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RESEARCH LETTER

Practice Patterns of Induction Therapy in Severe Anti-neutrophil Cytoplasmic Autoantibody-Associated Vasculitis

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INTRODUCTION

Anti-neutrophil cytoplasmic antibodies-associated vasculitis (ANCA-AAV) is a group of systemic necrotizing small vessel vasculitis characterized by the presence of circulating ANCA. AAV patients often present to various specialists whose management may differ. The few published surveys on AAV management among specialists are limited by their small sample size, single-center design, and lack of a comprehensive questionnaire.[1–3] Here, we present the first international comprehensive survey that sought to explore practice patterns in AAV management during the induction phase.

The online survey comprising of 65 items aimed at exploring AAV practice patterns within the last 5 years. It included sections on provider and patient demographics, and use of induction therapies, including pulse methylprednisolone (MeP), oral glucocorticoids, plasma exchange (PLEX), cyclophosphamide (CYC), rituximab, mycophenolate mofetil, methotrexate, and avacopan. The survey also evaluated the practice of obtaining baseline dual-energy X-ray absorptiometry scan, use of Pneumocystis Jiroveci Pneumonia prophylaxis, use of calcium and vitamin D supplements, and use of bisphosphonates and denosumab. In addition, the survey examined the frequency of laboratory monitoring. (Supplementary Methods)

RESULTS

Survey Participants and Their Practice

Of the 365 survey responses, 321 were considered complete (more than 80% of questions answered) and were included in the final analysis. Fifty-three percent of participants were nephrologists, 41% were rheumatologists, and 2% were pulmonologists. There was a geographic representation from 36 countries and 6 continents. Over half of the survey participants reported managing between 10 and 50 AAV patients per year and 10% cared for over 100 AAV patients per year. (Supplementary Table S1)

Overall Induction Therapy Practice Patterns

Among all participants, 94% used pulse MeP, 69% used reduced dose glucocorticoids per the Plasma Exchange and Glucocorticoids in Severe ANCA-AAV trial,[4] 92% used rituximab, 90% used CYC, 39% used PLEX, 22% used methotrexate, 20% used mycophenolate mofetil, and 12% used avacopan. Among the 39% of respondents who used PLEX, serum creatinine level (>5.7 mg/dl) and dialysis dependency at presentation were indications for PLEX for 47% and 54%, respectively. In addition, among those who used PLEX, 89.3% reported alveolar hemorrhage requiring mechanical ventilation, and 43.8% reported alveolar hemorrhage not requiring mechanical ventilation as indications for PLEX use. For AAV patients presenting with kidney failure requiring

dialysis or alveolar hemorrhage requiring mechanical ventilation, the most preferred induction therapy was rituximab with glucocorticoids and PLEX (24%) or without PLEX (22%). (Table 1)

Regarding the use of prophylactic therapies, 90% of participants used Pneumocystis Jiroveci Pneumonia prophylaxis and 92% used calcium and vitamin D supplements. Laboratory monitoring was conducted during the first month of treatment once every 2 weeks by 48% of participants and every 12 weeks after remission by 61% of participants. (Supplementary Table S2)

Differences in Induction Therapy Practice Patterns, Prophylactic Therapy Use, and Laboratory Monitoring Based on Physician Specialty, Patient Volume, and Continent of Practice

Use of pulse MeP differed significantly based on the continent of practice ($P = 0.006$), with 98%, 94%, and 87% of participants reporting its use in North America, Asia, and Europe, respectively. Seventy-six percent of respondents from North America reported stopping glucocorticoid at remission, a percentage much higher than those on other continents ($P < 0.001$). In addition, nephrologists used lower doses of pulse MeP as compared to rheumatologists (500 mg among 56% of nephrologists and 1000 mg among 63% of rheumatologists, $P < 0.001$). The use of reduced dose glucocorticoid was higher among nephrologists ($P < 0.001$), participants with higher AAV patient volume ($P = 0.001$), and participants in Asian countries ($P < 0.001$). Rituximab use was more frequent among participants with higher AAV patient volume ($P = 0.004$) and in North America and Europe ($P = 0.003$). A higher proportion of rheumatologists used rituximab biosimilar ($P = 0.001$). CYC was used more often in Europe and Asia ($P < 0.001$). Use of PLEX was higher among nephrologists ($P < 0.001$), participants with a higher AAV patient volume ($P = 0.011$), and in Europe ($P = 0.001$). Furthermore, active lesions on kidney biopsy served as an important indication for PLEX use for renal vasculitis among nephrologists ($P = 0.019$). The use of avacopan was higher in North America ($P < 0.001$) (Table 2).

Nephrologists were more likely to use Pneumocystis Jiroveci Pneumonia prophylaxis ($P = 0.023$). Rheumatologists were more likely to obtain a baseline dual-energy X-ray absorptiometry scan ($P < 0.001$) and use calcium and vitamin D supplements ($P = 0.039$). Bisphosphonates or denosumab were used more often by rheumatologists ($P < 0.001$), participants with higher AAV patient volume ($P = 0.002$), and in Asia ($P = 0.036$). Whereas rheumatologists were more likely to obtain serum

Table 1. Overall induction therapy practice patterns among all survey participants

Induction therapy	N (%)
Pulse MeP use	301 (94)
Reduced dose GC use[a]	218 (69)
Cessation of GC use at remission	187 (59)
Ongoing use of GC after remission	129 (42)
Duration of GC use among those who do not stop at remission	
6 mo	16 (12)
12 mo	35 (27)
18 mo	16 (13)
24 mo	26 (20)
Never stopped	36 (28)
Rituximab use ($n = 314$)	289 (92)
Use of	
Rituximab	81 (28.0)
Biosimilar	95 (33)
Both	113 (39)
CYC use ($n = 314$)	281 (90)
Mycophenolate mofetil use ($n = 312$)	59 (20)
Methotrexate use ($n = 301$)	68 (22)
PLEX use ($n = 314$)	121 (39)
Indications for PLEX ($n = 121$)	
Serum creatinine <5.7 mg/dl	12 (9.9)
Serum creatinine >5.7 mg/dl	71 (58.7)
Dialysis dependency	68 (56.2)
Concurrent anti-GBM disease	99 (81.8)
Alveolar hemorrhage requiring mechanical ventilation	108 (89.3)
Alveolar hemorrhage not requiring mechanical ventilation	53 (43.8)
Refractory vasculitis	61 (50.4)
Indications for PLEX use for renal vasculitis ($n = 121$)	
Serum creatinine level at presentation (>5.7 mg/dl)	57 (47)
Dialysis dependency	65 (54)
Serum creatinine trend	64 (53)
Oliguria	18 (15)
Active lesions on kidney biopsy	50 (41)
Preferred induction therapy for AAV patients with kidney failure requiring dialysis or alveolar hemorrhage requiring mechanical ventilation ($n = 297$)	
RTX plus GC	70 (22)
CYC plus GC	51 (16)
Combination of RTX and CYC plus GC	40 (13)
PLEX plus RTX with GC	73 (24)
PLEX plus CYC with GC	33 (11)
PLEX plus combination of RTX, CYC, and GC	43 (14)
Avacopan use ($n = 299$)	38 (12)
Time point of avacopan initiation ($n = 36$)	
Immediately after diagnosis	14 (38)
1 wk after diagnosis	9 (24)
2 wk after diagnosis	4 (11)
1 mo after diagnosis	1 (3)
Whenever insurance approves	9 (24)
Pulse MeP use with avacopan ($n = 38$)	33 (87)
Length of GC therapy after avacopan initiation ($n = 38$)	
1 wk	3 (8)
2 wk	5 (13)
3 wk	0 (0)
4 wk	17 (45)
>4 wk	13 (34)

CYC, cyclophosphamide; GC, glucocorticoids; MeP, methylprednisolone; PLEX, plasma exchange; RTX, rituximab.
[a]Reduced dose PEXIVAS glucocorticoid dosing.

Table 2. Differences in induction therapy practice patterns based on physician specialty, patient volume, and continent of practice

	Physician specialty n (%)			AAV patient volume n (%)			Continent of practice n (%)			
Practice patterns	**Nephrology**	**Rheumatology**	***P*-value**	**<50/yr**	**>50/yr**	***P*-value**	**North America**	**Europe**	**Asia**	***P*-value**
Pulse MeP use	160 (95)	122 (94)	0.759	231 (95)	67 (94)	0.920	110 (98)	73 (87)	85 (94)	0.006
Dose of pulse MeP										
250 mg	18 (11)	3 (3)	<0.001	15 (7)	7 (11)	0.194	7 (6)	13 (18)	1 (1)	<0.001
500 mg	89 (56)	37 (30)		96 (42)	34 (51)		44 (40)	45 (62)	26 (31)	
750 mg	3 (2)	5 (4)		6 (3)	2 (3)		2 (2)	1 (1)	5 (6)	
1000 mg	49 (31)	77 (63)		114 (49)	23 (35)		56 (52)	14 (19)	53 (62)	
Reduced dose GC use[a]										
Yes	135 (80)	71 (55)	<0.001	160 (66)	55 (77)	0.001	16 (14)	13 (16)	45 (50)	<0.001
No, standard dose	27 (16)	44 (34)		70 (29)	7 (10)		89 (80)	64 (77)	37 (41)	
Other	6 (4)	15 (11)		13 (5)	9 (13)		7 (6)	6 (7)	8 (9)	
Cessation of GC use at remission	101 (61)	74 (57)	0.589	143 (59)	42 (60)	0.892	84 (76)	41 (49)	43 (48)	<0.001
Duration of GC use among those who do not stop at remission										
6 mo	12 (18)	4 (7)	<0.001	14 (14)	2 (7)	0.153	2 (7)	4 (10)	26 (60)	<0.001
12 mo	28 (42)	6 (11)		22 (22)	13 (47)		10 (37)	4 (10)	1 (2)	
18 mo	7 (11)	7 (13)		13 (13)	2 (7)		10 (37)	15 (36)	6 (14)	
24 mo	10 (15)	13 (24)		20 (20)	6 (21)		4 (15)	6 (14)	2 (5)	
Never stopped	9 (14)	25 (45)		30 (31)	5 (18)		1 (4)	13 (31)	8 (19)	
Rituximab use	151 (91)	121 (94)	0.368	214 (89)	71 (100)	0.004	108 (96)	81 (98)	75 (85)	0.003
Use of										
Rituximab	56 (37)	21 (17)	0.001	70 (33)	10 (14)	0.010	37 (34)	13 (16)	22 (29)	<0.001
Biosimilar	39 (26)	51 (42)		65 (30)	28 (39)		19 (18)	41 (51)	24 (32)	
Both	56 (37)	49 (41)		78 (37)	33 (47)		52 (48)	27 (33)	29 (39)	
CYC use	147 (89)	118 (92)	0.497	211 (88)	66 (93)	0.262	87 (78)	82 (94)	81 (92)	<0.001
Duration of CYC use										
3 mo	65 (44)	23 (20)	<0.001	66 (31)	27 (41)	0.186	38 (44)	35 (43)	12 (15)	<0.001
3 to 6 mo	80 (55)	91 (78)		140 (67)	39 (59)		48 (55)	47 (57)	68 (84)	
More than 6 mo	2 (1)	3 (2)		5 (2)	0 (0)		1 (1)	0 (0)	1 (1)	
Formulation of CYC										
Oral	24 (16)	5 (4)	0.003	21 (10)	8 (12)	0.736	21 (24)	4 (5)	4 (5)	<0.001
Intravenous	104 (71)	101 (86)		161 (76)	51 (77)		49 (56)	72 (88)	70 (86)	
Oral and intravenous	19 (13)	12 (10)		29 (14)	7 (11)		17 (20)	6 (7)	7 (9)	
Methotrexate use	11 (7)	46 (37)	<0.001	40 (17)	28 (40)	<0.001	18 (16)	24 (29)	17 (19)	0.089
Mycophenolate mofetil use	25 (15)	28 (22)	0.145	33 (14)	25 (35)	<0.001	13 (12)	19 (23)	18 (21)	0.098
PLEX use	81 (49)	33 (26)	<0.001	83 (35)	36 (51)	0.011	33 (30)	46 (55)	29 (33)	0.001
Indications for PLEX										
SCr <5.7 mg/dl	9 (11.1)	3 (9.1)	1.00	7 (8.4)	5 (13.9)	0.364	2 (6.1)	6 (13.0)	3 (10.3)	0.663
SCr >5.7 mg/dl	50 (61.7)	19 (57.6)	0.681	45 (54.2)	24 (66.7)	0.206	15 (45.5)	33 (71.7)	16 (55.2)	0.058
Dialysis dependency	50 (61.7)	16 (48.5)	0.194	46 (55.4)	21(58.3)	0.769	19 (57.6)	28 (60.9)	13 (44.8)	0.391
Concurrent anti-GBM disease	72 (88.9)	21 (63.6)	0.002	67 (80.7)	30 (83.3)	0.736	29 (87.9)	41 (89.1)	20 (69.0)	0.072
Alveolar hemorrhage requiring mechanical ventilation	73 (90.1)	30 (90.9)	1.00	77 (92.8)	29 (80.6)	0.050	31 (93.9)	41 (89.1)	25 (86.2)	0.610
Alveolar hemorrhage not requiring mechanical ventilation	38 (46.9)	13 (39.4)	0.464	36 (43.4)	16 (44.4)	0.914	8 (24.2)	24 (52.2)	15 (51.7)	0.028
Refractory vasculitis	41 (50.6)	16 (48.5)	1.00	41 (49.4)	18 (50.0)	0.952	10 (30.3)	31 (67.4)	15 (51.7)	0.005
Indications for PLEX use for renal vasculitis										
SCr >5.7 mg/dl	41 (51)	15 (46)	0.617	38 (46)	17 (47)	0.483	10 (30)	28 (61)	13 (45)	0.027
Dialysis dependency	47 (58)	16 (49)	0.353	44 (53)	19 (53)	0.981	19 (58)	28 (61)	10 (35)	0.074
SCr trend	41 (51)	18 (55)	0.703	36 (43)	26 (72)	0.004	13 (39)	35 (76)	14 (48)	0.002
Oliguria	16 (20)	2 (6)	0.091	16 (16)	5 (14)	0.804	5 (15)	10 (22)	3 (10)	0.486
Active lesions on kidney biopsy	39 (48)	8 (24)	0.019	31 (37)	19 (53)	0.117	12 (36)	21 (46)	11 (38)	0.680
Avacopan use	21 (13)	13 (10)	0.458	21 (9)	17 (24)	0.656	28 (26)	8 (10)	0%	<0.001

AAV, ANCA-associated vasculitis; anti-GBM, anti-glomerular basement membrane; GC, glucocorticoid; MeP, methylprednisolone; PLEX, plasma exchange; SCr, serum creatinine.
[a]Defined as the reduced dose per the Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis (PEXIVAS) trial.[4]

immunoglobulins at baseline ($P = 0.003$) and monitor erythrocyte sedimentation rate/C-reactive protein ($P < 0.001$), nephrologists were more likely to monitor ANCA serology ($P < 0.001$) (Supplementary Table S3).

DISCUSSION

This first international AAV physician survey represents the largest sampling of physicians who provide direct care to patients with AAV. It highlights general

agreement in some areas of AAV management but also recognizes areas of variable consensus based on physician specialty, continent of practice, and AAV patient volume.

Though there is no clear consensus on the dose and number of pulse MeP used for induction therapy, higher doses were reported by rheumatologists as compared to nephrologists. The reason for this discrepancy is not clear because one would have anticipated use of higher doses of pulse MeP by nephrologists who may be encountering more severe disease presentations. Despite the demonstration of noninferiority of reduced dose glucocorticoid dose,[4] only 69% of participants reported use of reduced dose glucocorticoids. This finding was more common among participants with higher AAV patient volume likely owing to their greater clinical experience with the negative side effects. Despite achieving clinical remission and current society recommendations, 28% of respondents reported never stopping glucocorticoids. Interestingly, this shocking observation differed geographically and based on the subspecialty. European respondents and rheumatologists tended to follow this practice. We speculate that this may be related to the different disease phenotype with low grade grumbling disease encountered by rheumatologists with potential need for long-term glucocorticoids use. The geographic differences in the use of long-term glucocorticoids may be related to higher proportion of practitioners in North America using rituximab for remission induction. Though the Plasma Exchange and Glucocorticoids in Severe ANCA-AAV study suggested no significant added benefit to patients with diffuse alveolar hemorrhage,[4] a high percentage of respondents reported PLEX use in such patients. We found that nephrologists reported more use of PLEX compared to rheumatologists. This discrepancy is in part related to the discordance in guidelines as outlined by the Kidney Disease Improving Global Outcomes and American College of Rheumatology,[5,6] but may also be explained by the possibility that indications for PLEX are more frequently encountered by nephrologists, who also have the expertise in the technical aspect of this treatment[7–9,S1,S2]. New European guidelines have been officially published post-Plasma Exchange and Glucocorticoids in Severe ANCA-AAV, which may explain the significant use of PLEX in Europe.[S3,S4] New European Alliance of Associations for Rheumatology recommendations have been presented at the European Alliance of Associations for Rheumatology conference 2022 with a general trend toward using PLEX even at lower serum creatinine levels.

The finding that rituximab is the preferred option for severe presentations is worth highlighting. This contrasts with the recent Kidney Disease Improving Global Outcomes guideline which recommends using CYC with glucocorticoids or a combination of CYC and rituximab with glucocorticoids. Given that AAV is a disease of the elderly, we speculate that some providers may still prefer rituximab in the elderly and frail patients even when presenting with severe presentations. Only about a third of participants used brand rituximab whereas the remainder used biosimilar. This is encouraging because the efficacy and safety of the rituximab biosimilar has been shown to be noninferior to reference rituximab and can contribute to significant cost savings.[S5–S8] Most participants used avacopan with concurrent pulse MeP and continued oral prednisone for 4 weeks or longer, in contrast to the glucocorticoid protocol outlined in the ADVOCATE trial.[S9] More granular data on glucocorticoid use from the ADVOCATE trial and avacopan use from real-world data is needed to guide the use of avacopan in AAV.

Rheumatologists were more likely to provide care regarding bone health, which reflects their greater expertise in treating osteopenia and osteoporosis and their familiarity with the adverse outcomes of glucocorticoids when treating other rheumatological disorders.[S10–S12] Nephrologists monitored laboratory data more frequently during the first month which may be due to the more severe kidney disease in their cohort requiring close monitoring. Nephrologists were also more likely to follow ANCA serology, whereas rheumatologists were more likely to follow erythrocyte sedimentation rate/ C-reactive protein. This discrepancy is likely attributed to published data looking at the utility of erythrocyte sedimentation rate/ C-reactive protein in other rheumatological diseases.[S13–S15] Sixty-one percent of participants monitored serum immunoglobulin levels. Patients with hypogammaglobulinemia warrant evaluation for secondary antibody deficiency and identification of candidates for immunoglobulin replacement therapy.[S16]

Though the survey attracted many participants, it has several limitations. First, there was a difference in response rates between countries and a striking absence of response from other countries. Second, the survey focused on severe AAV, and the results are not generalizable to those with limited disease. Third, the survey covered practice patterns between 2017 and 2022 and the practice-changing trial, Plasma Exchange and Glucocorticoids in Severe ANCA-AAV,[4] was published in 2020. This might have contributed to some of the results we noted. Lastly, while it is encouraging to witness the interest in our survey on social media, open recruitment can introduce selection bias.

Despite the publication of landmark clinical trials and treatment guidelines, there are significant differences in standard induction therapy for severe AAV. The results of our survey can help acknowledge current gaps and challenges in AAV management, improve interdisciplinary communication among specialists, ensure management of AAV patients with severe disease at centers of expertise, and overall improve the care of AAV patients.

DISCLOSURE

DG is a consultant to ChemoCentryx, GSK and Aurinia Inc. TL receives research support from Aurinia Pharmaceuticals, Genentech, and Omeros Corporation, and reports consultancy agreements with ChemoCentryx, Travere Therapeutics, and GlaxoSmithKline. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Characteristics of survey participants and their practice.

Table S2. Overall prophylactic therapy use and laboratory monitoring among all survey participants.

Table S3. Prophylactic therapy use and laboratory monitoring based on physician specialty, patient volume, continent of practice.

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