Editorial

New therapeutics for ANCA-associated vasculitis: 10 years devoted to lessen toxicity

G.M. Rossi[1,2], F. Peyronel[1,2], P. Fenaroli[1,2], F. Maritati[3], A. Vaglio[4,5]

[1]U.O. Nefrologia, Azienda Ospedaliero-Universitaria di Parma;
[2]Dipartimento di Medicina e Chirurgia, Università di Parma;
[3]Nephrology, Dialysis and Kidney Transplant Unit, Ospedali Riuniti, Ancona;
[4]Department of Biomedical, Experimental and Clinical Sciences, University of Firenze;
[5]Nephrology and Dialysis Unit, Meyer Children's Hospital, Firenze, Italy.

Giovanni Maria Rossi, MD
Francesco Peyronel, MD
Paride Fenaroli, MD
Federica Maritati, MD, PhD
Augusto Vaglio, MD, PhD

Please address correspondence to:
Giovanni Maria Rossi,
U.O. Nefrologia, Azienda Ospedaliero-Universitaria di Parma,
Via Gramsci 14,
43126 Parma, Italy.
E-mail:
giovannimariarossi463@gmail.com

Received on March 26, 2020; accepted in revised form on April 14, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 124): S18-S22.

Key words: ANCA, vasculitis, cyclophosphamide, rituximab, toxicity

Competing interests: none declared.

ANCA-associated vasculitis (AAV) embraces a spectrum of fascinating diseases which, although phenotypically different, are sensitive to common treatment approaches. In the past decades, the knowledge of the pathogenesis and management of AAV has been revolutionised (1) and, despite their rarity, we now have solid evidence-based data to treat them using rational and standardised regimens. Several issues, however, remain.

Glucocorticoid monotherapy was the first treatment for vasculitis. When Fauci *et al*. proved the tremendous efficacy of cyclophosphamide on top of glucocorticoids in inducing remission of severe necrotising vasculitis in 1979, the devastating side-effects of the latter were already considered a serious problem that contributed to disease burden: as they wrote, "the daily use of high-dose corticosteroids in some patients often induces clinical deterioration of greater severity than the underlying disease" (2). The toxicity profile of cyclophosphamide, of course, was also considerable (3). The ensuing decades of clinical research in AAV were devoted to finding the minimum effective dose of these agents (cyclophosphamide and glucocorticoids) in order to minimise toxicity (4) while retaining efficacy, a path which was shared with clinical trials in lupus nephritis (5-8). The general approach was (i) to decrease the cumulative dose of cyclophosphamide needed to achieve remission (*e.g.*, by switching from an oral to an intravenous pulsed regimen) (4), and (ii) identify steroid-sparing drugs (9-11) and incorporate them in remission-maintenance regimens in order to taper glucocorticoids more rapidly while at the same time reduce the risk of relapse. Altogether, these efforts led to a progressive increase in overall survival of patients with AAV (12). In the last decade, this approach was taken several steps further thanks to the advent of new immunosuppressive drugs (particularly monoclonal antibodies) with a targeted and therefore narrower immunosuppressive action, driven by key discoveries in AAV mechanisms of disease (13, 14).

Despite toxicity, cyclophosphamide remained the mainstay of therapy until the early 2000s, when the first anecdotal reports on the efficacy of rituximab were published (15). As with cyclophosphamide, rituximab was imported from the onco-haematological *armamentarium* and already known to be efficacious in rheumatoid arthritis (16). However, it was not until 2010 that two large randomised controlled trials (RCTs) [RAVE (17) and RITUXVAS (18)] proved the non-inferiority of rituximab to cyclophosphamide for remission-induction in AAVs (patients with eosinophilic granulomatosis with polyangiitis [EGPA] were not included in either trial). The two trials differed in design, in that a standard cyclophosphamide-based regimen was compared with rituximab plus two cyclophosphamide pulses in RITUXVAS, whereas in RAVE cyclophosphamide was compared to a rituximab-only regimen. Notably, glucocorticoids were withdrawn by month 5 in remitting patients in RAVE, while they were tapered to 5 mg/day (of prednisone) in RITUXVAS. Despite minimising or substituting altogether cyclophosphamide, the rate and severity of adverse events in the rituximab arms did not change as compared with cyclophosphamide-based regimens. In the RAVE extended follow-up, however, a reduction in the proportion of patients who had developed pneumonia or leukopenia by month 18 was detected (19). Another

study aiming at cyclophosphamide avoidance in the induction phase, the MYCYC trial, compared mycophenolate mofetil and pulsed cyclophosphamide, demonstrating that the former was not inferior but resulted in a higher relapse rate (20). Mycophenolate, however, was less effective than azathioprine in preventing relapses in the IMPROVE (11) trial, therefore its role in AAV treatment is quite controversial. Collectively, these findings would lead us to use alternatives to cyclophosphamide for induction, but it must be kept in mind that cyclophosphamide is an incredibly effective drug, that often produces durable remission, and that using it wisely can help minimise its toxicity, without a significant increase in severe side-effects (21).

With regards to remission-maintenance, two further RCTs [MAINRITSAN (22) and MAINRITSAN2 (23)] explored the role of rituximab. MAINRITSAN investigators found rituximab (6-monthly infusions) to be superior to azathioprine in terms of reduction of major relapses (HR for relapse in those taking azathioprine 6.61, 95% CI [1.56, 27.96]) and also with respect to secondary outcomes such as physical abilities and quality of life (24). MAINRITSAN2 adopted a different approach in that it compared fixed-schedule (6-monthly infusions, as in MAINRITSAN) with individually-tailored rituximab infusions, *i.e.* rituximab infusions upon peripheral B-cell repopulation or reappearance of ANCA, both being monitored every three months. The authors found that the two regimens were equally effective but that the individually-tailored approach resulted in significantly fewer rituximab infusions. A third RCT, RITAZAREM (clinicaltrials.gov #NCT01697267), comparing azathioprine to rituximab as remission-maintenance agents after a rituximab-based induction regimen for relapsing disease is currently underway. Finally, a number of other observational studies or RCTs are exploring the best way to use rituximab as a maintenance agent, some extending the maintenance phase (such as MAINRITSAN3, clinicaltrials.gov #NCT02433522), some using repeat low-dose infusions especially in patients with limited/grumbling granulomatosis with polyangiitis (GPA) (25). Rituximab can also be used for maintenance after an aggressive cyclophosphamide-based induction, especially in patients with multiple relapses (26). In sum, we have at hand quite a safe and effective strategy for remission maintenance using reiterated rituximab infusions. But again, some questions are left unanswered, such as the duration of treatment and its long-term toxicity.

Efforts were then put into minimising exposure to glucocorticoids in order to reduce their well-documented toxicity (27, 28). Indeed, in all studies mentioned so far, patients were exposed to similar overall doses of glucocorticoids. Decreasing glucocorticoid doses needs to be weighed against the increased risk of relapse. Indeed, longer exposure to glucocorticoids was found to be associated with lower relapse rates: in a meta-analysis of therapeutic trials in AAV, the proportion of patients with a relapse was 14% in those taking glucocorticoids at study end as compared with 43% in those not receiving them (29). The REMAIN (30) trial, specifically designed to investigate the rate of relapse in patients receiving the same remission-maintenance regimen (azathioprine plus prednisone) until 48 months or 24 months since diagnosis, showed that the shorter course was associated with an odds ratio of 2.57 (95% CI [1.16, 5.68]) of having a relapse. So it wasn't without concern that CLEAR investigators explored the efficacy of a C5a receptor inhibitor (avacopan) as a substitute for glucocorticoids or as an add-on to low-dose glucocorticoids; in both instances they found avacopan to be effective in replacing high-dose glucocorticoids to induce remission in AAV (31). Patients with severe end-organ damage were excluded, as this was a phase II exploratory study, but results were promising: as expected, typical glucocorticoid-related adverse events (diabetes, psychiatric disorders, weight gain) had a lower incidence in the avacopan group. A phase III study of avacopan is underway (clinicaltrials.gov #NCT02994927). In fact, a reduced-dose glucocorticoid regimen was tested in patients with end-organ damage in the recently published PEXIVAS (32) trial. The study sought to determine whether patients with severe renal impairment and/or pulmonary haemorrhage at disease onset benefited from the addition of plasmapheresis to a standard remission-induction regimen (as was suggested by the MEPEX (33) trial) either with a standard or reduced-dose glucocorticoid regimen. While the study showed that plasmapheresis did not add any benefit in terms of risk reduction of hard outcomes (death or end-stage renal disease), the reduced-dose glucocorticoid arm achieved the same efficacy as the standard-dose arm with fewer serious infections. Finally, a single group performed two interesting retrospective studies of (i) a remission-induction regimen based on the combination of low-dose cyclophosphamide plus rituximab with low-dose glucocorticoids (34, 35), and (ii) two different remission-induction regimens with low-dose cyclophosphamide plus rituximab and minimal glucocorticoids followed by a glucocorticoid-free maintenance regimen (36). The authors found low-dose glucocorticoids and early glucocorticoid withdrawal to be as effective as standard regimens, and the combination of low dose cyclophosphamide with rituximab to be potentially superior to current standard of care. These studies are courageous and far-sighted, and shed light on the possibility of almost avoiding glucocorticoids; however, despite propensity-matching with cases from large EUVAS RCTs, they suffer from the inherent limits of retrospective analysis. The question is open, but the way is being paved.

The results of the trials aimed at reducing cyclophosphamide or glucocorticoid exposure in AAV are summarised in Table I.

Clinical trials in AAV mainly included patients with GPA and microscopic polyangiitis (MPA), while excluded those with EGPA (formerly Churg-Strauss), taking into account the differences between EGPA and GPA/MPA in terms of pathogenesis, clinical manifestations (and specifically the rarer occurrence of renal involvement/severe end-organ damage in EGPA) and response to treat-

Table I. Cyclophoshamide and glucocorticoid dosing for ANCA-associated vasculitis in selected clinical trials published in 2010-2020.

Trial name/Authors & characteristics	Induction	Maintenance	Overall CyC exposure	Overall GC exposure (equivalent PDN dose)
RAVE (17) Year: 2010 Design: double blinded RCT Analysed therapeutic phase: induction	**Both arms**: MEP pulses 1g x3, then oral PDN starting with 1mg/kg/d (max 80 mg) for 5 months; **CyC arm**: oral CyC 2mg/kg/d for 3 to 6 months plus placebo RTX **RTX arm**: 375mg/m2 x4 plus placebo Cyc	**Cyc arm**: AZA 2mg/kg/d starting at 3 or 6 months **RTX arm**: placebo AZA starting at 3 or 6 months	Remission by 3 months: 13.5 g Remission by 6 months: 27 g	3.75 g
RITUXVAS (18) Year: 2010 Design: open label RCT Analysed therapeutic phase: induction	**Both arms:** MEP pulse 1g, then oral PDN starting with 1mg/kg/d (max 60mg) for 18-24 months **CyC arm**: 15mg/kg pulses: fortnightly for the first 3, then triweekly (min 3 max 6 months) **RTX arm**: Cyc 15mg/kg x2 pulses and RTX 375mg/m2 x4	**CyC arm**: AZA 2 mg/kg/d (max 200mg) **RTX arm**: PDN	Remission by 3 months: 5.25 g (5 infusions) Remission by 6 months: 10.5 g (10 infusions)	18 months: 6.36 g (plus allowed pulses prior to enrolment) 24 months: 7.2 g (plus allowed pulses prior to enrolment)
MAINRITSAN1 (22) Year: 2014 Design: open label RCT Analysed therapeutic phase: maintenance	MEP 0.5-1g x3 pulses, then oral PDN with same dosing and taper as in RITUXVAS, then CyC 0.6g/m2 pulses fortnightly for the first 3, then 0.7mg/m2 triweekly (min 3 max 6 months)	**RTX arm**: RTX 500mg x2 then at 6, 12, and 18 months **AZA arm**: AZA 2mg/kg for 12 months, then 1.5 mg/kg for 6 months then 1 mg/kg for 4 months	Remission by 3 months: 5.54 g (5 infusions) Remission by 6 months: 11.6 g (10 infusions)	18 months: 5.1 g plus 1.875-3.75 g (= MEP 0.5-1 x3 pulses) 24 months: 5.95 g plus 1.875-3.75 g (= MEP 0.5-1 x 3 pulses)
CLEAR (31) Year: 2017 Design: double blinded RCT Analysed therapeutic phase: maintenance	CyC 15mg/kg x5 pulses (max 1.2g per pulse) or RTX 375mg/m2 x4 **Avacopan plus PDN arm**: oral PDN starting at 60mg/d then taper to zero in 5 months **Avacopan plus low-dose PDN**: oral PDN starting at 20mg/d then taper to zero in 4 months **Avacopan only arm**: no PDN	AZA 2mg/kg/d starting at 3 months for those who received a CyC-based induction	5.25 g (5 infusions)	**Avacopan plus PDN arm**: 2.45 g **Avacopan plus low-dose PDN**: 0.805 g
REMAIN (39) Year: 2017 Design: open label RCT Analysed therapeutic phase: maintenance	CyC and prednisone for at least 3 months	**Continuation arm**: AZA and PDN for another 24-30 months after 18-24 months since disease onset **Withdrawal arm**: AZA and PDN withdrawal for 0-6 months after 18-24 since disease onset	Same as CyC arm in RITUXVAS	**Continuation arm**: same as the 24-month PDN course in RITUXVAS plus 1.6-1.785 g **Withdrawal arm**: same as the 24-month PDN course in RITUXVAS
McAdoo *et al*. (35) Year: 2018 Design: retrospective Analysed therapeutic phase: induction	RTX 1g x 2 and CyC 10mg/kg x2 (max 750mg per pulse) then CyC 500mg x4 pulses and PDN 1mg/kg/d (max 60mg)	AZA 1-2 mg/kg/d or MMF 1-2 g/d starting at 3 months	3.4 g	4.2 g in the first 6 months, dosing in the following months at clinician's discretion
Pepper *et al*. (36) Year: 2018 Design: retrospective Analysed therapeutic phase: maintenance	**Group 1**: RTX 1g x2 and CyC 500-750mg x6 fortnightly pulses and MEP 0.25-0.5g x2 pulses then oral PDN 0.5 mg/kg (max 30mg) for 5 days **Group 2**: RTX 1g x2 and CyC 10mg/kg x2 pulses (max 750mg) then CyC 500mg x4 pulses, and PDN 60mg/d for 1 week then PDN 40mg/d for 1 week then stop	AZA 1-2 mg/kg/d starting at 3 months	**Group 1**: 3-4.5 g **Group 2**: 3.4 g	**Group 1**: 0.65-1.15 g **Group 2**: 0.735 g
MAINRITSAN2 (23) Year: 2018 Design: open label RCT Analysed therapeutic phase: maintenance	CyC or RTX or MTX (investigator's choice)	**RTX individually-tailored arm**: RTX 500mg x2 then at ANCA reappearance/B cell repopulation (checked quarterly) **RTX fixed-schedule arm**: RTX 500mg x2 then at 6, 12, and 18 months	Variable	Same as MAINRITSAN1
MYCYC (20) Year: 2019 Design: open label RCT Analysed therapeutic phase: induction	**MMF arm**: MMF 2-3 g/day and standard-dose GC **CYC arm**: CYC pulses (12.5-15 mg/kg every 2–3 weeks), same as RITUXVAS	**AZA** 2 mg/kg/day	**CYC arm**: Remission by 3 months 5.25 g (5 infusions) Remission by 6 months 10.5 g (10 infusions)	Same as RITUXVAS (approximately)
PEXIVAS (32) Year: 2020 Design: double blinded RCT Analysed therapeutic phase: induction	CyC or RTX plus standard-dose GC with or without PEX CyC or RTX plus low-dose GC with or without PEX		**MMF arm**: no CYC Same as RITUXVAS	Standard-dose GC: same as RITUXVAS Low-dose GC: 55% of standard-dose GC in RITUXVAS

For weight-based dosing, a 70-kg person with 1.73 m^2 body-surface area and normal renal function was chosen as example.
CyC: cyclophosphamide; GC: glucocorticoids; PDN: prednisone; MEP: methylprednisolone; RTX: rituximab; MMF: mycophenolate mofetil; MTX: methotrexate; PEX: plasma exchange.

ment. However, therapeutic advances in the fields of GPA and MPA were often incorporated into the management of patients with severe, "vasculitic" forms of EGPA [and particularly ANCA-positive EGPA (37, 38)]. Few prospective RCTs of remission-induction regimens specifically addressed patients with EGPA (39-41), while only one RCT of a remission-maintenance regimen was specifically conducted in patients with EGPA (42). Thus, maintenance regimens for EGPA have been historically translated into clinical practice from evidence on GPA/MPA and/or based on large retrospective cohorts of EGPA patients (43).

Paradigm shifts are ongoing in EGPA therapeutics, too. Mepolizumab (on top of prednisone), an anti-IL5 agent, was found to induce remission in roughly half the patients with EGPA in the setting of a large RCT (44). Rituximab was used successfully in small retrospective studies (45-48), and is being tested in RCTs such as the REOVAS, exploring its role for induction (clinicaltrials.gov #NCT02807103), and the MAINRITSEG (clinicaltrials.gov #NCT0316447), testing it for remission-maintenance. The accruing evidence of two distinct etiologies for ANCA-positive/vasculitic EGPA and upper respiratory tract-limited EGPA (49) supports the use of more aggressive immunosuppressive therapy in the former. Real-life experiences with mepolizumab and rituximab, however, were less satisfying: in a retrospective study, patients with EGPA treated with conventional immunosuppressants (methotrexate, azathioprine, leflunomide) who had similar entry criteria to those of patients enrolled in the aforementioned rituximab and mepolizumab trials, were found to have slightly higher remission rates than the latter (50). Overall, however, current evidence supports the use of mepolizumab in the subset of patients with difficult-to-control asthma or ear-nose-throat manifestations with relapsing or refractory, non-severe EGPA (51). Sequential induction/maintenance therapy with rituximab followed by mepolizumab is a rational option that needs to be tested.

Advances in ANCA therapeutics have led to a tremendous increase in overall survival. Cyclophosphamide and glucocorticoids have been the cornerstones of therapy for more than 40 years. While RCTs showed that decreasing the overall exposure to cyclophosphamide or substituting cyclophosphamide with rituximab lessens toxicity while retaining efficacy, attempts at significantly reducing glucocorticoids have thus far been unsatisfying, the only promising exception being the reduced-dose glucocorticoid regimen in PEXIVAS. Local experience of combined rituximab-low-dose cyclophosphamide and low-dose glucocorticoids (and even a glucocorticoid-free maintenance regimen) from a respected vasculitis tertiary care centre is encouraging, but needs confirmation in large RCTs. Insights into pathogenetic mechanisms and genetic background of AAVs have led to trials targeting the complement cascade in GPA/MPA and IL-5 in EGPA, hopefully leading to glucocorticoid-free regimens. While severe forms of AAVs (*i.e.*, acute kidney injury with need for renal replacement therapy at onset, severe pulmonary haemorrhage, severe central/peripheral nervous system involvement) will likely still need the older and heavier weaponry for quite a while, the next ten years might finally see the day when disease- and patient-tailored therapeutics finally substitute the toxic broad immunosuppression offered by cyclophosphamide and glucocorticoids.

References

1. EMMI G, SALVARANI C, PRISCO D, JAYNE DRW, VAGLIO A: Highlights of the 2nd EUVAS Vasculitis Course. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S3-11.
2. FAUCI AS, KATZ P, HAYNES BF, WOLFF SM: Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *N Engl J Med* 1979; 301: 235-8.
3. JUNG M, BARRA L: Rate of infections in severe necrotising vasculitis patients treated with cyclophosphamide induction therapy: a meta-analysis. *Clin Exp Rheumatol* 2018; 36 (Suppl. 111): S129-34.
4. DE GROOT K, HARPER L, JAYNE DR *et al.*: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670-80.
5. BOUMPAS DT, AUSTIN HA, 3RD, VAUGHN EM *et al.*: Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741-5.
6. GOURLEY MF, AUSTIN HA, 3RD, SCOTT D *et al.*: Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. *Ann Intern Med* 1996; 125: 549-57.
7. ILLEI GG, AUSTIN HA, CRANE M *et al.*: Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves long-term renal outcome without adding toxicity in patients with lupus nephritis. *Ann Intern Med* 2001; 135: 248-57.
8. HOUSSIAU FA, VASCONCELOS C, D'CRUZ D *et al.*: Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46: 2121-31.
9. JAYNE D, RASMUSSEN N, ANDRASSY K *et al.*: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; 349: 36-44.
10. PAGNOUX C, MAHR A, HAMIDOU MA *et al.*: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359: 2790-803.
11. HIEMSTRA TF, WALSH M, MAHR A *et al.*: Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; 304: 2381-8.
12. HILHORST M, WILDE B, VAN PAASSEN P *et al.*: Improved outcome in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis: a 30-year follow-up study. *Nephrol Dial Transplant* 2013; 28: 373-9.
13. CHARLES JENNETTE J, XIAO H, HU P: Complement in ANCA-associated vasculitis. *Semin Nephrol* 2013; 33: 557-64.
14. ROUFOSSE F: Targeting the interleukin-5 pathway for treatment of eosinophilic conditions other than asthma. *Front Med* (Lausanne) 2018; 5: 49.
15. SPECKS U, FERVENZA FC, MCDONALD TJ, HOGAN MC: Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. *Arthritis Rheum* 2001; 44: 2836-40.
16. EDWARDS JC, CAMBRIDGE G: Sustained improvement in rheumatoid arthritis following a protocol designed to deplete B lymphocytes. *Rheumatology* (Oxford) 2001; 40: 205-11.
17. STONE JH, MERKEL PA, SPIERA R *et al.*: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221-32.
18. JONES RB, TERVAERT JW, HAUSER T *et al.*: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20.
19. SPECKS U, MERKEL PA, SEO P *et al.*: Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med* 2013; 369: 417-27.
20. JONES RB, HIEMSTRA TF, BALLARIN J *et al.*: Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-asso-

ciated vasculitis: a randomised, non-inferiority trial. *Ann Rheum Dis* 2019; 78: 399-405.
21. CALATRONI M, BUZIO C, VAGLIO A: The evolving paradigm of cancer risk related to cyclophosphamide therapy in granulomatosis with polyangiitis. *Rheumatology* (Oxford) 2015; 54: 1339-41.
22. GUILLEVIN L, PAGNOUX C, KARRAS A *et al*.: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 2014; 371: 1771-80.
23. CHARLES P, TERRIER B, PERRODEAU E *et al*.: Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis* 2018; 77: 1143-9.
24. PUGNET G, PAGNOUX C, TERRIER B *et al*.: Rituximab versus azathioprine for ANCA-associated vasculitis maintenance therapy: impact on global disability and health-related quality of life. *Clin Exp Rheumatol* 2016; 34 (Suppl. 97): S54-9.
25. PUECHAL X, IUDICI M, CALICH AL *et al*.: Rituximab for induction and maintenance therapy of granulomatosis with polyangiitis: a single-centre cohort study on 114 patients. *Rheumatology* (Oxford) 2019; 58: 401-9.
26. LIONAKI S, FRAGOULIS GE, VENETSANOPOULOU A, VLACHOYIANNOPOULOS P, BOLETIS JN, TZIOUFAS AG: Cyclophosphamide followed by rituximab for aggressive multiple-relapsing antineutrophil cytoplasmic antibody-associated vasculitis. *Clin Exp Rheumatol* 2017; 35 (Suppl. 103): S155-64.
27. HUSCHER D, THIELE K, GROMNICA-IHLE E *et al*.: Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009; 68: 1119-24.
28. CURTIS JR, WESTFALL AO, ALLISON J *et al*.: Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006; 55: 420-6.
29. WALSH M, MERKEL PA, MAHR A, JAYNE D: Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis. *Arthritis Care Res* (Hoboken) 2010; 62: 1166-73.
30. KARRAS A, PAGNOUX C, HAUBITZ M *et al*.: Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis* 2017; 76: 1662-8.
31. JAYNE DRW, BRUCHFELD AN, HARPER L *et al*.: Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis. *J Am Soc Nephrol* 2017; 28: 2756-67.
32. WALSH M, MERKEL PA, PEH CA *et al*.: Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. *N Engl J Med* 2020; 382: 622-31.
33. JAYNE DR, GASKIN G, RASMUSSEN N *et al*.: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; 18: 2180-8.
34. MANSFIELD N, HAMOUR S, HABIB AM *et al*.: Prolonged disease-free remission following rituximab and low-dose cyclophosphamide therapy for renal ANCA-associated vasculitis. *Nephrol Dial Transplant* 2011; 26: 3280-6.
35. MCADOO SP, MEDJERAL-THOMAS N, GOPALUNI S *et al*.: Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis. *Nephrol Dial Transplant* 2019; 34: 63-73.
36. PEPPER RJ, MCADOO SP, MORAN SM *et al*.: A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology* (Oxford) 2019; 58: 260-8.
37. SABLE-FOURTASSOU R, COHEN P, MAHR A *et al*.: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann Intern Med* 2005; 143: 632-8.
38. SINICO RA, DI TOMA L, MAGGIORE U *et al*.: Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. *Arthritis Rheum* 2005; 52: 2926-35.
39. COHEN P, PAGNOUX C, MAHR A *et al*.: Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum* 2007; 57: 686-93.
40. RIBI C, COHEN P, PAGNOUX C *et al*.: Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum* 2008; 58: 586-94.
41. GAYRAUD M, GUILLEVIN L, COHEN P *et al*.: Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. French Cooperative Study Group for Vasculitides. *Br J Rheumatol* 1997; 36: 1290-7.
42. MARITATI F, ALBERICI F, OLIVA E *et al*.: Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial. *PLoS One* 2017; 12: e0185880.
43. MOOSIG F, BREMER JP, HELLMICH B *et al*.: A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients. *Ann Rheum Dis* 2013; 72: 1011-7.
44. WECHSLER ME, AKUTHOTA P, JAYNE D *et al*.: Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017; 376: 1921-32.
45. EMMI G, ROSSI GM, URBAN ML *et al*.: Scheduled rituximab maintenance reduces relapse rate in eosinophilic granulomatosis with polyangiitis. *Ann Rheum Dis* 2018; 77: 952-4.
46. MOHAMMAD AJ, HOT A, ARNDT F *et al*.: Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Ann Rheum Dis* 2016; 75: 396-401.
47. NOVIKOV P, MOISEEV S, SMITIENKO I, ZAGVOZDKINA E: Rituximab as induction therapy in relapsing eosinophilic granulomatosis with polyangiitis: A report of 6 cases. *Joint Bone Spine* 2016; 83: 81-4.
48. THIEL J, TROILO A, SALZER U *et al*.: Rituximab as Induction Therapy in Eosinophilic Granulomatosis with Polyangiitis Refractory to Conventional Immunosuppressive Treatment: A 36-Month Follow-Up Analysis. *J Allergy Clin Immunol Pract* 2017; 5: 1556-63.
49. LYONS PA, PETERS JE, ALBERICI F *et al*.: Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. *Nat Commun* 2019; 10: 5120.
50. DOUBELT I, PULENZAS N, CARETTE S, PAGNOUX C, CANADIAN VASCULITIS NETWORK (CANVASC): Efficacy of conventional immunosuppressants in relapsing or refractory eosinophilic granulomatosis with polyangiitis: evidence from a Canadian single-centre cohort. *Clin Exp Rheumatol* 2020; 38 (Suppl. 124): S171-5.
51. ENNIS D, LEE JK, PAGNOUX C: Mepolizumab for the treatment of eosinophilic granulomatosis with polyangiitis. *Expert Opin Biol Ther* 2019; 19: 617-30.