

# RMD Open

Rheumatic &  
Musculoskeletal  
Diseases

## ORIGINAL ARTICLE

## Validation of the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis by disease content experts

Max Yates,<sup>1,2</sup> Richard Watts,<sup>2,3</sup> Ingeborg Bajema,<sup>4</sup> Maria Cid,<sup>5</sup> Bruno Crestani,<sup>6</sup> Thomas Hauser,<sup>7</sup> Bernhard Hellmich,<sup>8</sup> Julia Holle,<sup>9</sup> Martin Laudien,<sup>10</sup> Mark A Little,<sup>11</sup> Raashid Ahmed Luqmani,<sup>12</sup> Alfred Mahr,<sup>13</sup> Peter Merkel,<sup>14</sup> John Mills,<sup>15</sup> Janice Mooney,<sup>1</sup> Mårten Segelmark,<sup>16</sup> Vladimir Tesar,<sup>17</sup> Kerstin W A Westman,<sup>18</sup> Augusto Vaglio,<sup>19</sup> Nilüfer Yalçında,<sup>20</sup> David R Jayne,<sup>21</sup> Chetan Mukhtyar<sup>1</sup>

**To cite:** Yates M, Watts R, Bajema I, *et al.* Validation of the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis by disease content experts. *RMD Open* 2017;**3**:e000449. doi:10.1136/rmdopen-2017-000449

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2017-000449>).

Received 2 February 2017

Revised 14 March 2017

Accepted 21 March 2017

### ABSTRACT

The European League Against Rheumatism recommendations for the management of antineutrophil cytoplasmic antibody-associated vasculitis have been recently published. Unique to recommendation development, they were also voted on by members of a learned society. This paper explores the wider validity of the recommendations among people who self-identify as clinicians caring for patients with vasculitis. In addition to the task force, a learned society (European Vasculitis Society—EUVAS) was invited, through online survey, to rate independently the strength of evidence of each recommendation to obtain an indication of the agreement among the final target audience and ultimate end-users of the recommendations. The survey took place in June 2015. Of the 158 EUVAS members surveyed, there were 88 responses (55.7%). There was a large degree of agreement in the voting patterns between EUVAS survey participants and task force members. Notable exceptions were lower grades for the recommendation of the use of rituximab for remission induction in patients with eosinophilic granulomatosis with polyangiitis and for methotrexate and mycophenolate mofetil as remission maintenance agents in patients with granulomatosis with polyangiitis/microscopic polyangiitis by EUVAS members. These results are encouraging and suggest that the voting patterns of the task force are representative of the wider vasculitis community. We recommend future recommendations adopt this approach for data/expert-based treatment guidelines, especially for multisystem diseases.

### INTRODUCTION

The European League Against Rheumatism (EULAR) recommendations for the management of small-vessel and medium-vessel vasculitides were recently updated, with a focus on antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis, and were coendorsed by the European Renal

### Key messages

- The results reveal a large degree of agreement in the voting patterns among EUVAS members who responded to the survey and the members of the task force.
- The generalisability of the findings is strengthened because the survey members derive from 29 countries from around the world.
- One noted exception was the lower grade of recommendation for the use of rituximab in patients with EGPA amongst EUVAS survey responders.

Association-European Dialysis and Transplant Association and European Vasculitis Society (EUVAS).<sup>1</sup> The process for formation of such recommendations follows a standard methodology.<sup>2,3</sup> Since ANCA-associated vasculitis can present to physicians from a wide range of specialities, a task force was convened with representation from different subspecialisations.

Standard practice for voting on the recommendations was followed but, for the first time, they were also voted on by members of a learnt society, which in this case was the EUVAS. EUVAS allows members to join the Society from around the world and as such is an open collaboration of physicians which aims to promote research and education in vasculitis.

Results from the Canadian Vasculitis Network revealed significant variations in practice highlighting the need for evidence-based management recommendations for ANCA-associated vasculitis.<sup>4</sup> In addition, the publication of large collaborative trials, involving patients



CrossMark

For numbered affiliations see end of article.

#### Correspondence to

Dr Max Yates, Norwich Medical School; [maxyates@doctors.org.uk](mailto:maxyates@doctors.org.uk)

with ANCA-associated vasculitis, has advanced the evidence from which conclusions on treatment can be drawn.

This paper explores the wider validity of the recommendations among people who self-identify as clinicians caring for patients with vasculitis.

## METHODS

### Developing the recommendations

Systematic review of several medical literature databases was used to identify clinical trials relevant for the purposes of developing the recommendations. Standardised procedures were followed in line with guidance from EULAR with evidence from clinical trials graded from A (highest—from at least one randomised controlled trial) to D (lowest—expert opinion).<sup>2,3</sup> This evidence informed the development of statements. Finally, voting took place with individuals giving a strength of recommendation to the individual statements. Each task force member had a single independent vote for each statement. Strengths of recommendation are in part constrained by the category of evidence used to inform each statement.

## DESIGN

### Wider validity exercise

In addition to the task force, a learnt society (EUVAS) was invited to rate independently the strength of evidence of each recommendation to obtain an indication of the agreement among the final target audience and ultimate end-users of the recommendations. Members of the task force whom were also members of EUVAS did not vote twice.

### EUVAS membership

EUVAS is an open collaboration of physicians interested in research and education in vasculitis and evolved from the European Vasculitis Study Group. EUVAS is a non-political, non-profit organisation with a primary objective to unite researchers and clinicians to promote the study and treatment of vasculitis. Five of the task force members form the current presidential council (DRJ, KWAW, IB, TH and AM). Membership to EUVAS is subject to approval by the presidential council after written application. Ordinary membership is open to any clinician or scientist with a specific interest in the field of vasculitis. Associate membership is available to other individuals or institutions sharing an interest in vasculitis. There are 158 members of EUVAS from 28 different countries across Europe and across the globe.

### Sampling frame

The EUVAS membership was emailed and invited to take part in an online survey. Non-responders were sent a second invitation to encourage uptake.

### Analysis

Tables of the spread of results, in this case the strength of recommendation, for each statement were constructed with the most popular (mode) presented first.

## Results

The survey took place in June 2015. The first email message was sent on 4 June 2015 with a link to an online survey. Two reminder emails were sent on 9 and 22 June. Of the 158 EUVAS members surveyed there were 88 responses (55.7%). The members were from 29 countries, distributed across the continents of Asia, Europe, North America, Oceania and South America.

The most popular (mode) vote was considered the grade of recommendation with the corresponding median also presented (table 1).

The results reveal a high degree of concordance between the task force and EUVAS survey votes. Lower grades of recommendation by the EUVAS survey occurred for the use of rituximab (D vs C) in patients with eosinophilic granulomatosis with polyangiitis (EGPA) suffering new-onset ANCA-associated vasculitis (AAV) and for maintenance therapy regimens using methotrexate or mycophenolate mofetil (B vs A). In non-organ, non-life threatening ANCA-associated vasculitis, no task force members voted grade A for use of methotrexate or mycophenolate in such situations, compared with 35% and 12% of the EUVAS group choosing these as options, respectively.

The task force also voted in a greater proportion for grade C than the EUVAS group for either methotrexate or mycophenolate for remission maintenance (35% vs 30% and 31%, respectively, for the EUVAS votes). Although both the task force and EUVAS voting patterns spread across the strengths of recommendation for methotrexate and mycophenolate mofetil, there was much greater agreement for the use of azathioprine for remission maintenance therapy in AAV, reflecting favouring azathioprine as the agent of choice in such situations.

## Discussion

The results reveal a large degree of agreement in the voting patterns among EUVAS members who responded to the survey and the members of the task force. These results are encouraging and suggest that the voting patterns of the task force are representative of the wider vasculitis community. In addition, the generalisability of the findings is strengthened due to the distribution of countries from which the survey participants derive with representations from 29 countries around the world. However, the EUVAS group is likely to be a more research interested and active group compared with all clinicians who care for patients with AAV. We hope that the recommendations are adopted by all involved in the care of patients with AAV and draw attentions to the first statement. The purpose of surveying the EUVAS membership was to check that the task force did not hold widely different views.

There were key exceptions with lower grades of recommendation for the use of rituximab in patients with EGPA among EUVAS survey participants. The reasons for this small discrepancy are unclear but may reflect EUVAS members' familiarity with the previous recommendations

**Table 1** Recommendation statements

Statement	Level of evidence	Grade of recommendation					
		Task force (n=21)		EUVAS (n=88)		Combined (n=109)	
		Mode	Median	Mode	Median	Mode	Median
1. We recommend that patients with ANCA-associated vasculitis are managed in close collaboration with, or at, centres of expertise.	3	C	C	C	C	C	C
2. A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis.	3	C	C	C	C	C	C
3. For remission induction of new-onset organ or life-threatening ANCA-associated vasculitis we recommend treatment with a combination of glucocorticoids and either <b>cyclophosphamide or rituximab</b> .	1	A	A	A	A	A	A
cyclophosphamide and GPA/MPA							
cyclophosphamide and EGPA	3	C	C	C	C	C	C
rituximab and GPA/MPA	1	A	A	A	A	A	A
rituximab and EGPA	3	C	C	D	D	D	D
4. For remission induction of non-organ-threatening ANCA-associated vasculitis we recommend treatment with a combination of glucocorticoid and either <b>methotrexate or mycophenolate mofetil</b> .*	IB	B	B	B	B	B	B
methotrexate							
mycophenolate mofetil	IB	C	C	C	C	C	C
5. For a major relapse of organ-threatening or life-threatening disease in ANCA-associated vasculitis we recommend treatment as per new disease with a combination of glucocorticoids and either <b>cyclophosphamide or rituximab</b> .	1	A	A	A	A	A	A
cyclophosphamide and GPA/MPA							
cyclophosphamide and EGPA	3	C	C	C	C	C	C
rituximab and GPA/MPA	1	A	A	A	A	A	A
6.i. Plasma exchange should be considered for patients with ANCA-associated vasculitis and a serum creatinine level of greater than 500 µmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease.	1B	B	B	B	B	B	B
6.ii. Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage.	3	C	C	C	C	C	C
7. For remission maintenance of ANCA-associated vasculitis we recommend treatment with a combination of low-dose glucocorticoids and either <b>azathioprine, rituximab, methotrexate or mycophenolate mofetil</b> .*	1B	A	A	A	A	A	A
azathioprine and GPA/MPA							
azathioprine and EGPA	3	C	C	C	C	C	C
rituximab and GPA/MPA	1B	A	A	A	A	A	A
methotrexate and GPA/MPA	1B	A	A	B	B	B	B
mycophenolate mofetil and GPA/MPA	1B	A	A	B	B	B	B

Continued

**Table 1** Continued

Statement	Level of evidence	Grade of recommendation					
		Task force (n=21)		EUVAS (n=88)		Combined (n=109)	
		Mode	Median	Mode	Median	Mode	Median
8. We recommend that remission-maintenance therapy for ANCA-associated vasculitis be continued for at least 24 months following induction of sustained remission.	4	D	D	NA	NA	NA	NA
9. For patients with ANCA-associated vasculitis refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials.	3	C	C	C	C	C	C
10. We recommend that structured clinical assessment rather than ANCA testing should inform decisions on changes in treatment for ANCA-associated vasculitis.	4	D	D	NA	NA	NA	NA
11. We recommend the investigation of persistent unexplained haematuria in patients with prior exposure to cyclophosphamide.	2B	C	C	C	C	C	C
12. Hypoimmunoglobulinaemia has been noted after treatment with rituximab. We recommend testing of serum immunoglobulin levels prior to each course of rituximab and in patients with recurrent infection.	3	C	C	C	C	C	C
13. We recommend periodic assessment of cardiovascular risk for patients with ANCA-associated vasculitis.	2B	B	B	B	B	B	B
14. We recommend that patients with ANCA-associated vasculitis should be given a clear verbal explanation of the nature of their disease, the treatment options, the side effects of treatment, and the short-term and long-term prognosis.	3	C	C	C	C	C	C
15. We recommend that following the remission-induction phase of treatment, patients with ANCA-associated vasculitis be assessed for the extent and ongoing impact of comorbidities associated with their diagnosis. Patients should then be advised where they might find the necessary therapies or support for these conditions.	4	D	D	NA	NA	NA	NA

\*The drugs are listed in order of the strength of vote.

ANCA, antineutrophilic cytoplasmic antibodies; EGPA, eosinophilic granulomatosis with polyangiitis; EUVAS, European Vasculitis Society; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; NA, not applicable.

in which rituximab was assigned as grade 4 evidence.<sup>5</sup> The large rituximab in ANCA-associated vasculitis trial (RAVE) and rituximab versus cyclophosphamide in ANCA-associated vasculitis (RITUXVAS) trials did not include participants with EGPA and, generally, trials of agents used to treat patients with EGPA are of smaller size. In addition, most of the trials involving patients with EGPA included those with relapsing or refractory disease states. In addition, many disease-specific consequences of EGPA, such as asthma, are very glucocorticoid responsive making extrapolations from other medications used to treat other types of AAV difficult. This may have contributed to a lower grade being recommended by the EUVAS membership.

None of the task force considered a grade 'A' vote for mycophenolate mofetil, given appropriate situations, for remission induction. Indeed, the EULAR recommendations list a careful set of situations when these agents can be considered in non-organ, non-life-threatening presentations of AAV.<sup>1</sup>

The survey revealed the task force voted grade A recommendation for methotrexate or mycophenolate mofetil as remission-induction agents, the strength of agreement was low (53%). The EUVAS survey revealed a grade B vote. However, a greater proportion of task force members voted for grade C in such scenarios compared with the EUVAS survey members (35% vs 15%). This may represent a loss in confidence in these two drugs in the practising community as compared with the results of the clinical trials that were interpreted by the task force.

#### Author affiliations

<sup>1</sup>Department of Rheumatology, Norfolk and Norwich University Hospital, Norwich, UK

<sup>2</sup>Norwich Medical School, Bob Champion Research and Education Building, Colney Lane, Norwich, UK

<sup>3</sup>Department of Rheumatology, Ipswich Hospital NHS Trust, Norwich Medical School, Norwich, UK

<sup>4</sup>Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

<sup>5</sup>Vasculitis Research Unit, Department of Autoimmune Diseases, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

<sup>6</sup>Assistance Publique-Hôpitaux de Paris, Department of Pulmonology, Bichat-Claude Bernard University Hospital, Paris, France

<sup>7</sup>Immunologie-Zentrum Zürich, Zürich, Switzerland

<sup>8</sup>Vaskulits-Zentrum Süd, Klinik für Innere Medizin, Rheumatologie und Immunologie, Medius Klinik Kirchheim, Kirchheim-Teck, Germany

<sup>9</sup>Rheumazentrum Schleswig-Holstein Mitte, Kuhberg 5a-7, Neumünster, Germany

<sup>10</sup>Department of Otorhinolaryngology, Head and Neck Surgery, University of Kiel, Kiel, Germany

<sup>11</sup>Trinity Health Kidney Centre, Tallaght Hospital, Dublin, Ireland

<sup>12</sup>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Botnar Research Centre, University of Oxford, Oxford, UK

<sup>13</sup>Department of Internal Medicine, Hôpital Saint-Louis, Université Paris 7 René Diderot, Paris, France

<sup>14</sup>Division of Rheumatology and the Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

<sup>15</sup>Vasculitis UK, West Bank House, Winster, Matlock, UK

<sup>16</sup>Department of Medical and Health Sciences Nephrology, Linköping University, Linköping, Sweden

<sup>17</sup>Department of Nephrology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

<sup>18</sup>Department of Nephrology, Lund University, Skåne University Hospital, Lund and Malmö, Sweden

<sup>19</sup>Nephrology Unit, University Hospital of Parma, Parma, Italy

<sup>20</sup>Department of Ophthalmology, School of Medicine, Ankara University, Ankara, Turkey

<sup>21</sup>Lupus and Vasculitis Unit, Addenbrooke's Hospital, Cambridge, UK

**Acknowledgements** We thank the patients, clinicians and administrative staff who have improved the standard of knowledge and care of patients with AAV, through well thought-out clinical trials.

**Contributors** MY drafted the manuscript. All authors have contributed to editing the drafts of the paper.

**Funding** MY is a recipient of a Clinical Research PhD Fellowship from Arthritis Research UK.

**Competing interests** None declared.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Data from this survey are available from the corresponding author on request.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

#### REFERENCES

1. Yates M, Watts RA, Bajema IM, *et al.* EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75.
2. Dougados M, Betteridge N, Burmester GR, *et al.* EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172–6.
3. van der Heijde D, Aletaha D, Carmona L, *et al.* Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
4. Farnor L, Twilt M, Barra L, *et al.* Development of canadian recommendations for the management of ANCA-Associated vasculitides: results of the National needs Assessment Questionnaire. *Open Rheumatol J* 2015;9:16–20.
5. Mukhtyar C, Guillevin L, Cid MC, *et al.* EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis* 2009;68:310–7.



## Validation of the EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis by disease content experts

Max Yates, Richard Watts, Ingeborg Bajema, Maria Cid, Bruno Crestani, Thomas Hauser, Bernhard Hellmich, Julia Holle, Martin Laudien, Mark A Little, Raashid Ahmed Luqmani, Alfred Mahr, Peter Merkel, John Mills, Janice Mooney, Mårten Segelmark, Vladimir Tesar, Kerstin W A Westman, Augusto Vaglio, Nilüfer Yalçındag, David R Jayne and Chetan Mukhtyar

*RMD Open* 2017 3:  
doi: 10.1136/rmdopen-2017-000449

---

Updated information and services can be found at:  
<http://rmdopen.bmj.com/content/3/1/e000449>

---

*These include:*

### References

This article cites 4 articles, 3 of which you can access for free at:  
<http://rmdopen.bmj.com/content/3/1/e000449#ref-list-1>

### Open Access

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Notes

---

To request permissions go to:  
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:  
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:  
<http://group.bmj.com/subscribe/>