2022; 81(3): 321-6. https://doi.org/10.1136/annrheumdis-2021-221796
8. GRAYSON PC, PONTE C, SUPPIAH R *et al*.: 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for Eosinophilic Granulomatosis with Polyangiitis. *Ann Rheum Dis* 2022; 81(3): 309-14. https://doi.org/10.1136/annrheumdis-2021-221794
9. PYO JY, LEE LE, PARK YB, LEE SW: Comparison of the 2022 ACR/EULAR Classification Criteria for Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Previous Criteria. *Yonsei Med J* 2023; 64(1): 11-7. https://doi.org/10.3349/ymj.2022.0435
10. BIZJAK M, EMERŠIČ N, ZAJC AVRAMOVIČ M *et al*.: High incidence of multisystem inflammatory syndrome and other autoimmune diseases after SARS-CoV-2 infection compared to COVID-19 vaccination in children and adolescents in south central Europe. *Clin Exp Rheumatol* 2022 Nov 12. https://doi.org/10.55563/clinexprheumatol/i1l2xn

11. CHRISTODOULOU M, IATRIDI F, CHALKIDIS G *et al*.: ANCA-associated vasculitis may result as a complication to both SARS-CoV-2 infection and vaccination. *Life* (Basel) 2022; 12(7): 1072. https://doi.org/10.3390/life12071072
12. NGUYEN AAK, SAMMEL AM, MOLLAN SP, SUBRAMANIAN PS, FRASER CL: Giant cell arteritis incidence during the COVID pandemic. *J Neuroophthalmol* 2022 Jul 8. https://doi.org/10.1097/WNO.0000000000001638.
13. METTLER C, JONVILLE-BERA AP, GRAND-VUILLEMIN A, TRELUYER JM, TERRIER B, CHOUCHANA L: Risk of giant cell arteritis and polymyalgia rheumatica following COVID-19 vaccination: a global pharmacovigilance study. *Rheumatology* (Oxford) 2022; 61(2): 865-7. https://doi.org/10.1093/rheumatology/keab756
14. VACCHI C, TESTONI S, VISENTINI M *et al*.: COVID-19 vaccination rate and safety profile in a multicentre Italian population affected by mixed cryoglobulinaemic vasculitis. *Clin Exp Rheumatol* 2023; 41 (4): 787-91. https://doi.org/10.55563/clinexprheumatol/ldv88a
15. VISENTINI M, GRAGNANI L, SANTINI SA *et al*.: Flares of mixed cryoglobulinaemia vasculitis after vaccination against SARS-CoV-2. *Ann Rheum Dis* 2022; 81(3): 441-3. https://doi.org/10.1136/annrheumdis-2021-221248
16. FERRI C, GRAGNANI L, RAIMONDO V *et al*.: Absent or suboptimal response to booster dose of COVID-19 vaccine in patients with autoimmune systemic diseases. *J Autoimmun* 2022; 131: 102866. https://doi.org/10.1016/j.jaut.2022.102866
17. DE MIGUEL E, SANCHEZ-COSTA JT, ESTRADA P *et al*.: Influence of the EULAR recommendations for the use of imaging in large vessel vasculitis in the diagnosis of giant cell arteritis: results of the ARTESER register. *RMD Open* 2022; 8(2): e002507. https://doi.org/10.1136/rmdopen-2022-002507
18. HEMMIG AK, GOZZOLI D, WERLEN L *et al*.: Subclinical giant cell arteritis in new onset polymyalgia rheumatica A systematic review and meta-analysis of individual patient data. *Semin Arthritis Rheum* 2022; 55: 152017. https://doi.org/10.1016/j.semarthrit.2022.152017
19. CASADEPAX-SOULET C, BENALI K, CRESTANI B *et al*.: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in polymyalgia rheumatica: an observational study. *Clin Exp Rheumatol* 2022 Dec 15. https://doi.org/10.55563/clinexprheumatol/kqyki5
20. PREARO I, DEKORSY FJ, BRENDEL M *et al*.: Diagnostic yield of axillary artery ultrasound in addition to temporal artery ultrasound for the diagnosis of giant cell arteritis. *Clin Exp Rheumatol* 2022; 40(4): 819-25. https://doi.org/10.55563/clinexprheumatol/v1bvfz
21. CAMELLINO D, PAPARO F, MORBELLI SD *et al*.: Clinical and FDG-PET/CT correlates in patients with polymyalgia rheumatica. *Clin Exp Rheumatol* 2022; 40(1): 78-85. https://doi.org/10.55563/clinexprheumatol/4r78yg
22. VAN SLEEN Y, THERKILDSEN P, NIELSEN BD *et al*.: Angiopoietin-2/-1 ratios and MMP-3 levels as an early warning sign for the presence of giant cell arteritis in patients with polymyalgia rheumatica. *Arthritis Res Ther* 2022; 24(1): 65. https://doi.org/10.1186/s13075-022-02754-5
23. WADSTRÖM K, JACOBSSON LTH, MOHAMMAD AJ *et al*.: Analyses of plasma inflammatory proteins reveal biomarkers predictive of subsequent development of giant cell arteritis: a prospective study. *Rheumatology* (Oxford) 2022 Oct 18. https://doi.org/10.1093/rheumatology/keac581
24. ESPITIA O, SCHANUS J, AGARD C *et al*.: Semi-Quantitative [^{18}F]FDG-PET/CT ROC-analysis-based cut-offs for aortitis definition in giant cell arteritis. *Int J Mol Sci* 2022; 23(24): 15528. https://doi.org/10.3390/ijms232415528
25. DASHORA HR, ROSENBLUM JS, QUINN KA *et al*.: Comparing semiquantitative and qualitative methods of vascular ^{18}F-FDG PET activity measurement in large-vessel vasculitis. *J Nucl Med* 2022; 63(2): 280-6. https://doi.org/10.2967/jnumed.121.262326
26. DE SOUZA SANTOS MP, RAMOS CD, PAIXÃO M, PIGNATON NASERI E, BARROS BERTOLO M, SACHETTO Z: ^{18}F-FDG PET/CT in late acquisition identifies sites of active disease in treated Takayasu arteritis. *J Clin Rheumatol* 2022; 28(1): 14-20. https://doi.org/10.1097/RHU.0000000000001801
27. JAMAR F, GORMSEN LC, YILDIZ H, SLART RH, VAN DER GEEST KS, GHEYSENS O: The role of PET/CT in large vessel vasculitis and related disorders: diagnosis, extent evaluation and assessment of therapy response. *Q J Nucl Med Mol Imaging* 2022; 66(3): 182-93. https://doi.org/10.23736/S1824-4785.22.03465-3
28. CLEMENTE G, DE SOUZA AW, LEÃO FILHO H *et al*.: Does [^{18}F] F-FDG-PET/MRI add metabolic information to magnetic resonance image in childhood-onset Takayasu's arteritis patients? A multicenter case series. *Adv Rheumatol* 2022; 62(1): 28. https://doi.org/10.1186/s42358-022-00260-5
29. PADOAN R, CRIMÌ F, FELICETTI M *et al*.: Fully integrated [^{18}F] FDG PET/MR in large vessel vasculitis. *Q J Nucl Med Mol Imaging* 2022; 66(3): 272-9. https://doi.org/10.23736/S1824-4785.19.03184-4
30. ZHANG N, PAN L, LIU J *et al*.: Comparison of different thoracic aortic wall characteristics for assessment of disease activity in Takayasu arteritis: a quantitative study with 3.0 T magnetic resonance imaging. *Rev Cardiovasc Med* 2022; 23(3): 92. https://doi.org/10.31083/j.rcm2303092
31. DENTEL A, CLAVEL G, SAVATOVSKY J *et al*.: Use of retinal angiography and MRI in the diagnosis of giant cell arteritis with early ophthalmic manifestations. *J Neuroophthalmol* 2022; 42(2): 218-25. https://doi.org/10.1097/WNO.0000000000001517
32. LECLER A, HAGE R, CHARBONNEAU F *et al*.: Validation of a multimodal algorithm for diagnosing giant cell arteritis with imaging. *Diagn Interv Imaging* 2022; 103(2): 103-10. https://doi.org/10.1016/j.diii.2021.09.008
33. DING J, WU D, HAN Q, ZHANG K, ZHENG Z, ZHU P: Follow-up contrast-enhanced ultrasonography of the carotid artery in patients with Takayasu arteritis: a retrospective study. *J Rheumatol* 2022; 49(11): 1242-9. https://doi.org/10.3899/jrheum.220114
34. NAKAOKA Y, ISOBE M, TAKEI S *et al*.: Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study). *Ann Rheum Dis* 2018; 77(3): 348-54. https://doi.org/10.1136/annrheumdis-2017-211878
35. LIAO H, DU J, LI T, PAN L: Tocilizumab for faster and safer remission of Takayasu's arteritis. *Ther Adv Chronic Dis* 2022; 13: 20406223221131715. https://doi.org/10.1177/20406223221131715
36. ADRIAWAN IR, ATSCHEKZEI F, DITTRICH-BREIHOLZ O *et al*.: Novel aspects of regulatory T cell dysfunction as a therapeutic target in giant cell arteritis. *Ann Rheum Dis* 2022; 81(1): 124-31. https://doi.org/10.1136/annrheumdis-2021-220955
37. ABE N, KONO M, KONO M *et al*.: Cytokine and chemokine multiplex analysis-based exploration for potential treatment and prognostic prediction in large-vessel vasculitis: a preliminary observational study. *Front Immunol* 2022; 13: 1066916. https://doi.org/10.3389/fimmu.2022.1066916
38. RATHORE U, THAKARE DR, PATRO P, AGARWAL V, SHARMA A, MISRA DP: A systematic review of clinical and preclinical evidences for Janus kinase inhibitors in large vessel vasculitis. *Clin Rheumatol* 2022; 41(1): 33-44. https://doi.org/10.1007/s10067-021-05973-4
39. VIEIRA M, RÉGNIER P, MACIEJEWSKI-DUVAL A *et al*.: Interferon signature in giant cell arteritis aortitis. *J Autoimmun* 2022; 127: 102796. https://doi.org/10.1016/j.jaut.2022.102796
40. WU S, KONG X, SUN Y *et al*.: FABP3 overexpression promotes vascular fibrosis in Takayasu's arteritis by enhancing fatty acid oxidation in aorta adventitial fibroblasts. *Rheumatology* (Oxford) 2022; 61(7): 3071-81. https://doi.org/10.1093/rheumatology/keab788
41. FAN L, CHEN J, PAN L *et al*.: Alterations of gut microbiome, metabolome, and lipidome in Takayasu arteritis. *Arthritis Rheumatol* 2023; 75(2): 266-78. https://doi.org/10.1002/art.42331
42. GUO Q, GAO J, DUAN J, HOU R, LU TH, ZHANG L: Secular trends in cryoglobulinemia mortality in the USA in the era of direct-acting antivirals. *Arthritis Res Ther* 2022; 24(1): 41. https://doi.org/10.1186/s13075-022-02720-1
43. BOLETO G, GHILLANI-DALBIN P, MUSSET L *et al*.: Cryoglobulinemia after the era of chronic hepatitis C infection. *Semin Arthritis Rheum* 2020; 50(4): 695-700. https://doi.org/10.1016/j.semarthrit.2020.05.004
44. GALLI M, ORENI L, SACCARDO F *et al*.: HCV-unrelated cryoglobulinaemic vasculitis: the results of a prospective observational study by the Italian Group for the Study of Cryoglobulinaemias (GISC). *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): S67-76.
45. STERGIOU IE, BAKASIS AD, GIANNOULI S, VOULGARELIS M: Biomarkers of lymphoma in Sjögren's syndrome: what's the latest?

Expert Rev Clin Immunol 2022; 18(11): 1155-71. https://doi.org/10.1080/1744666X.2022.2123794
46. CHATZIS LG, STERGIOU IE, GOULES AV *et al*.: Clinical picture, outcome and predictive factors of lymphoma in primary Sjögren's syndrome: results from a harmonized dataset (1981-2021). *Rheumatology* (Oxford) 2022; 61(9): 3576-85. https://doi.org/10.1093/rheumatology/keab939
47 ROUBERTOU Y, MAINBOURG S, HOT A *et al*.: Cryoglobulinemia in systemic lupus erythematosus: a retrospective study of 213 patients. *Arthritis Res Ther* 2022; 24(1): 167. https://doi.org/10.1186/s13075-022-02857-z
48. QUARTUCCIO L, ISOLA M, CORAZZA L *et al*.: Validation of the classification criteria for cryoglobulinaemic vasculitis. *Rheumatology* (Oxford) 2014; 53(12): 2209-13. https://doi.org/10.1093/rheumatology/keu271
49. STOYANOV A, TOONG C, KONG Y, CHEN R, URRIOLA N: Serum protein electrophoresis and rheumatoid factor analysis is an effective screening strategy for cryoglobulinaemia. *Pathology* 2023; 55(3): 391-6. https://doi.org/10.1016/j.pathol.2022.09.004
50. VISENTINI M, QUARTUCCIO L, DEL PADRE M *et al*.: Late relapses of hepatitis C virus-cured mixed cryoglobulinaemia associated with infection or cancer. *Rheumatology* (Oxford) 2018; 57(10): 1870-1. https://doi.org/10.1093/rheumatology/key157
51. BONACCI M, LENS S, MARIÑO Z *et al*.: Long-term outcomes of patients with HCV-associated cryoglobulinemic vasculitis after virologic cure. *Gastroenterology* 2018; 155(2): 311-315.e6. https://doi.org/10.1053/j.gastro.2018.04.024
52. QUARTUCCIO L, BORTOLUZZI A, SCIRÈ CA *et al*.: Management of mixed cryoglobulinemia with rituximab: evidence and consensus-based recommendations from the Italian Study Group of Cryoglobulinemia (GISC). *Clin Rheumatol* 2023; 42(2): 359-70. https://doi.org/10.1007/s10067-022-06391-w
53. GALLI M, MONTI G, MARSON P *et al*.: Recommendations for managing the manifestations of severe and life-threatening mixed cryoglobulinemia syndrome. *Autoimmun Rev* 2019; 18(8): 778-85. https://doi.org/10.1016/j.autrev.2019.06.008
54. FENOGLIO R, SCIASCIA S, ROSSI D, NARETTO C, ALPA M, ROCCATELLO D: Non HCV-related mixed cryoglobulinemic vasculitis with biopsy-proven renal involvement: the effects of rituximab. *Front Med* (Lausanne) 2022; 9: 819320. https://doi.org/10.3389/fmed.2022.819320
55. POUCHELON C, VISENTINI M, EMMI G *et al*.: Management of nonviral mixed cryoglobulinemia vasculitis refractory to rituximab: Data from a European collaborative study and review of the literature. *Autoimmun Rev* 2022; 21(4): 103034. https://doi.org/10.1016/j.autrev.2022.103034
56. GRAGNANI L, LORINI S, MARRI S *et al*.: B-cell activating factor (BAFF), BAFF promoter and BAFF receptor allelic variants in hepatitis C virus related cryoglobulinemic vasculitis and Non-Hodgkin's Lymphoma. *Hematol Oncol* 2022; 40(4): 658-66. https://doi.org/10.1002/hon.3008
57. LIU P, WU J, SUN D *et al*.: Proteomic profiling of cryoglobulinemia. *Front Immunol* 2022; 13: 855513. https://doi.org/10.3389/fimmu.2022.855513
58. WEISEL FJ, MULLETT SJ, ELSNER RA *et al*.: Germinal center B cells selectively oxidize fatty acids for energy while conducting minimal glycolysis. *Nat Immunol* 2020; 21(3): 331-42. https://doi.org/10.1038/s41590-020-0598-4
59. REDONDO-RODRIGUEZ R, MENA-VÁZQUEZ N, CABEZAS-LUCENA AM, MANRIQUE-ARIJA S, MUCIENTES A, FERNÁNDEZ-NEBRO A: Systematic review and metaanalysis of worldwide incidence and prevalence of antineutrophil cytoplasmic antibody (ANCA) associated vasculitis. *J Clin Med* 2022; 11(9): 2573. https://doi.org/10.3390/jcm11092573
60. GUILLEVIN L, TERRIER B: Optimising ANCA-associated vasculitis management and infectious risks during the COVID-19 pandemic. *Clin Exp Rheumatol* 2022; 40(4): 688-90. https://doi.org/10.55563/clinexprheumatol/ixatxh
61. BELLOS I, BOLETIS I, LIONAKI S: A meta-analysis of the safety and efficacy of maintenance therapies for antineutrophil cytoplasmic antibody small-vessel vasculitis. *Kidney Int Rep* 2022; 7(5): 1074-1083. https://doi.org/10.1016/j.ekir.2022.02.020
62. STONE JH, MERKEL PA, SPIERA R *et al*.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363(3): 221-32. https://doi.org/10.1056/NEJMoa0909905
63. PUÉCHAL X, IUDICI M, PERRODEAU E *et al*.: Rituximab vs cyclophosphamide induction therapy for patients with granulomatosis with polyangiitis. *JAMA Netw Open* 2022; 5(11): e2243799. https://doi.org/10.1001/jamanetworkopen.2022.43799
64. TERRIER B, DARBON R, DUREL CA *et al*.: French recommendations for the management of systemic necrotizing vasculitides (polyarteritis nodosa and ANCA-associated vasculitides) [published correction appears in *Orphanet J Rare Dis* 2021; 16(1): 155]. *Orphanet J Rare Dis* 2020; 15 (Suppl 2): 351. https://doi.org/10.1186/s13023-020-01621-
65. ROCCATELLO D, SCIASCIA S, MURGIA S *et al*.: Treating patients with ANCA-associated vasculitis and very severe renal injury with an intensified b cell depletion therapy: comparison with a control cohort receiving a conventional therapy. *Front Immunol* 2022; 13: 777134. https://doi.org/10.3389/fimmu.2022.777134
66 THIETART S, KARRAS A, AUGUSTO JF *et al*.: Evaluation of rituximab for induction and maintenance therapy in patients 75 years and older with antineutrophil cytoplasmic antibody-associated vasculitis. *JAMA Netw Open* 2022; 5(7): e2220925. https://doi.org/10.1001/jamanetworkopen.2022.20925
67. XU T, CHEN Z, JIANG M *et al*.: Association between different infection profiles and one-year outcomes in ANCA-associated vasculitis: a retrospective study with monthly infection screening. *RMD Open* 2022; 8(2): e002424. https://doi.org/10.1136/rmdopen-2022-002424
68. HARADA M, YAMAGUCHI A, SONODA K *et al*.: Comparison of the factors associated with the short-term prognosis between elderly and non-elderly patients with anti-neutrophil cytoplasmic antibody-associated vasculitis: a retrospective observational study. *Clin Exp Rheumatol* 2022; 40(4): 705-13. https://doi.org/10.55563/clinexprheumatol/3qb95d
69. WALSH M, MERKEL PA, PEH CA *et al*.: Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials* 2013; 14: 73. https://doi.org/10.1186/1745-6215-14-73
70. WALSH M, COLLISTER D, ZENG L *et al*.: The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. *BMJ* 2022; 376: e064604. https://doi.org/10.1136/bmj-2021-064604
71. ZENG L, WALSH M, GUYATT GH *et al*.: Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis: a clinical practice guideline. *BMJ* 2022; 376: e064597. https://doi.org/10.1136/bmj-2021-064597
72. WALSH M, CHAUDHRY A, JAYNE D: Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). *Ann Rheum Dis* 2008; 67(9): 1322-7. https://doi.org/10.1136/ard.2007.081661
73. GOPALUNI S, SMITH R, GOYMER D *et al*.: Alemtuzumab for refractory primary systemic vasculitis-a randomised controlled dose ranging clinical trial of efficacy and safety (ALEVIATE). *Arthritis Res Ther* 2022; 24(1): 81. https://doi.org/10.1186/s13075-022-02761-6
74. GABILAN C, PFIRMANN P, RIBES D *et al*.: Avacopan as first-line treatment in antineutrophil cytoplasmic antibody-associated vasculitis: a steroid-sparing option. *Kidney Int Rep* 2022; 7(5): 1115-8. https://doi.org/10.1016/j.ekir.2022.01.1065
75. JAYNE DRW, MERKEL PA, SCHALL TJ, BEKKER P: ADVOCATE Study Group. Avacopan for thetTreatment of ANCA-associated vasculitis. *N Engl J Med* 2021; 384(7): 599-609. https://doi.org/10.1016/j.ekir.2022.01.1065
76. HARIGAI M, KANAME S, TAMURA N, DOBASHI H, KUBONO S, YOSHIDA T: Efficacy and safety of avacopan in Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis: A subanalysis of a randomized Phase 3 study. *Mod Rheumatol* 2023; 33(2): 338-45. https://doi.org/10.1093/mr/roac037
77. CHUNG SA, LANGFORD CA, MAZ M *et al*.: 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Care Res* (Hoboken) 2021; 73(8): 1088-105. https://doi.org/10.1002/acr.24634
78. BETTIOL A, URBAN ML, DAGNA L *et al*.: Mepolizumab for eosinophilic granulomatosis with polyangiitis: a European multicenter observational study. *Arthritis Rheumatol* 2022; 74(2): 295-306.

https://doi.org/10.1002/art.41943
79. NAKAMURA Y, FUKUTOMI Y, SEKIYA K *et al*.: Low-dose mepolizumab is effective as an add-on therapy for treating long-lasting peripheral neuropathy in patients with eosinophilic granulomatosis with polyangiitis. *Mod Rheumatol* 2022; 32(2): 387-95. https://doi.org/10.1093/mr/roab005
80. UENO M, MIYAGAWA I, ARITOMI T *et al*.: Safety and effectiveness of mepolizumab therapy in remission induction therapy for eosinophilic granulomatosis with polyangiitis: a retrospective study. *Arthritis Res Ther* 2022; 24(1): 159. https://doi.org/10.1186/s13075-022-02845-3
81. BELLO F, EMMI G, TAMBURINI C *et al*.: Eosinophilic granulomatosis with polyangiitis-related myocarditis during mepolizumab therapy reveals a Th1/Th17-mediated vasculitic response. *Clin Exp Rheumato* 2022; 40(4): 863-4. https://doi.org/10.55563/clinexprheumatol/envpc5
82. BERTI A, ATZENI F, DAGNA L *et al*.: Targeting the interleukin-5 pathway in EGPA: evidence, uncertainties and opportunities. *Ann Rheum Dis* 2023; 82(2): 164-8. https://doi.org/10.1136/ard-2022-223044