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An international Delphi exercise to identify items of importance for measuring response to treatment in ANCA-associated vasculitis☆

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ABSTRACT

Objective: ANCA-associated vasculitis (AAV) is characterized by fluctuating levels of disease activity, but no formal criteria exist to measure response to treatment. This Delphi exercise aimed to reach consensus about which measures are considered by patients and physicians to be most important when assessing response to treatment in clinical trials of AAV.

Methods: An international 3-round online Delphi exercise was conducted. Survey participants included patients with AAV and physicians with expertise in AAV. Survey participants were asked to rate (on a scale of 1–9) the importance of each item when assessing response to treatment in AAV. Items scored 7–9 by ≥70% participants were considered highly important.

Results: 89 patients and 176 physicians completed three rounds of the Delphi exercise. The most highly rated items of response involved disease activity [extent of organ involvement, physician global assessment], mortality [survival], and patient-reported outcomes [patient global assessment and health-related quality of life measures]. Achievement of specific BVAS scores were highly rated only by physicians. Items highly rated only by patients included laboratory measures [changes on urinalysis and acute phase reactants], pain, and fatigue. Additional items related to damage and adverse events were highly rated by both groups.

Conclusion: There is consensus between patients and physicians on many items considered important to measure when assessing response to treatment in AAV. There are some items considered important by only patients or only physicians. These data will inform the next steps in the development criteria of response to treatment in AAV.

☆ We request that all the participants named in the Supplementary Material be listed as "Collaborators" per Medline.

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Introduction

Development of outcome measures for use in randomized controlled trials (RCTs) in ANCA-associated vasculitis (AAV) is challenging given the complex, multi-system nature of the disease, and no formal criteria exist to measure response to treatment in AAV beyond the dichotomous states of "active" and "remission". The current approach does not take into account that disease activity in AAV fluctuates on a continuum from complete remission to fulminant organ-threatening disease. To help reduce variability in outcome measures used in RCTs a core set of domains and outcome instruments that should be assessed in all clinical trials in AAV was developed and received endorsement by the Outcome Measures in Rheumatology (OMERACT) group [1]. This core set includes the domains of disease activity, damage assessment, mortality, and patient-reported outcomes (PROs)/health-related quality of life (HRQoL).

The OMERACT core set of outcomes for AAV has proven quite useful in multiple RCTs, especially regarding the outlined set of domains to study. Nonetheless, there is substantial opportunity to improve the selection and use of instruments in the study of AAV [2,3]. Specifically, there is a need to add granularity in quantification of treatment response and incorporate patient-reported outcomes (PROs). Almost all RCTs of AAV rely on one of the versions of the Birmingham Vasculitis Activity Score (BVAS) [4–7] for assessment of disease activity. However, significant variability exists in endpoint-definitions, including criteria for relapse/remission/response to treatment, timing of outcome assessments, and PROs are often omitted [8].

Given the variability in disease assessment in trials of AAV [8], the lack of input by patients, and an interest in gaining input by a broad range of investigators, an international Delphi exercise was conducted to reach consensus about which measures are considered by patients and physicians to be most important when assessing response to treatment in future RCTs in AAV.

Methods

Study participants

Physicians with expertise in AAV and patients with AAV [granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA)] were recruited to participate in an online 3-round Delphi exercise (with a subsequent fourth round/ranking round). The survey was conducted in English. Physicians were recruited from the Vasculitis Clinical Research Consortium (VCRC) and European Vasculitis Study Group (EUVAS). The VCRC and EUVAS are international multicenter research infrastructures conducting clinical research in different forms of vasculitis. Patients with AAV were recruited from the Vasculitis Patient-Powered Research Network (VPPRN), a network that includes over 3000 patients with vasculitis from twenty-nine different countries, the Vasculitis Foundation, and Vasculitis UK.

Survey elements

Physician and patient participants were asked a series of background demographic questions. Items included for rating in the Delphi exercise were based on the previous systematic literature review (SLR) of outcomes measures collected in previous RCTs of AAV [8], and additional suggestions from a Steering Committee comprised of 8 vasculitis experts, 1 methodologist, and 2 patients with AAV. Items included in the survey related to disease activity, patient-reported outcomes, organ damage, biomarkers, and adverse events. Additional descriptions/explanations of medical terminology used in the survey were also included.

Survey design

The 3-round Delphi survey was conducted from July 1, 2020, to November 30, 2020. A predefined Delphi protocol, based on relevant guidelines from OMERACT, was followed using DelphiManager software [9]. Survey participants were asked to rate the importance of each item when assessing response to treatment in a clinical trial in AAV. Items were rated on a scale of 1–9, where 1–3 corresponds to "Not important", 4–6 "Important but not critical", and 7–9 "Critical" to measure. Items scored 7–9 by $\geq$70% participants were considered to be highly important, and items scored 1–3 by $\geq$70% participants were considered to be of limited importance. Survey participants were also asked to rate at which time points response to treatment should be assessed in a clinical trial in AAV, using the same scoring system.

In the first round, participants were given the option to suggest new items for inclusion in subsequent rounds. In rounds 2 and 3, participants received feedback comparing their own scores to the distribution of scores from other participants and were provided with an opportunity to re-rate items [9]. Items scored 1–3 or 7–9 by $\geq$70% participants in both stakeholder groups (physicians and patients) in the first two rounds were considered to have reached consensus and not included in round 3; all other remaining items were included in round 3. Following completion of the 3-round Delphi Survey, a fourth round/ranking round was conducted to rate items within a domain in order of importance when assessing response to treatment in an RCT in AAV.

Statistical analysis

The proportion of physicians and patients scoring each item as highly important [7–9] after 3 rounds of the Delphi was calculated. For highly rated items (items scored 7–9 by $\geq$70% participants), pooled proportions from both stakeholder groups, relative strength of agreement, and the relative precision of each item was also calculated.

Ethics and informed consent

All patients and physicians consented to participate in the study. An Institutional Review Board at Georgetown University approved the research (Georgetown University Biomedical IRB Committee AB #STUDY0000796).

Results

Study participants

Two-hundred and sixty-five participants completed three rounds of the Delphi, including 176 physicians with expertise in AAV and 89 patients with AAV (see online Supplementary Material). Physicians were from six continents: the majority from Europe [n = 81 (46%)] or North America [n = 50 (28%)]. Most physicians specialized in rheumatology [n = 105 (60%)] or nephrology [n = 50 (28%)]. All physicians were in practice for at least 2 years (two-thirds >10 years) and responsible for primarily managing $\geq$30 patients with AAV; over half of the physicians managed >75 patients with AAV (**Table 1**). Patients with AAV were from four continents, with most located in North America [n = 63 (71%)] or Europe [n = 23 (26%)], with a diagnosis of GPA [n = 72 (81%)] or MPA [n = 17 (19%)]. The majority of patients with AAV were female [n = 61 (69%)], ages 50–79 years [n = 67 (75%)], were diagnosed in the past 10 years [n = 62 (70%)], and were currently on treatment for AAV [n = 62 (70%)] (**Table 2**).

Combined patient and physician 3-Round Delphi

After completion of 3-rounds, the most highly rated items by patients and physicians to measure when assessing response to treatment in an RCT in AAV (**Table 3**) involved disease activity [extent of organ

Table 1
Demographics of Physician Survey Participants.

	Physicians ($n = 176$)
Continent currently practicing in	Africa: 1 (1%) Asia: 13 (7%) Australia: 23 (13%) Europe: 81 (46%) North America: 50 (28%) South America: 8 (5%)
Area of specialization	Rheumatology: 105 (60%) Nephrology: 50 (28%) Internal Medicine: 11 (6%) Other: 10 (6%)
Practice setting	Academic: 151 (86%) Other: 25 (14%)
Time since completion of specialty training*	2–5 years: 22 (13%) 6–10 years: 28 (16%) 11–20 years: 54 (31%) 21–30 years: 42 (24%) >30 years: 18 (10%)
Experience managing patients with ANCA-associated vasculitis** (Number of patients responsible for primarily managing)	30–50: 46 (26%) 51–75: 30 (17%) 76–100: 28 (16%) >100: 68 (39%)

*Missing response:12 (6%); **Missing response: 4 (2%).

Table 2
Demographics of Patient Survey Participants.

	Patients with ANCA-associated vasculitis* ($n = 89$)
Continent currently located in	Africa: 1 (1%) Australia: 2 (2%) Europe: 23 (26%) North America: 63 (71%)
Diagnosis	GPA: 72 (81%) MPA: 17 (19%)
Gender (Female,%)	61 (69%)
Age	18–29 years: 4 (5%) 30–49 years: 16 (18%) 50–79 years: 67 (75%) ≥80 years: 2 (2%)
Time since diagnosis	<5 years: 35 (39%) 6–10 years: 27 (30%) 11–20 years: 18 (20%) 21–30 years: 8 (9%) >30 years: 1 (1%)
Time since last on treatment for vasculitis	Currently: 62 (70%) <1 years: 9 (10%) 1–5 years: 13 (15%) 6–10 years: 4 (4%) >10 years: 1 (1%)

*Percentages may not total 100 due to rounding.

involvement, physician global assessment], mortality [survival], and patient-reported outcomes [patient global assessment and health-related quality of life measures]. Achievement of BVAS ≤1, BVAS of 0, and reduction in BVAS were highly rated only by physicians. Pain and fatigue were highly rated by patients, but not by physicians. Additionally, changes on urinalysis and acute phase reactants were highly rated only by patients. Other items relating to organ damage and treatment-related adverse events were highly rated by both patients and physicians (**Table 3**). There were no items rated of limited importance by both patients and physicians. **Fig. 1** presents the pooled proportions and relative levels of agreement and differences in opinion of patients and physicians for highly rated items.

Timing for assessment of response to treatment

Time points that were highly rated (scored 7–9) by patients and physicians for assessment of response to treatment in an RCT in AAV are detailed in **Table 4**. Assessment at baseline, 6, 12, and 24 months were rated as highly important time points for assessment of response to treatment by ≥90% of patients and physicians. Assessments at 1, 3, and 18 months were rated as highly important by ≥70% of patients and physicians. Assessment at 9 months was highly rated only by patients. None of the other time points were highly rated by patients or physicians.

Round four (ranking round)

All physicians who completed rounds 1–3 (176 physicians) and 62/89 (70%) patients who completed rounds 1–3 completed round 4 (ranking round). Physicians and patients ranked the items previously rated as highly important to measure in the 3-round Delphi, within the domains of patient-reported outcomes and disease activity assessment.

Within the domain of patient-reported outcomes, the highest ranked items by physicians were "improved patient global assessment" (ranked highest by 61% of physicians) and "improved HRQoL measures" (ranked highest by 28% of physicians). Only 4% of physicians ranked "improvement in fatigue" most highly, and 7% of physicians ranked "improved pain" most highly. There was greater variability in the highest ranked items by patients: "improved pain" was ranked highest by 35% of patients, "improved HRQoL measures" was ranked highest by 33% of patients, "improved patient global assessment" was ranked highest by 19% of patients, and improved fatigue was ranked highest by 13% of patients.

Within the domain of disease activity, the highest ranked items by physicians were "no new/worse major organ involvement" (ranked highest by 64% of physicians) and "improvement/reduction in BVAS" (ranked highest by 32% of physicians). The highest ranked items by patients were "no new/worse major organ involvement" (ranked highest by 60% of patients) and "improved physician global assessment" (ranked highest by 20% of patients).

Discussion

This Delphi exercise demonstrated consensus between international experts in AAV and patients with AAV on many items considered important to measure when assessing response to treatment in RCTs in AAV. Items that were considered highly important by patients and physicians encompassed all domains from the OMERACT core set: disease activity, patient-reported outcomes, damage assessment, and mortality [1]. There was also a lack of agreement between patients and physicians on several items, highlighting differences in the perspectives of each stakeholder group.

The items most highly rated by both patients and physicians related to disease activity included no new/worse major organ involvement, improved kidney function, no development of end-stage kidney disease, and improved physician global assessment. Acute phase reactants were favored as more important by patients than physicians. Results of the prior SLR found that biomarkers (most frequently acute phase reactants) were incorporated into trial outcomes in only approximately 1/3 of RCTs in AAV [8]. However, a specific biomarker of disease activity in AAV is still lacking and acute phase reactants are nonspecific and do not always track well with disease activity in AAV, all of which may explain why acute phase reactants were considered less important by physicians. In contrast, BVAS measures were favored as more important by physicians than patients, specifically achievement of BVAS scores of 0 or 1, more so than reduction in the absolute BVAS score. BVAS is a physician-based disease measure which uses a complex scoring system that is not well-understood by many patients with AAV, and patient input was also not part of the development of BVAS, possibly explaining

Table 3
Proportion of physicians and patients after 3 rounds of the Delphi who rated candidate items as highly important to measure when assessing response to treatment in a clinical trial in ANCA-associated vasculitis.

Category	Delphi Item	Physicians N†	Count	%	Patients N†	Count	%
Patient-reported outcomes	Improved fatigue	176	24	14%	89	65	73%
	Improved pain	176	50	28%	89	66	74%
	Improved patient global assessment	182	133	73%	107	77	72%
	Improved HRQoL measures	176	133	76%	89	76	85%
Disease activity	**BVAS (any version)**						
	BVAS of 0	176	167	95%	89	53	60%
	BVAS ≤1	176	167	95%	89	55	62%
	>50% reduction in BVAS	176	127	72%	89	59	66%
	Kidney function						
	Improved kidney function (eGFR)	181	173	96%	104	86	83%
	No development of ESKD	181	176	97%	104	101	97%
	Ability to discontinue dialysis	176	148	84%	89	56	63%
	Resolution of hematuria on urinalysis	176	75	43%	89	62	70%
	Resolution of proteinuria on urinalysis	176	89	51%	89	65	73%
	Other						
	No new/worse major organ involvement	181	173	96%	103	98	95%
	Improved physician global assessment	181	145	80%	96	77	80%
	No rise in acute phase reactants	176	47	27%	89	63	71%
Mortality	Survival	182	182	100%	113	109	97%
Damage	No new major organ damage	180	170	94%	104	101	97%
	No new non-major organ damage	176	142	81%	89	75	84%
Adverse events	Severe medication-related adverse events	181	171	94%	105	95	91%
	Severe infections	176	172	98%	89	80	90%

HRQoL: health-related quality of life; BVAS: Birmingham Vasculitis Activity Score; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease.
† Some participants did not respond to every question accounting for differences in total numbers of responses. The items approved after round 2 and not included in round 3 had greater responses due to drop out of some participants between rounds 2 and 3.

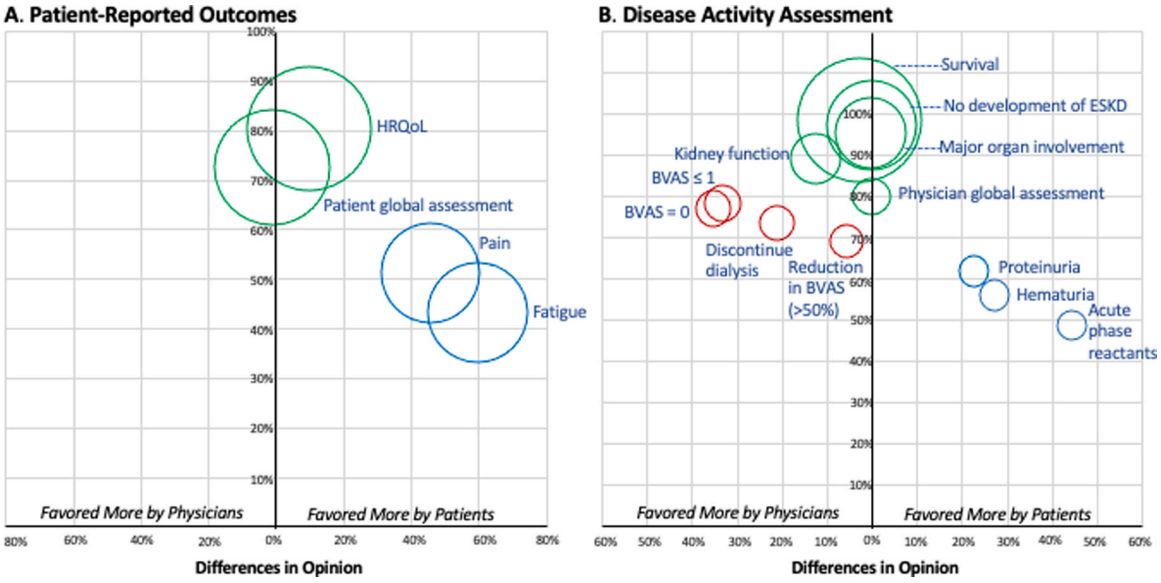

Fig. 1. Items Rated as Highly Important to Measure when Assessing Response to Treatment in a Clinical Trial in ANCA-Associated Vasculitis. The combined proportions (y axis) and differences in opinion (x axis) of patients and physicians rating items as highly important to measure. Bubble size reflects the relative precision of each item (larger = higher precision). Items related to patient-reported outcomes are shown in panel A and items related to disease activity assessment are shown in panel B. Blue circles indicate ≥70% patients rated the item as highly important, Red circles indicate ≥70% physicians rated the item as highly important, Green circles indicate ≥70% patients and physicians rated the item as highly important.
HRQoL: health-related quality of life; BVAS: Birmingham Vasculitis Activity Score; ESKD: end-stage kidney disease. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

this discrepancy.

Although BVAS has helped to advance the conduct of RCTs in AAV, many challenges remain with its use as an instrument for disease activity assessment. BVAS provides a numerical score which is most often reduced in RCTs to a dichotomous variable representing active disease (BVAS > 0) or remission (BVAS = 0) [10–19]. Additionally, the score is not linear (e.g. BVAS = 12 does not indicate the disease is three times worse than BVAS = 4) and, therefore, intermediate disease states are not easily captured, leading to difficulty with use of BVAS to assess partial response to treatment in RCTs in AAV. Experience with the use of BVAS in RCTs has also demonstrated that even experienced investigators have difficulty consistently applying the central concept to only score items that truly represent active vasculitis, admixing items of active vasculitis with items of disease that may take longer to resolve (or never will), such

Table 4
Proportion of physicians and patients rating timepoints as highly important for assessment of response to treatment in a clinical trial in ANCA-associated vasculitis.

	Physicians			Patients		
Time Points	N	Count	%	N	Count	%
Baseline	180	174	97%	96	89	93%
1 month	176	133	76%	89	63	71%
2 months	177	30	17%	89	56	63%
3 months	182	177	97%	96	83	86%
4 months	177	31	18%	89	37	41%
5 months	177	11	6%	89	36	40%
6 months	182	176	97%	96	88	92%
7 months	177	6	3%	89	29	33%
8 months	177	3	2%	89	29	33%
9 months	177	120	68%	89	69	78%
10 months	177	4	2%	89	28	31%
11 months	177	3	2%	89	36	40%
12 months	182	177	97%	97	91	94%
18 months	182	148	81%	97	86	89%
24 months	182	177	97%	97	91	94%

as sensory neuropathy or proteinuria. Many trials in AAV incorporate an adjudication process for reviewing BVAS data and disease state determinations.

There is now broad recognition of the importance of incorporating patients' self-assessments of disease status and impact into outcome measures in clinical research. In previous RCTs in AAV, PROs were often not included as an outcome [8]; in trials where PROs were assessed, HRQoL was most frequently evaluated through the use of the 36-Item Short Form Survey (SF-36) in 28 (41%) RCTs, and patient global assessment was rarely considered as an outcome (assessed as primary or secondary outcome in only 2 RCTs) [8]. This Delphi exercise demonstrated that among items related to PROs, improved HRQoL and improvement in patient global assessment were highly rated by both patients and physicians, while only patients rated pain and fatigue highly. These findings are consistent with previous reports showing significant differences in perspectives between patients and physicians with how life impact factors are incorporated into disease activity assessment in AAV [20,21]. Results from this Delphi exercise, combined with prior work demonstrating that patient global assessment captures unique information about disease activity in AAV, support potential incorporation of a patient's global assessment into outcome assessment in AAV [22]. HRQoL was most frequently assessed by SF-36 in prior RCTs, which is not disease-specific for AAV; the AAV-PRO, a recently-developed disease-specific PRO, is now available for inclusion in RCTs of AAV [23]. Fatigue and pain were also infrequently considered specifically as outcomes in prior RCTs (fatigue in 5 (7%) RCTs and pain in 4 (6%) RCTs) but are incorporated to some extent in generic HRQoL measures [8]. The causes of fatigue may be multi-factorial, including active vasculitis, treatment side-effects, comorbidities, and psychosocial factors all potentially causing this symptom. It can be difficult to know to what extent fatigue is attributable to AAV versus other factors, and fatigue may be a more difficult aspect of the disease to treat. These issues may explain why fatigue was considered less important as a measure of response by physicians compared to patients. However, items identified as highly important to measure by at least one stakeholder group should still be considered during the development process of criteria for response to treatment in AAV.

Multiple time points were identified as highly important by patients and physicians for assessment of response to treatment in AAV. One specific time point to assess response was not identified, as ≥70% of both stakeholder groups rated seven unique time points as highly important. Time points that were highly rated included the most frequently applied time points for assessment of outcomes identified in the prior SLR (baseline, 3, 6, and 12 months) [8]. This survey also identified seven time points that were not highly rated by either stakeholder group. Ultimately, a time point for assessing response to treatment in AAV needs to incorporate the study design, the pharmacokinetics and biologic action of an intervention, and balance assessing treatment efficacy in a relatively short period of time, as AAV can lead to organ-threatening manifestations, with a long enough duration for the treatment to have biologic effect.

There are several strengths of this study. Physicians with expertise in AAV and patients with AAV were surveyed in parallel, and opinions of both stakeholder groups were considered equally. There has been recent emphasis in clinical research on the importance of integrating patients' perspectives, which is highlighted by this study. This study was also conducted internationally and included the opinions of physicians from six continents and patients from four continents. Survey responses were anonymous and because survey participants in a Delphi study do not interact directly with each other, the group is not dominated by views of a few individuals [24].

Several limitations of this study should also be noted. The survey was only conducted in English and relative to English-speaking countries fewer patient survey participants were from non-English speaking countries. Of a long list of items, few items were considered to be "not important". Therefore, although the final round of ranking items provided focus on key items, additional items within a sub-domain could be consolidated when creating an outcome measure. Finally, some participants did not respond to every question, accounting for differences in total numbers of responses for each item, and only 70% patients completed the ranking round.

In conclusion, this Delphi exercise delivers a set of items to consider when assessing treatment response in AAV that are considered important to patients, physicians, or both patients and physicians. This set includes measures related to disease activity, PROs, mortality, and damage assessment. AAV has a multi-faceted impact on patients and development of a composite response measure is likely to best capture the full spectrum of disease [25]. The results of this Delphi exercise will inform a draft set of response criteria for additional discussion by an Expert Panel, comprised of experts in AAV and patient research partners. Further testing of these draft criteria will be completed through a data-driven process, with subsequent validation of new composite response criteria for use in clinical trials in AAV [25].

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152021.

References

[1] Merkel PA, Aydin SZ, Boers M, Direskeneli H, Herlyn K, Seo P, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. J Rheumatol 2011;38(7):1480–6.

[2] Beaton DE, Maxwell LJ, Shea BJ, Wells GA, Boers M, Grosskleg S, et al. Instrument selection using the OMERACT Filter 2.1: the OMERACT methodology. J Rheumatol 2019;46(8):1028–35.

[3] Beaton D., Maxwell L., Grosskleg S., Shea B., Tugwell P., Bingham C., et al. The OMERACT Handbook. Available from: https://omeracthandbook.org/handbook. 2021.

[4] Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, et al. Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM 1994;87(11):671–8.

[5] Luqmani RA, Exley AR, Kitas GD, Bacon PA. Disease assessment and management of the vasculitides. Baillieres Clin Rheumatol 1997;11(2):423–46.

[6] Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68(12):1827–32.

[7] Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, 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(4):912–20.

[8] Monti S, Quinn KA, Christensen R, Jayne D, Langford C, Lanier GE, et al. Use and reporting of outcome measures in randomized trials for anti-neutrophil cytoplasmic antibody-associated vasculitis: a systematic literature review. Semin Arthritis Rheum 2020;50(6):1314–25.

[9] Humphrey-Murto S, Crew R, Shea B, Bartlett SJ, March L, Tugwell P, et al. Consensus Building in OMERACT: recommendations for Use of the Delphi for Core Outcome Set Development. J Rheumatol 2019;46(8):1041–6.

[10] Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniene J, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003;349(1):36–44.

[11] De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52(8):2461–9.

[12] Wegener's. Granulomatosis Etanercept Trial Research G. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352(4):351–61.

[13] Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, et al. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol 2007;18(7):2180–8.

[14] Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008;359(26):2790–803.

[15] de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, 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(10):670–80.

[16] Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA 2010;304(21):2381–8.

[17] Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363(3):211–20.

[18] Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363(3):221–32.

[19] Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371(19):1771–80.

[20] Milman N, Boonen A, Tugwell P, Merkel PA, Group OVW. Clinicians' perspective on key domains in ANCA-associated vasculitis: a Delphi exercise. Scand J Rheumatol 2017;46(2):112–7.

[21] Milman N, McConville E, Robson JC, Boonen A, Tugwell P, Wells GA, et al. Updating OMERACT Core Set of Domains for ANCA-associated Vasculitis: patient perspective using the international classification of function, disability, and health. J Rheumatol 2019;46(10):1415–20.

[22] Tomasson G, Davis JC, Hoffman GS, McCune WJ, Specks U, Spiera R, et al. Brief report: the value of a patient global assessment of disease activity in granulomatosis with polyangiitis (Wegener's). Arthritis Rheumatol 2014;66(2):428–32.

[23] Robson JC, Dawson J, Doll H, Cronholm PF, Milman N, Kellom K, et al. Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire. Ann Rheum Dis 2018;77(8):1157–64.

[24] Sinha IP, Smyth RL, Williamson PR. Using the Delphi technique to determine which outcomes to measure in clinical trials: recommendations for the future based on a systematic review of existing studies. PLoS Med 2011;8(1):e1000393.

[25] Quinn KA, Monti S, Christensen R, Jayne D, Langford CA, Lanier GE, et al. Developing a composite outcome tool to measure response to treatment in ANCA-associated vasculitis: a mixed methods study from OMERACT 2020. Semin Arthritis Rheum 2021.