REVIEW ARTICLE

How to treat ANCA-associated vasculitis: practical messages from 2016 EULAR/ERA-EDTA recommendations

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KEY WORDS

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ABSTRACT

The European League against Rheumatism (EULAR) with the European Renal Association – European Dialysis and Transplant Association recently published an update of 2009 EULAR recommendations with a focus on the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). In this article, we discuss the following key messages for clinical practice derived from these recommendations: 1) biopsy should be performed if possible to confirm new diagnosis or relapse; 2) glucocorticoid therapy is an extremely important adjunct to the management of AAV, but it is also responsible for the majority of adverse effects; the dose should be tapered to 7.5 to 10 mg/d at 3 to 5 months; 3) cyclophosphamide or rituximab are the mainstay of remission induction; 4) patients with major relapse should be treated like those with new disease, but rituximab is the preferred option in those patients who relapse after prior cyclophosphamide; 5) minor relapse should not be treated with glucocorticoid alone, and a change in immunosuppressive regimen should be considered; 6) rituximab can be used not only for remission induction but also for maintenance; 7) maintenance therapy should continue for at least 2 years, after which gradual taper could be considered; 8) while ANCA are extremely useful for diagnosis and rising ANCA levels seem to be associated with relapse, serial monitoring should not guide treatment decisions; 9) monitoring of AAV patients should be holistic with a structured assessment tool and monitoring for effects related to the vasculitis as well as treatment; 10) management should be either at or in conjunction with an expert center; and 11) patients should be involved in decision making and have access to educational resources.

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Introduction The European League Against Rheumatism (EULAR) published recommendations for the management of primary small and medium vessel vasculitis in 2009.[1] Among these are a group of vasculitides united in their association with antibodies directed against antigenic targets (myeloperoxidase [MPO] or proteinase 3 [PR3]) in the neutrophil cytoplasm—the antineutrophil cytoplasmic antibodies (ANCA). ANCA-associated vasculitides (AAV) predominantly affect the vessels of small or medium caliber, producing necrotizing inflammation with a few or no immune deposits. The 3 distinct phenotypes in this group are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Since 2009, there have been many advances in the therapeutics and long-term monitoring of these conditions, leading to a sea change in the way that they are treated. In the interest of cross-specialty working, the EULAR and the European Renal Association joined hands and commissioned a task force of experts from 13 countries to update the 2009 recommendations with a focus on AAV. Those recommendations have just been published.[2]

Why do we need recommendations? AAV are rare, with an annual incidence of 10 to 20 per million in Northern Europe.[3] This means that the average clinician might not see more than a handful of patients in their career. It is important to empower

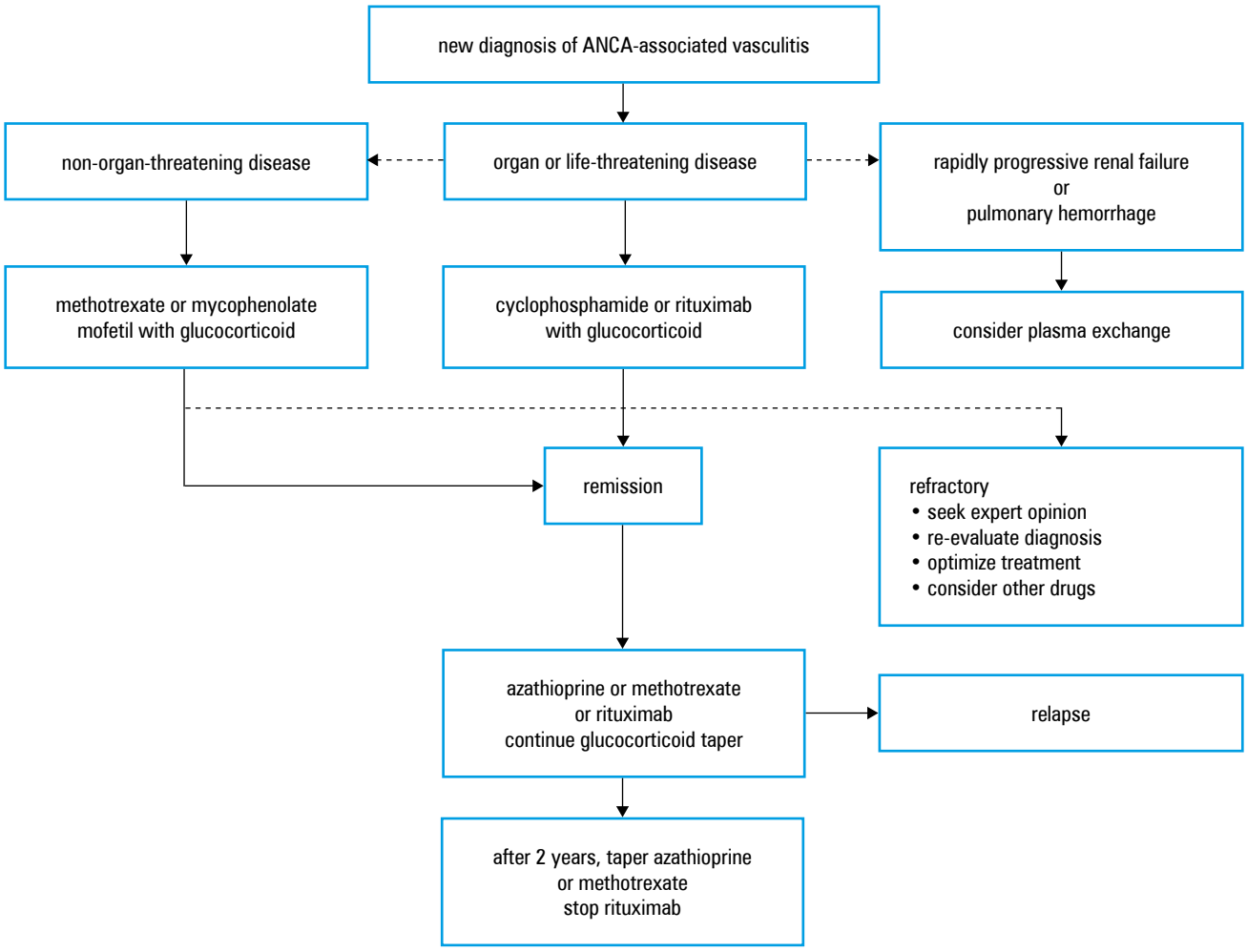

FIGURE 1 EULAR/ERA-EDTA algorithm for the management of new antineutrophil cytoplasmic antibody (ANCA)--associated vasculitis. Dashed lines indicate suggested alternative or supplementary action to consider. Reproduced from "EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Yates M, Watts RA, Bajema IM, et al. 2016; 75 (9): 1583--1594" with permission from BMJ Publishing Group Ltd.

the average clinician to be able to make decisions in a standardized way and know when to ask for help from a specialist center. Recommendations provide an authoritative way for patients and clinicians to access specialist services and high-cost drugs. AAV have a high mortality rate if they remain untreated.[4] With improved therapeutics, patients are surviving longer,[5] but their monitoring and educational needs are changing.[6,7] The recommendations form the basis for regulatory authorities to plan availability of high-cost drugs and access to specialist services. Recommendations allow standardization of teaching undergraduate and postgraduate trainees. They provide the primary and secondary care physicians with surrogate experience from experts in the field.

AAV crosses organ boundaries and can present to various specialists. To allow for true multisystem collaboration in the formation of these recommendations, the EULAR / European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) task force consisted of representation from rheumatology, renal medicine, internal medicine, ororhinolaryngology (ear, nose & throat – ENT), ophthalmology, pathology, chest medicine, clinical immunology, nursing, and a patient support group. In this article, we discuss the key messages for clinical practice derived from these multispecialty recommendations. However, we will restrict our discussion to GPA and MPA because of the paucity of evidence for the treatment of EGPA.

Diagnosis AAV do not have any diagnostic criteria or any pathognomonic tests. Diagnostic criteria are in development but currently diagnosis relies on pattern recognition.[8] When classification criteria are used for diagnostic purposes, the results are disappointing.[9] The new recommendations do not make specific recommendations about diagnostic workup but do comment on the role of biopsy. A positive biopsy is strongly supportive of a diagnosis of vasculitis; therefore, this confirmation should be sought whenever possible. A positive ANCA test (anti-PR3 or anti-MPO) in the correct clinical context has a very high specificity for the diagnosis of small vessel vasculitis.[10] However, localized disease may be ANCA negative.[11] Therefore, a positive biopsy has a greater role to play in ANCA-negative disease. The diagnostic yield depends on the biopsied organ. Generally, renal biopsies have a greater diagnostic yield compared to ENT biopsies.[2] Transbronchial biopsies have a much lower yield than open lung biopsies and are generally reserved for situations of diagnostic uncertainty where tissue may not be available from other sources. Biopsies also offer prognostic information.[12,13] For example, a greater proportion of sclerotic glomeruli in a biopsy is associated with an adverse prognosis.

TABLE 1 EUVAS trials pulsed cyclophosphamide[a] dose adjustment for age and renal function

Age, y	Creatinine levels, <300 μmol/l	Creatinine levels, 300–500 μmol/l
<60	15 mg/kg	12.5 mg/kg
60–70	12.5 mg/kg	10 mg/kg
>70	10 mg/kg	7.5 mg/kg

a Oral continuous cyclophosphamide dose should be reduced by 25% in patients older than 60 years and by 50% in those older than 70 years.

Remission induction therapy Remission is defined as the absence of any disease activity.[14] The assessment of disease state should be done by using a validated clinical tool such as Birmingham Vasculitis Activity Score version 3 (BVASv3) or BVAS for Wegener's granulomatosis (BVAS/WG).[15,16] AAV are usually associated with organ or life-threatening disease. The 2009 recommendations suggested that methotrexate use was reasonable for patients with localized disease. This was based on the results of a randomized controlled clinical trial that demonstrated noninferiority of methotrexate to oral cyclophosphamide in this group.[17] However, this time the recommendations have differentiated even localized disease into that with and without cartilage and bony involvement, the argument being that destruction of nasal tissues is an organ-threatening manifestation. This argument is well founded in the long-term results of the above clinical trial. Not only did the cases in the methotrexate arm trend towards getting more relapses, but they also had a greater exposure to glucocorticoids and further immunosuppression.[18] The authors have also given up using methotrexate unless the disease is genuinely nonthreatening. The 2016 recommendations provide example scenarios where it could be used: ENT disease without bony or cartilage involvement and without olfactory dysfunction or deafness, skin involvement without ulceration, skeletal muscle myositis, or noncavitating pulmonary disease without hemoptysis. Thus, as shown in FIGURE 1, patients with genuinely non-organ-threatening disease can be treated with methotrexate or mycophenolate mofetil. Mycophenolate mofetil could be used in the niche area of localized disease where methotrexate might not be appropriate. The fall from grace of these 2 drugs is also noted in the grade of recommendation (B for methotrexate and C for mycophenolate mofetil). The majority of patients should therefore receive either cyclophosphamide or rituximab for remission induction (FIGURE 1).

Cyclophosphamide is the tried and tested remedy, which has been the drug that revolutionized the survival of patients with AAV.[19] The authors use the pulsed intravenous regimen of 15 mg/kg intravenously (usually a maximum of 1200 mg), initial 3 pulses every 2 weeks, then every 3 weeks. Daily oral cyclophosphamide at a dose of 2 mg/kg/d can also be used, but it delivers a much greater cumulative dose, with the resultant increase in the risk of toxicity. However, this regimen would prove effective in centers without infusion facilities. With either regimen, induction therapy is given until remission is achieved, but for not less than 3 months and not more than 6 months. The dose should be adjusted for age and renal function (TABLE 1). It is recommended that standard protocols used in oncology are adapted for use of cyclophosphamide in rheumatic diseases. All patients should be well hydrated during therapy, and prehydration with antiemetic medications is recommended with an intravenous protocol. Mesna (2-mercaptoethane sulfonate sodium) can be given either orally or intravenously to prevent bladder toxicity. Patients should be monitored for leukopenia and the dose should be reduced according to local protocols. Oral daily cyclophosphamide requires more frequent blood monitoring (usually once or twice a week) with temporary suspension and appropriate dose reduction in case of neutropenia (usually initially by 25 mg). It is recommended that all patients are given cotrimoxazole for the time of treatment, either 480 mg daily or 960 mg thrice weekly, to prevent *Pneumocystis jiroveci* (*P. jiroveci*) infection. In case of intolerance or contraindications to cotrimoxazole, alternatives include dapsone, atovaquone, or inhaled pentamidine, although they have not been shown to be cost-effective and are not generally recommended.

In 2 separate clinical trials published together, the efficacy of rituximab was demonstrated for renal and systemic disease.[20,21] The trials are summarized in TABLE 2. It is perhaps the biggest change from the 2009 recommendations. However, when compared to cyclophosphamide, remission is not induced any sooner and the incidence of serious adverse events is also unchanged.

Although the clinical trial dose (and the licensed dose) is as in TABLE 2, practically the use of the rheumatoid arthritis regimen is also permissible and we use that on a regular basis.

For patients with rapidly progressive renal involvement or pulmonary hemorrhage, plasma exchange has been recommended in the past and remains an option. This remains a controversial topic because long-term follow-up of patients in the largest trial to date of plasma exchange in AAV fails to show significant benefit.[22]

Glucocorticoids are an essential part of remission induction. The recommended initial dose of glucocorticoids is prednisolone 1 mg/kg/d (or equivalent) but not more than 60 mg/d, with gradual reduction to achieve daily prednisolone dose of 7.5 to 10 mg at 3 to 5 months. There is a strong possibility that the initial adverse effects of remission induction are related to glucocorticoid treatment as evidenced by the similar rate of adverse events in the randomized controlled trial of rituximab vs cyclophosphamide.[20]

Remission maintenance therapy The treatment paradigm for AAV has mirrored that for cancer. Thus, we use the phrases "remission induction" and "remission maintenance". This came

TABLE 2 Overview of 2 randomized controlled trials of rituximab for remission induction in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides

Reference	Patients	Intervention	Control	Outcome
Jones et al[20]	new AAV, ANCA positive, renal involvement (n = 44)	RTX, 375 mg/m²/wk × 4 + IV CYC, 15 mg/kg with 1st and 3rd RTX + 1 mg/kg/d pred reduced to 5 mg at 6 months (n = 33)	IV CYC, 15 mg/kg pulse at 0, 2, 4, 7, 10, and 13 weeks, followed by AZA, 2 mg/kg/d + 1 mg/kg/d pred reduced to 5 mg at 6 months (n = 11)	sustained remission in 25/33 in intervention arm and 9/11 in control arm at 12 months; no difference between the 2 arms on superiority analysis ($P = 0.68$)
Stone et al[21]	new AAV, ANCA positive, BVAS/WG ≥3 (n = 96)	RTX 375 mg/m²/wk × 4 + daily placebo CYC followed by daily placebo AZA + 1–3 pulses of 1 g IV MP followed by 1 mg/kg/d pred reduced to 0 mg at 6 months (n = 48)	placebo RTX + daily oral CYC 2 mg/kg/d followed by AZA 2 mg/kg/d after 3–6 months + 1 mg/kg/d pred reduced to 5 mg at 0 months (n = 48)	sustained remission in 29/48 in intervention arm and 31/48 in control arm at 6 months

Abbreviations: AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's granulomatosis; CYC, cyclophosphamide; MP, methylprednisolone; pred, prednisolone; RTX, rituximab

TABLE 3 Overview of clinical trials of rituximab for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculities

Reference	Patients	Intervention	Control	Outcome
Guillevin et al[24]	new or relapsing GPA/MPA complete remission post-pulsed CYC ANCA-positive or histology (n = 115)	RTX at day 0, 14; months 6, 12, 18 (n = 57)	AZA 2 mg/kg/d for 12 months then 1.5 mg/kg/d for 6 months then 1 mg/kg/d for 4 months (n = 58)	at month 28, 3/57 relapsed in intervention arm, 7/58 relapsed in control arm hazard, 6.61 (1.56–27.96)
Smith et al[25]	GPA/MPA ANCA-positive or histology one of the following: • never achieved remission • relapsing disease on standard immunosuppression • standard therapies contraindicated • partial remission needing >10 mg/d pred (n = 73)	RTX 375 mg/m²/wk × 4 OR RTX 1g/2 weeks × 2 followed by repeat RTX 1 g every 6 months for 2 years (n = 28)	RTX 375 mg/m²/wk × 4 OR RTX 1g/2 weeks × 2 followed by repeat RTX at clinical relapse (n = 45)	at 48 months, 11/43 relapse in intervention arm, 21/26 relapse in control arm $P < 0.001$

Abbreviations: GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; others, see TABLE 2

into being because of the recognition that cyclophosphamide had unacceptable cumulative toxicity and therefore it was used for "inducing remission", but we needed a safer alternative for "maintaining remission". The drug that has the best track record for this is azathioprine, which was shown to be safer than and as effective as cyclophosphamide in a randomized controlled trial.[23] This paradigm has now been challenged by the demonstration of the efficacy of rituximab in maintaining remission (TABLE 3). Guillevin et al[24] successfully demonstrated that 5 pulses of low-dose rituximab over 18 months were superior to azathioprine for maintaining remission in a randomized controlled trial. Smith et al[25] used a different dose of rituximab and showed that using rituximab for 2 years after remission induction was more effective than letting patients relapse. Patients who receive multiple doses of rituximab should have their immunoglobulin (Ig) levels monitored because the IgG levels will fall in the majority of cases.[26] Currently, we advise that those patients be watched for the development of serious infections. In that scenario, it would be advisable to liaise with a clinical immunologist to use intravenous immunoglobulins.

As in remission induction, the previously recommended dose of methotrexate, 20–25 mg/kg/wk, and of mycophenolate mofetil, 2 g/d, finds less favor. While all 4 drugs have been recommended at Grade A, the consensus falls from 94% for azathioprine, to 59% for rituximab, and to 53% for methotrexate and mycophenolate mofetil.

TABLE 4 Subanalysis of the efficacy of rituximab in relapsing ANCA-associated vasculitis in the RAVE trial

Reference	Patients	Intervention	Control	Outcome
Stone et al[21]	relapsing AAV ANCA positive BVAS/WG ≥3 (n = 101)	RTX 375 mg/m²/wk × 4 + daily placebo CYC followed by daily placebo AZA + 1–3 pulses of 1 g IV MP followed by 1 mg/kg/d pred reduced to 0 mg at 6 months (n = 51)	placebo RTX + daily oral CYC 2 mg/kg/d followed by AZA 2 mg/kg/d after 3–6 months + 1 mg/kg/d pred reduced to 5 mg at 0 months (n = 50)	sustained remission in 34/51 in intervention arm and 21/50 in control arm at 6 months superiority of intervention proven odds ratio, 1.4 (1.03–1.91) $P = 0.03$

Relapsing disease Relapse is an unfortunate part of AAV. The relapse rate rises from about 20% at 12 months to about 60% at 5 years.[27] The best evidence for the treatment of relapsing disease is part of the subanalysis of the American rituximab trial (TABLE 4).[21] The majority of these patients had already received cyclophosphamide for their new disease. Therefore, the authors suggest that rituximab is used in preference to cyclophosphamide in those patients who relapse after prior cyclophosphamide use. It is also worth noting that the consensus for the voting in the 2016 recommendations is higher for rituximab (94%, Grade A) than for cyclophosphamide (88%, Grade A).

In the past, there has been a trend to treat minor relapses with a short course of increment in the glucocorticoid dose. However, there is recognition that this is perhaps a bad strategy just as it is so for patients with rheumatoid arthritis. Miloslavsky et al[28] demonstrated that these patients with "minor relapses" treated with an increase in their glucocorticoid dose had a high rate of severe relapse. Therefore, the 2016 recommendations suggest that even minor relapses should be treated with a change in immunosuppressive regimen.

The current general consensus is to discontinue rituximab remission maintenance after 2 years. Similarly, the EULAR/ERA-EDTA task force also concluded that other immunosuppressive agents should be continued for at least 2 years, after which gradual taper could be considered. This recommendation was made purely on the basis of expert opinion rather than evidence. But the consensus was strongest for PR3-persistent disease. For other ANCA states during remission, the experts tended to start tapering immunosuppression even before the 2 years were up.

Refractory disease In most cases, remission can be achieved within 3 months, although in some cases it may take longer. No improvement in 4 weeks or improvement of less than 50% in 6 weeks of treatment (as measured by a validated clinical tool such as BVASv3 or BVAS/WG), or chronic persistent disease (defined as the presence of at least 1 major or 3 minor items on the disease activity score) after more than 12 weeks of treatment is consistent with refractory disease[14] and warrants change in therapy. In patients treated with cyclophosphamide, a switch to rituximab, and vice versa, is recommended.[29] In patients who do not respond to pulsed cyclophosphamide and fail on rituximab, or rituximab is not available, continuous oral cyclophosphamide therapy may be considered.[30] Patients who fail to achieve full remission and remain in the state of persistent low disease activity may benefit from adjunctive therapy with intravenous immunoglobulins (0.4 g/kg for 5 days; total of 2 g per cycle). However, it is important to recognize potential pitfalls related to presumed refractoriness. The first and most obvious question is whether the diagnosis of AAV is correct and treatment regimen adequate, and secondly, whether symptoms are related to active disease as opposed to damage, infection, or other comorbidity (eg, malignancy). Good examples of symptoms that may represent damage rather than active disease are persistent ENT symptoms, proteinuria, or chronic neuropathy. Similarly, exacerbation of ENT symptoms or new lung infiltrates may reflect infective complication and not a flare of vasculitis. As a rule of a thumb, refractory patients should be treated in close collaboration with an expert center or referred to such center for evaluation and consideration of experimental therapies.

Long-term monitoring Improving survival means that the prevalence of AAV is rising. Long-term problems of a chronic inflammatory disease are becoming apparent. At every follow-up visit, a patient suffering from AAV should have their urine checked. Those patients thought to have nonglomerular hematuria should be referred for a urological examination, especially if there is a history of cyclophosphamide exposure. In those with prior rituximab, immunoglobulin levels may need monitoring and treating if they suffer with severe infections. The risk of post-rituximab *P. jirovecii* pneumonia is low.[31] However, there is some evidence from the hematology literature that repeated rituximab-based chemotherapy puts patients at a higher risk of *P. jirovecii* pneumonia, and the risk can be mitigated with addition of cotrimoxazole.[32] The authors commence *P. jirovecii* prophylaxis in those patients who have an IgG level of less than 6 g/l.

Cardiovascular risk factors should be assessed regularly as should other problems related to long-term glucocorticoid and immunosuppressive use (type 2 diabetes, osteoporosis, cancer).[7,33]

At every follow-up, disease assessment should be led by a structured interview with the help of a validated assessment tool such as BVASv3 or BVAS/WG rather than ANCA monitoring. Clinicians who do not have experience in using activity or damage tools in AAV can sign up for virtual training in vasculitis assessment at www.bvasvdi.org, an online training platform providing certification of competence, which is free for noncommercial purposes.[34] Serial ANCA titers should not be used to guide immunosuppression, but patients with persistent or rising ANCA titers may need to be closely monitored.

Patients with AAV end up with a poor quality of life even when considered to be in clinical remission.[35] Their educational needs in the context of a chronic debilitating disease should be met and each decision should be taken with a clear explanation of the pros and cons.

Relevance to Polish medicine There are no published data whether patients with AAV in Poland have been treated in accordance with European recommendations. The recently launched Polish Registry of Vasculitis, which collects data on patients with various vasculitides and currently includes 13 academic centers across the country, will shed more light on the management of vasculitis in Poland.[36] Until recently, Polish patients with AAV have had very limited access to rituximab. It has been prescribed only in selected patients with refractory disease upon approval of hospital management. The high cost of the medication and the lack of guaranteed reimbursement by the National Health Fund have restricted its wider use. In some cases, it has been prescribed in a lower than the currently licensed dose to overcome financial restrictions.[37] In 2015, a special funding scheme with stringent eligibility criteria for use of rituximab in AAV was approved by the Polish Ministry of Health, which guaranteed funding for the medication.[38] Patients with organ or life-threatening GPA or MPA who are ANCA positive and fail to respond to standard induction therapy with cyclophosphamide or in whom such therapy is contraindicated are eligible. Rescue therapy with rituximab is approved after 12 weeks of cyclophosphamide for refractory disease, and after 6 months for persistent disease following cyclophosphamide treatment. Rituximab has also been funded to treat relapses but not as yet for maintenance therapy. Individual funding requests can be submitted for patients who do not fulfil all eligibility criteria. We hope that the 2016 recommendations will influence the current policy in time.

Summary The 2016 recommendations are a distillation of the literature and evidence base as it exists at this point in time. Where there is little or no evidence, the recommendations offer clear expert consensus on the management of these challenging conditions. There are a number of take-home messages:

1 These conditions are rare and their management is challenging. The management should be either at or in conjunction with an expert center.
2 Glucocorticoid therapy is an extremely important adjunct for the management of AAV, but it is also responsible for the majority of adverse effects. It should be tapered down to 7.5 to 10 mg/d at 3 to 5 months. The temptation to treat a "minor relapse" with glucocorticoid alone should be resisted.
3 Rituximab can be used for remission induction and maintenance, changing our paradigm of the way that AAV has been treated so far. It can lead to a hypoimmunoglobulinemic state, and IgG levels should be monitored.
4 Most patients will not be suitable for treatment with therapies besides cyclophosphamide or rituximab.
5 Monitoring of these patients should be holistic with a structured assessment tool and monitoring for effects related to the vasculitis as well as treatment. Serial ANCA monitoring should not guide treatment changes.
6 Involve patients in decision making at every stage and ensure that they have access to the educational resources they need to make the best of a long-term potentially life-threatening chronic condition.

REFERENCES

1 Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis. 2009; 68: 310-317.

2 Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016; 75: 1583-1594.

3 Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gross WL. Stable incidence of primary systemic vasculitides over five years: results from the German vasculitis register. Arthritis Rheum. 2005; 53: 93-99.

4 Anderson G, Coles ET, Crane M, et al. Wegener's granuloma. A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. Q J Med. 1992; 83: 427-438.

5 Mukhtyar C, Flossmann O, Hellmich B, et al. Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. Ann Rheum Dis. 2008; 67: 1004-1010.

6 Mooney J, Spalding N, Poland F, et al. The informational needs of patients with ANCA-associated vasculitis-development of an informational needs questionnaire. Rheumatology (Oxford). 2014; 53: 1414-1421.

7 Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. Ann Rheum Dis. 2011; 70: 488-494.

8 Nataraja A, Mukhtyar C, Hellmich B, et al. Outpatient assessment of systemic vasculitis. Best Pract Res Clin Rheumatol. 2007; 21: 713-732.

9 Rao JK, Allen NB, Pincus T. Limitations of the 1990 American College of Rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med. 1998; 129: 345-352.

10 Choi HK, Liu S, Merkel PA, et al. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies. J Rheumatol. 2001; 28: 1584-1590.

11 Luqmani RA, Bacon PA, Beaman M, et al. Classical versus non-renal Wegener's granulomatosis. Q J Med. 1994; 87: 161-167.

12 Berden AE, Jones RB, Erasmus DD, et al. Tubular lesions predict renal outcome in antineutrophil cytoplasmic antibody-associated glomerulonephritis after rituximab therapy. J Am Soc Nephrol. 2012; 23: 313-321.

13 Bajema IM. Pathological classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis. Clin Exp Immunol. 2011; 164 (Suppl 1): 14-16.

14 Hellmich B, Flossmann O, Gross WL, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007; 66: 605-617.

15 Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis. 2009; 68: 1827-1832.

16 Stone JH, Hoffman GS, Merkel PA, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS). Arthritis Rheum. 2001; 44: 912-920.

17 De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2005; 52: 2461-2469.

18 Faurschou M, Westman K, Rasmussen N, et al. Brief Report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012; 64: 3472-3477.

19 Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med. 1983; 98: 76-85.

20 Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med. 2010; 363: 211-220.

21 Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med. 2010; 363: 221-232.

22 Walsh M, Casian A, Flossmann O, et al. Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. Kidney Int. 2013; 84: 397-402.

23 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.

24 Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014; 371: 1771-1780.

25 Smith RM, Jones RB, Guerry MJ, et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum. 2012; 64: 3760-3769.

26 Venhoff N, Effelsberg NM, Salzer U, et al. Impact of rituximab on immunoglobulin concentrations and B cell numbers after cyclophosphamide treatment in patients with ANCA-associated vasculitides. PLoS One. 2012; 7: e37626.

27 Mukhtyar C, Luqmani R. Disease-specific quality indicators, guidelines, and outcome measures in vasculitis. Clin Exp Rheumatol. 2007; 25 (6 Suppl 47): 120-129.

28 Miloslavsky EM, Specks U, Merkel PA, et al. Outcomes of nonsevere relapses in antineutrophil cytoplasmic antibody-associated vasculitis treated with glucocorticoids. Arthritis Rheumatol. 2015; 67: 1629-1636.

29 Miloslavsky EM, Specks U, Merkel PA, et al. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody--associated vasculitis. Arthritis Rheum. 2013; 65: 2441-2449.

30 Seror R, Pagnoux C, Ruivard M, et al. Treatment strategies and outcome of induction-refractory Wegener's granulomatosis or microscopic polyangiitis: analysis of 32 patients with first-line induction-refractory disease in the WEGENT trial. Ann Rheum Dis. 2010; 69: 2125-2130.

31 Besada E, Nossent JC. Should Pneumocystis jiroveci prophylaxis be recommended with Rituximab treatment in ANCA-associated vasculitis? Clin Rheumatol. 2013; 32: 1677-1681.

32 Jiang X, Mei X, Feng D, Wang X. Prophylaxis and treatment of pneumocystis jiroveci pneumonia in lymphoma patients subjected to rituximab--contained therapy: a systemic review and meta-analysis. PLoS One. 2015; 10: e0122171.

33 Suppiah R, Judge A, Batra R, et al. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. Arthritis Care Res (Hoboken). 2011; 63: 588-596.

34 Ponte C, Sznajd J, O'Neill L, Luqmani RA. Optimisation of vasculitis disease assessments in clinical trials, clinical care and long-term databases. Clin Exp Rheumatol. 2014; 32(5 Suppl 85): S118-S125.

35 Boomsma MM, Bijl M, Stegeman CA, et al. Patients' perceptions of the effects of systemic lupus erythematosus on health, function, income, and interpersonal relationships: a comparison with Wegener's granulomatosis. Arthritis Rheum. 2002; 47: 196-201.

36 Padjas A, Sznajd J, Szczeklik W, et al. Rare disease registries: an initiative to establish vasculitis registry in Poland. Pol Arch Med Wewn. 2014; 124: 143-144.

37 Wawrzycka-Adamczyk K, Zugaj A, Wludarczyk A, et al. Lower doses of rituximab in remission induction for refractory granulomatosis with polyangiitis. Przegl Lek. 2014; 71: 663-665.

38 [Treatment of active granulomatosis with polyangiitis [GPA] or microscopic polyangiitis [MPA] (ICD-10 m^{3}1.3, m 31.8). Ministry of Health. 2015. Available from: http://www.mz.gov.pl/leki/refundacja/programy-lekowe/. Accessed October 10, 2016. Polish.

ARTYKUŁ POGLĄDOWY

Jak leczyć zapalenie naczyń związane z obecnością ANCA: praktyczne wskazówki z zaleceń EULAR/ERA-EDTA 2016

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SŁOWA KLUCZOWE

ANCA, praktyka kliniczna, zapalenie naczyń, zalecenia

STRESZCZENIE

European League Against Rheumatism (EULAR) z European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) opublikowały niedawno uaktualnienie zaleceń EULAR z 2009 r. dotyczące postępowania w zapaleniach naczyń związanych z obecnością przeciwciał przeciw cytoplazmie neutrofilów (*antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides* – AAV). W poniższym artykule omówiono główne przesłania kliniczne wynikające z tych zaleceń: 1) w celu potwierdzenia nowego rozpoznania lub nawrotu AAV, jeśli to możliwe należy wykonać biopsję narządu; 2) glikokortykosteroidy (GKS) są bardzo ważnym elementem leczenia AAV, ale są odpowiedzialne za większość działań niepożądanych; docelowa dawka GKS po 3–5 miesiący leczenia wynosi 7,5–10 mg/d; 3) cyklofosfamid lub rytuksymab stanowią podstawę leczenia indukującego remisję; 4) chorych z ciężkim zaostrzeniem powinno się leczyć tak samo jak tych z nowym rozpoznaniem, ale u pacjentów z nawrotem choroby po leczeniu cyklofosfamidem preferuje się rytuksymab; 5) w przypadku łagodnego zaostrzenia należy rozważyć zmianę leku immunosupresyjnego, a nie jedynie zwiększenie dawki GKS; 6) rytuksymab można stosować nie tylko w celu indukcji remisji, ale także jej podtrzymania; 7) leczenie podtrzymujące remisję należy prowadzić przez co najmniej 2 lata i po tym czasie rozważyć stopniowe zmniejszanie dawek leków aż do ich odstawienia; 8) ANCA są bardzo pomocne w ustaleniu rozpoznania, a zwiększenie ich stężenia łączy się z ryzykiem nawrotu choroby, niemniej nie wolno używać seryjnych pomiarów stężeń ANCA do podejmowania decyzji leczniczych; 9) monitorowanie chorych na AAV powinno obejmować różne aspekty choroby, w tym jej skutki i działania niepożądane leków; do tego celu zaleca się używanie złożonych narzędzi oceny klinicznej; 10) diagnostykę i leczenie chorych na AAV powinno się prowadzić w porozumieniu z ośrodkiem eksperckim lub w takim ośrodku; 11) pacjenci z AAV powinni brać udział w podejmowaniu decyzji dotyczących ich leczenia i mieć dostęp do źródeł edukacyjnych.

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