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ANCA Vasculitis Induction Management During the COVID-19 Pandemic

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As the severe acute respiratory syndrome coronavirus 2 pandemic evolved and became a global health threat, the safety of immunosuppression in antineutrophil cytoplasmic antibody-associated vasculitis (AAV) became of utmost important for clinicians and patients. Although timely initiation of immunosuppressive therapy is critical to quell the acute inflammation and prevent AAV-associated mortality and morbidity, concerns for increased susceptibility to Coronavirus Disease 2019 (COVID-19), delayed viral clearance, and decreased humoral response to infection led to speculation about modification in induction therapy practices may be deployed by physicians caring for patients with AAV. This international retrospective cohort study investigated the influence of the COVID-19 pandemic on AAV induction therapy and patient outcomes in different parts of the world by studying differences in treatment regimens in the United States, United Kingdom, and Europe.

RESULTS

Of the 191 patients, mean age was 65 (SD 14), 52% were women with most (89%) being Caucasian. Kidney involvement was present in 155 (81%) patients and mean entry estimated glomerular filtration rate was 34 (SD 31) ml/min per 1.73 m^2, with 21% requiring dialysis at presentation. Baseline characteristics of patients are outlined in Table 1.

With regard to induction immunosuppression, mean cumulative steroid dose for remission induction was 2962 mg (SD 1841), with the United States having the highest average dose, which was 4153 mg (SD 2427), $P < 0.001$. Prednisone regimen stratified by time course, center, and region is presented in Table 2. Forty-six patients (26%) in the whole cohort were off corticosteroids at 6 months, whereas 14 (36%) US patients, 16 (21%) UK patients, and 16 (26%) European

Table 1. Demographics and baseline clinical characteristics of patients at the time of diagnosis or relapse

AAV-specific variables	Number of subjects	Entire cohort $n = 191$	United States $n = 44$	United Kingdom $n = 83$	Europe $n = 64$	*P* value
Age at diagnosis	Mean years (SD)	65 (14)	68 (12)	65 (15)	61 (13)	0.038
Sex, *n* (%)	Female	99 (52)	22 (50)	40 (48)	27 (42)	0.493
Race, *n* (%)	White	170 (89)	38 (86)	68 (82)	64 (100)	<0.001
	Black	5 (3)	4 (9)	1 (1)	0	
	Asian	16 (8)	2 (5)	14 (17)	0	
Diagnosis, *n* (%)	GPA	97 (51)	25 (57)	43 (52)	29 (45)	0.09
	MPA	84 (44)	19 (43)	32 (39)	33 (52)	
	EGPA	10 (5)	0	8 (10)	2 (3)	
ANCA type, *n* (%)	PR3	90 (47)	17 (40)	42 (51)	30 (47)	0.366
	MPO	94 (49)	25 (58)	36 (43)	33 (52)	
	Negative	7 (4)	1 (2)	5 (6)	1 (2)	
Organs involved during study period, *n* (%)	Kidney	155 (81)	41 (93)	61 (73)	53 (83)	0.024
	Lung	96 (50)	19 (43)	44 (53)	33 (52)	0.555
	Sinus	44 (23)	7 (16)	26 (31)	11 (17)	0.058
	Eyes	13 (7)	2 (5)	9 (11)	2 (3)	0.146
	Ears	12 (6)	3 (7)	7 (8)	2 (3)	0.415
	Peripheral nerve	20 (10)	6 (14)	8 (10)	6 (9)	0.736
	Joints	31 (16)	3 (7)	9 (11)	19 (30)	0.001
	Skin	22 (12)	4 (9)	10 (12)	8 (13)	0.845
	Cardiac	8 (4)	1 (2)	7 (8)	0	0.031
	Gastrointestinal	3 (2)	0	0	3 (5)	0.049
Underwent kidney biopsy, *n* (%)	$n = 155$ patients with kidney disease on entry	111 (72)	35 (85); $n = 41$	44 (73); $n = 61$	32 (60); $n = 53$	0.027
Proportion of patients presenting in relapse, *n* (%)		59 (31)	6 (14)	31 (37)	22 (34)	0.017
Comorbidities, *n* (%)	Diabetes	27 (14)	5 (11)	13 (16)	9 (14)	0.803
	Hypertension	111 (58)	30 (68)	42 (51)	39 (61)	0.139
	Heart disease	35 (18)	13 (30)	9 (11)	13 (20)	0.031
	Lung disease	46 (24)	11 (25)	20 (24)	15 (23)	0.983
	Cerebrovascular disease	9 (5)	4 (9)	2 (2)	3 (5)	0.239
	Chronic kidney disease	52 (27)	16 (36)	19 (23)	17 (27)	0.265
	Cancer	18 (9)	8 (18)	4 (5)	6 (9)	0.049
	No comorbidities	52 (27)	8 (18)	24 (29)	20 (31)	0.292
Alveolar hemorrhage, *n* (%)		28 (15)	8 (18)	10 (12)	10 (16)	0.626
Dialysis on admission, *n* (%)	$n = 155$ patients with kidney disease on entry	33 (21)	12 (29); $n = 41$	11 (18); $n = 61$	10 (19); $n = 53$	0.345
GFR (ml/min per 1.73 m^2) at baseline	Mean (SD)	34 (31); $n = 189$	21 (28); $n = 44$	41 (32); $n = 83$	35 (31); $n = 62$	0.0027
Creatinine (mg/dl)	Mean (SD)	3.46 (2.97); $n = 189$	4.81 (3.27); $n = 44$	2.91 (2.7); $n = 83$	3.2 (2.8); $n = 62$	0.0019

AAV, antibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; EGPA, eosinophilic granulomatosis with polyangiitis; GFR, glomerular filtration rate; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3.

patients were no longer given steroid treatment at 6 months ($P = 0.21$).

Eighty-four patients (44%) received rituximab treatment without cyclophosphamide, with the United States having the highest proportion undergoing this treatment regimen (64% of patients; $P = 0.005$). On the other hand, 49 (26%) patients were treated with cyclophosphamide without rituximab for induction treatment and Europe had the highest proportion of patients given cyclophosphamide alone (33%; $P = 0.037$) (Table 2).

The outcomes of remission induction therapy are depicted in Supplementary Table S1. At 6 months, 73 (92%) patients in the rituximab group, 42 (91%) patients in the cyclophosphamide group, and 39 (87%) patients who underwent combined therapy reached remission ($P = 0.564$). Mean estimated glomerular filtration rate at 6 months was 43 (SD 29) ml/min per 1.73 m^2 in the rituximab group, 33 (SD 24) ml/min per 1.73 m^2 in the cyclophosphamide group, and 47 (SD 36) ml/min per 1.73 m^2 for those who received combination therapy ($P = 0.0659$). In addition, the rituximab, cyclophosphamide, and combination groups all had a median increase in glomerular filtration rate of 6 ml/min per 1.73 m^2 over 6 months ($P = 0.68$) (Supplementary Table S1; Supplementary Methods).

Nineteen patients (61%) of the surviving 31 (2 patients died) had kidney recovery at the end of the study after presenting with dialysis-dependent kidney failure. Nineteen patients reached end-stage kidney disease at the end of follow-up with similar incidence across the different induction regimens.

Table 2. Treatment differences among different cohorts

Treatment variables	Number of subjects	Entire cohort $n = 191$	United States $n = 44$	United Kingdom $n = 83$	Europe $n = 64$	*P* value
Use of pulse steroids, *n* (%)		117 (61)	35 (80)	44 (53)	38 (59)	0.013
Cumulative dose of i.v. pulse methylprednisolone (mg)	Mean (SD)	930 (981); $n = 175$	1658 (1243); $n = 43$	730 (755); $n = 74$	647 (733); $n = 58$	<0.001
Cumulative steroid dose for remission induction (mg)	Mean (SD)	2962 (1841); $n = 171$	4153 (2427); $n = 35$	2174 (1229); $n = 83$	3408 (1642); $n = 53$	<0.001
Daily prednisone dose at 16 wk (mg)	Mean (SD)	8.27 (6.51); $n = 174$	8.85 (6.94); $n = 36$	7.39 (5.1); $n = 80$	9.14 (7.79); $n = 58$	0.2487
Daily prednisone dose at 6 mo (mg)	Mean (SD)	5.10 (4.43); $n = 171$	4.02 (3.70); $n = 35$	5.24 (3.73); $n = 75$	5.57 (5.47); $n = 61$	0.2463
Proportion off steroids at 6 mo, *n* (%)		46 (26); $n = 178$	14 (36); $n = 39$	16 (21); $n = 77$	16 (26); $n = 62$	0.214
Rituximab use only, *n* (%)	($n = 191$)	84 (44)	28 (64)	28 (34)	28 (44)	0.005
Dosing of rituximab, *n* (%)[a]	1 g every 2 wk for 2 doses	100 (75); $n = 133$	22 (58); $n = 38$	43 (77); $n = 56$	35 (90); $n = 39$	0.036
	375 mg/m^2 once weekly for 4 wk	31 (23); $n = 133$	14 (37); $n = 38$	13 (23); $n = 56$	4 (10); $n = 39$	
	Single 1-g dose	1 (1); $n = 133$	1 (3); $n = 38$	0; $n = 56$	0; $n = 39$	
	Single 500-mg dose	1 (1); $n = 133$	1 (3); $n = 38$	0; $n = 56$	0; $n = 39$	
Cyclophosphamide use only, *n* (%)	($n = 191$)	49 (26)	5 (11)	23 (28)	21 (33)	0.037
Rituximab and cyclophosphamide, *n* (%)	($n = 191$)	49 (26)	10 (23)	28 (34)	11 (17)	0.066
Cyclophosphamide cumulative dose in grams	Mean (SD)	3.4 (2.6); $n = 95$	4.9 (4); $n = 15$	3 (2.4); $n = 51$	3.5 (1.9); $n = 29$	0.047
Cyclophosphamide route of administration, *n* (%)	Oral	10 (10); $n = 98$	5 (33); $n = 15$	4 (8); $n = 51$	1 (3); $n = 32$	0.002
	IV	84 (86); $n = 98$	8 (53); $n = 15$	45 (88); $n = 51$	31 (97); $n = 32$	
	Both	4 (4); $n = 98$	2 (13); $n = 15$	2 (4); $n = 51$	0; $n = 32$	
PLEX, *n* (%)	$n = 191$	26 (14)	8 (18)	13 (16)	5 (8)	0.234
Use of hydroxychloroquine	$n = 188$	1 (1); $n = 188$	0; $n = 42$	0; $n = 82$	1 (2); $n = 64$	0.378
Use of PJP prophylaxis	$n = 191$	162 (84)	36 (82)	80 (96)	46 (72)	<0.001
i.v.Ig	$n = 191$	5 (3)	3 (7)	1 (1)	1 (2)	0.137
MMF	$n = 191$	6 (3)	2 (5)	2 (2)	2 (3)	0.4375
Tocilizumab	$n = 191$	1 (1)	0	0	1 (2)	0.369
MTX use	$n = 191$	1 (1)	0	1 (1)	0	0.52
Avacopan	$n = 191$	1 (1)	0	1 (1)	0	0.52

MMF, Mycophenolate mofetil; MTX, methotrexate; PJP, Pneumocystis Jiroveci pneumonia; PLEX, plasma exchange.
[a]Proportions are calculated with the denominator including all patients on rituximab (patients receiving rituximab alone or combined rituximab and cyclophosphamide therapy).

Sixteen patients were diagnosed with COVID-19 during the induction period, with similar cyclophosphamide and rituximab exposure, and half of these patients received combined therapy (Supplementary Table S2; Supplementary Methods). The median interval from AAV diagnosis or relapse to COVID-19 infection was 33 (interquartile range 4–168) days. Patients who had COVID-19 infection had similar treatment regimens compared with patients who tested negative for severe acute respiratory syndrome coronavirus 2 (Supplementary Table S2). Of the patients with COVID-19, 4 patients died of COVID-19, of whom 3 (75%) had received combined rituximab and cyclophosphamide therapy, and the other patient received cyclophosphamide alone. The median cumulative steroid induction dose for patients who died and had COVID-19 was 2423 (interquartile range 1210–5370) mg and the mean cumulative methylprednisolone dose for this group was 937.5 mg (SD 125). Of the patients with COVID-19, 7 were hospitalized for infectious causes (1 of whom had cellulitis and another had bacteremia). Outcomes of patients diagnosed with COVID-19 are summarized in Supplementary Table S3 (Supplementary Methods).

Differences in outcomes among the United States, United Kingdom, and European cohorts, between with new and relapsing AAV, and in treatment of patients with relapsing and new disease are summarized in Supplementary Tables S4, S5, and S6, respectively (Supplementary Methods).

DISCUSSION

This international multicentered retrospective cohort study demonstrates that there was no deviation in the standard of care induction therapy of AAV during the pandemic, and, more importantly, a less aggressive regimen was not used, highlighting the importance of optimal vasculitis management. Both rituximab and

cyclophosphamide induction regimens had similar infectious risk, remission rate, and kidney function outcomes in our study. This complements previous studies that suggest that adverse events, remission induction, and kidney function improvement are similar in both regimens.[1,2] Our data also show that there were no differences in susceptibility to COVID-19 in our AAV cohort. Therefore, a change in induction regimen may not be warranted, and robust control of disease activity should continue to be prioritized in the current pandemic. This study additionally demonstrates significant center-based differences in induction treatment regimens and predominant use of rheumatoid arthritis dosing regimen for rituximab.

Interestingly, the rituximab group had the lowest mean cumulative steroids dose for induction and had the lowest proportion of patients who received pulse methylprednisolone therapy, whereas the cyclophosphamide group had the highest proportion of patients given pulse methylprednisolone and had the highest mean cumulative steroid dose for induction. Notably, a reduced steroid exposure in rituximab-treated patients compared with cyclophosphamide-treated patients was also reported in the RAVE trial, despite using the same glucocorticoid regimen in both treatment arms.[1] This might reflect a higher confidence in the long-acting effect of B-cell depletion by the prescribing physician or a higher rate of true remission.

In our patients, there was a high proportion of patients still treated with glucocorticoids at the 6-month follow-up, which is consistent with multiple centers having corticosteroid taper regimens extending past this period. In addition, this cohort was enriched with rituximab-treated patients receiving 2 doses of 1000 mg given 2 weeks apart compared with the Food and Drug Administration–approved regimen of 375 mg/m^2 once weekly for 4 weeks. This trend in dosing regimen likely evolved with the need to minimize exposure to severe acute respiratory syndrome coronavirus 2 virus in health care settings, although it is possible that some centers use this regimen as their standard of rituximab treatment for AAV induction. Use of PLEX therapy was low in our study population, which may be influenced by changes to practice patterns after the PEXIVAS study, which showed that PLEX therapy did not improve mortality or end-stage kidney disease outcomes in patients with severe AAV.[3]

There were multiple differences in AAV induction therapy practices among the United States, United Kingdom, and Europe. Despite the United Kingdom having the highest proportion of patients presenting in AAV relapse, the United States had the highest proportion of patients given rituximab treatment, which is consistent with recent AAV treatment trends in the United States.[4] On the other hand, patients in the United Kingdom and Europe used cyclophosphamide therapy more than those in the United States. The United States had the highest corticosteroid use among all locations studied. A more widespread usage of the initial high-dose intravenous steroid pulse in the US cohort resulted in the highest cumulative steroid dose for induction among all locations studied. Despite the difference in steroid dosing, no differences were observed in the daily steroid doses of patients at 16-week and 6-month intervals or in the proportion of patients off glucocorticoids at 6 months.

A high proportion of patients with COVID-19 in this cohort were hospitalized for infection and died. This study was conducted before the RECOVERY trial, which showed favorable data about use of oral dexamethasone and tocilizumab for COVID-19 management,[5,6] and may help explain why the patients with COVID-19 in our cohort had poor outcomes. Immunosuppressed patients with these updated therapies may have improved outcomes compared with our study.

Our study is subject to limitations inherent in a retrospective study. We were unable to assess long-term kidney outcome and relapse because of the short follow-up period. Our analysis on COVID-19 susceptibility was limited by the lack of universal testing for severe acute respiratory syndrome coronavirus 2 infection.

This is the first study evaluating AAV induction therapy patterns and outcomes during the COVID-19 pandemic, highlighting the importance of optimal management of active vasculitis in times of the pandemic. Preliminary experience from case cohort studies highlights that immunosuppression may not confer the highest risk of COVID-19 vulnerability.[7–9] Therefore, it is recommended that standard immunotherapy be continued in AAV to minimize vasculitis-related morbidity and mortality.

DISCLOSURES

US receives grants and nonfinancial support from Alexion Pharma, and grants and nonfinancial support from Ablynx and Chemocentryx. BCT; and personal fees from Vifor Pharma and Alexion. VKD has been a consultant to Novartis, on the advisory board for Bayer and Travere, and received roylaties and honoraria from UpToDate. AK received personal fees from Novartis, Terumo BCT, Miltenyi Biotech, Vifor Pharma, and Alexion. DG has been a consultant to ChemoCentryx and Aurinia. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

Table S1. Different clinical outcomes by different treatment regimens.

Table S2. Treatment differences among patients who tested positive and negative for COVID-19.

Table S3. Outcomes of patients diagnosed with COVID-19.

Table S4. Patient outcomes of the US, UK, and European cohorts.

Table S5. Outcomes of patients with new and relapsing AAV.

Table S6. Treatment variables of patients with new and relapsing AAV.

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