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COMMENTARY

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Update to the ASFA guidelines on the use of therapeutic apheresis in ANCA-associated vasculitis

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Abstract

Since 1986, the American Society for Apheresis (ASFA) has published practice guidelines on the use of therapeutic apheresis in the Journal of Clinical Apheresis (JCA) Special Issue. Since 2007, updated guidelines have been published every 3 years to reflect current evidence based apheresis practice with the most recent edition (8th) published in 2019. With each edition, the guidelines are reviewed and updated based on any newly published literature since the last review. The PEXIVAS study, an international, randomized controlled trial comparing therapeutic plasma exchange (TPE) vs no TPE and standard vs reduced dose steroid regimen on the primary composite outcome of end stage renal disease or death in patients with ANCA-associated vasculitis (AAV), was published in February 2020. This study represents the largest study on the role of therapeutic apheresis in AAV published to date and prompted the JCA

Special Issue Writing Committee to reassess the current AAV fact sheet for updates based on this newly available evidence. This interim fact sheet summarizes current ASFA recommendations for the evidence-based use of therapeutic apheresis in AAV and supersedes the recommendations published in the 2019 guidelines.

KEYWORDS

ANCA, therapeutic apheresis, vasculitis

1 | INTRODUCTION

The PEXIVAS trial, published in February 2020, is the largest randomized controlled trial published to date in ANCA-associated vasculitis (AAV).[1] This study significantly expands the current evidence guiding the use of therapeutic apheresis (TA) in this disorder. This prompted the Writing Committee of the Journal of Clinical Apheresis (JCA) Special Issue to reconvene to perform a review of the existing literature, analyze the quality of evidence, determine the strength of recommendation derived from this evidence, and produce an updated interim fact sheet summarizing evidence-based guidelines on the use of therapeutic apheresis in AAV.

2 | METHODOLOGY

The JCA Special Issue Writing Committee is composed of 13 members from diverse fields including Transfusion Medicine/Apheresis, Hematology/Oncology, Pediatrics, Nephrology, and Critical Care Medicine from locations across the United States and Europe. For the AAV fact sheet update, we invited a guest author (AS) with specialty expertise in Nephrology and Apheresis Medicine to serve as the fact sheet co-author along with an experienced committee member (RB). These co-authors carefully reviewed the PEXIVAS study and any other new publications on the use of TA in AAV since the last fact sheet update (December 2018) to determine whether the newly available evidence warranted any changes in the recommendations on the use of TA as a treatment modality for AAV. Only peer-reviewed PubMed-indexed publications available in English were considered. The primary co-authors updated the fact sheet table, disease description, current management, rationale for TA, technical notes (eg, volumes treated, frequency, replacement fluid), duration and discontinuation of treatment, and provided a maximum of 20 key references highlighting important or new studies and/or reviews. The references are not meant to be exhaustive but rather serve as a starting point in a search for more information.

The updated fact sheet was then reviewed by two committee members with experience authoring the AAV fact sheet in previous editions (RK, VW). The entire writing committee performed a third and final review of the updated fact sheet with category and grade assigned by consensus in the same manner as described in previous editions.[2-4] The definition of the four ASFA categories (Table 1) and use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[5,6] to assign recommendation grades (Table 2) were maintained as in previous editions.

3 | SUMMARY OF CHANGES

The category recommendation for rapidly progressive glomerulonephritis (RPGN) in the setting of microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), or renal-limited vasculitis (RLV) with Cr ≥5.7 mg/dL (includes "on dialysis") was changed from I to II (Table 1). The committee felt that this change in categorization was necessary based on the primary conclusion of the PEXIVAS study, which found that the addition of therapeutic plasma exchange (TPE) did not reduce the incidence of end stage renal disease (ESRD) or death. However, while the subgroup analysis of patients with Cr ≥5.7 mg/dL did not show a statistically significant benefit of TPE, wide confidence intervals suggest that the study may have been underpowered to detect subgroup differences. Further, study design did not limit enrollment to patients with an initial presentation nor did it require a renal biopsy to assess for degree of renal injury. AAV is known to frequently relapse and eventually lead to irreversible renal scarring. The committee recognized that the study was not necessarily designed to identify patients at the onset of disease who may benefit from TPE before irreversible renal injury occurs. The decision to change from I to II (instead of III) was based on the committee agreement that a category II

TABLE 1 Category definitions for therapeutic apheresis

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

Abbreviation: IRB, institutional review board.

recommendation would better support the use of TPE as immediate therapy, in addition to immunosuppression, in select patients with biopsy proven acute RPGN in an effort to potentially prevent irreversible renal damage. The change in grade of evidence from IA to IB was to acknowledge previously described important limitations of the PEXIVAS study[7-10] including the lack of biopsy to define disease severity and the long follow-up period, which may make it difficult to detect initial improvement in the subset of patients at first presentation. It is important to note that a change to category II in this context must be not interpreted as postponing the use of TPE after failure of the first line treatment, as all prior studies that demonstrated a benefit with the addition of TPE included it as part of initial induction therapy.

No other changes were made to the category or grade recommendations for the other indications in AAV. The committee considered whether a change was warranted for treatment of diffuse alveolar hemorrhage (DAH) in

TABLE 2 Grading recommendations, strength, and quality of evidence

Recommendation	Description	Methodological quality of supporting evidence	Implications
Grade 1A	Strong recommendation, high-quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1B	Strong recommendation, moderate quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
Grade 1C	Strong recommendation, low-quality or very low-quality evidence	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
Grade 2A	Weak recommendation, high quality evidence	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2B	Weak recommendation, moderate-quality evidence	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
Grade 2C	Weak recommendation, low-quality or very low-quality evidence	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Note: Adopted from Guyatt, 2006; 2008.
Abbreviation: RCT, randomized controlled trial.

the setting of AAV based on the finding in the PEXIVAS study that patients with DAH failed to show benefit from TPE. However, very few patients with severe DAH were included and the confidence intervals were once again large suggesting that the study may not have been adequately powered to detect differences in this group. Given the life-threatening nature of severe DAH and the lack of alternate options for therapy, the committee opted to retain the category I recommendation with the acknowledgement that the recommendation is based on weak or low quality evidence.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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APPENDIX: VASCULITIS, ANCA-ASSOCIATED (AAV)

Incidence: 1-3/100000/year (geographical and ethnic differences; MPA: 48%-65%, GPA: 25%-40%, EGPA: 10%-12%)				
Indication	**Procedure**		**Category**	**Grade**
MPA/GPA/RLV				
RPGN, Cr ≥5.7 mg/dL*	TPE		II	1B
RPGN, Cr <5.7 mg/dL*	TPE		III	2C
DAH	TPE		I	1C
EGPA	TPE		III	2C
# reported patients: >300	**RCT**	**CT**	**CS**	**CR**
	10(1091)	5(345)	NA	NA

Note: *Cr thresholds for renal function at presentation adopted from Yates, 2016; Cr ≥5.7 mg/dL includes "on dialysis."
Abbreviations: DAH, diffuse alveolar hemorrhage; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; RLV, renal-limited vasculitis; RPGN, rapidly progressive glomerulonephritis.

Description of the disease

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is defined as necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. ANCA can be specific for myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA). AAV is clinically subdivided into MPA, GPA, the most infrequent and clinically separate entity of EGPA, and RLV. Overlapping features between AAV subtypes occur. Besides the clinical diagnosis, ANCA specificity separates patients into groups with different relapse risk and treatment response. AAV can affect any organ but commonly involves the kidneys in 70%, typically exhibiting RPGN with high risk of end stage renal disease (ESRD), lungs (>50% at onset), ear-nose-throat, joints, skin and nerves. Worse renal prognosis is predicted by AAV histology classification with tubulointerstitial fibrosis and atrophy, and in MPO-ANCA positive patients. Lung involvement can range from asymptomatic pulmonary lesions to life-threatening DAH. EGPA hardly ever is associated with RPGN or DAH. The presentation of the pulmonary-renal syndrome associated with ANCA can be clinically similar to anti-glomerular basement membrane (GBM) disease (Goodpasture's Syndrome). When ANCA and anti-GBM are both present, the disease should be considered to represent anti-GBM disease (see separate fact sheet).

Current management/treatment

Mortality of AAV has been fundamentally improved over the last 5 decades by the use of steroids and other immunosuppression agents. The long-term course is now determined by the frequency of disease flares and by accruing damage caused by disease activity and treatment related complications. The treatment of all AAV subtypes is usually divided into two phases, that is, induction of remission and maintenance of remission. Urgent treatment is required to prevent irreversible organ damage. Standard induction treatment of AAV includes steroids, cyclophosphamide or rituximab, inducing remission in up to 90% at 6 months. Leflunomid no longer plays a substantial role; bortezomib or inhibitors of C5a-receptors (eg, avacopan), or, for EGPA, mepolizumab (anti-IL5), may become future options. Maintenance treatment usually entails standard dose steroids plus an additional immunomodulatory agent (azathioprine, mycophenolate mofetil, or rituximab) for 12-18 months. Reduced dose steroids (50% of previous standard) was recently found non-inferior in outcomes (Walsh, 2020). The safety of rituximab has become a topic of major attention with its increasing use in both remission induction and maintenance therapy, thus reducing the toxicity from cumulative doses of cyclophosphamide and ongoing maintenance therapy. However, its long-term safety is still being debated. Infection related morbidity and mortality due to immunosuppressive therapy remains a significant issue in AAV. Therefore, individual risk-benefit analysis is a major principle for any treatment of AAV.

Rationale for therapeutic apheresis

The cytotoxic role for ANCAs underlies the scientific rationale for therapeutic apheresis in the treatment of

Technical notes	
Volume treated: 1-1.5 TPV	
Replacement fluid: Albumin; plasma when DAH present	**Frequency**: Daily in DAH, typically every other day in absence of DAH

AAV. Before the clear ANCA guided definition of AAV, clinical studies on TPE enrolled patients by the clinical syndrome of RPGN, which is not exclusive for AAV. A meta-analysis of these trials concluded, that additional use of TPE may reduce the composite of ESRD or death (Walsh, 2011). The addition of TPE was recommended to increase the chance of renal recovery, if renal function is severely impaired (defined as Cr ≥5.7 mg/dL or requirement of dialysis). TPE in patients with AAV and DAH has weaker supportive evidence; however, retrospective analyses reported clinically relevant benefit (Uechi, 2018). For EGPA in general, due to its low incidence and separate clinical characteristics, the evidence base for the use of TPE is substantially less (Groh, 2015).

The MEPEX trial with 137 AAV patients presenting with Cr >500 μmol/L (5.7 mg/dL) or requiring dialysis, demonstrated that 7 TPE sessions additional to oral cyclophosphamide and oral corticosteroids, when compared to pulse methylprednisone (1000 mg/day x 3 days), increased the rate of renal recovery at 3 to 12 months without a benefit for survival (Jayne, 2007). In dialysis-dependent patients, TPE was superior with respect to the chance of coming off dialysis (de Lind van Wijngaarden, 2007). After a median of almost 4 years follow-up, there was no longer a net benefit of TPE in clinical outcomes (Walsh, 2013). In addition, in subsequent non-randomized CTs or CSs benefit of TPE was not always confirmed. The limited positive outcome seen in MEPEX was reproduced with IV cyclophosphamide in an uncontrolled retrospective study (Pepper, 2013).

PEXIVAS was a large (n = 704) international RCT that assessed the effect of TPE vs no TPE and a standard vs a reduced dose steroid regimen on the primary composite outcome of ESRD or death in patients with AAV (Walsh, 2020). After induction with pulse steroids (IV) and cyclophosphamide (oral or IV) or rituximab, randomization to receive 60 mL/kg volume TPE (7) or no TPEs and standard dose or reduced dose steroid regimen, follow up for 2 to 7 years (median 2.9 years) was done. The primary conclusion of this study was that addition of TPE did not reduce incidence of composite outcome (ESRD or death) and a reduced-dose steroid regimen was not inferior to standard dose regimen. Subgroup analysis of patients with Cr ≥5.7 mg/dL or DAH also failed to show a statistically significant benefit of TPE. However, review of supplemental data (online) suggested outcomes may favor the TPE groups with DAH and when Cr ≥5.7 mg/dL; confidence intervals were large, that is, PEXIVAS may be underpowered to detect differences in these subgroups. An accompanying editorial pointed out several issues regarding the generalizability of results. The severity of kidney biopsy findings is a known prognostic indicator for long-term kidney outcomes, and in PEXIVAS, renal biopsy was not required. This, together with the fact that enrollment was not limited to initial presentation or first relapse in a condition known to frequently relapse, raises the question that some enrolled patients may have had significant, irreversible scarring prior to the intervention. An initial course of 7 TPE also cannot be expected to have an enduring impact on 7 year data and outcomes, particularly in a disease known to have a high rate of recurrence.

In cases of biopsy proven RPGN with acute glomerular inflammation and/or fibrinoid necrosis, crescents, with minimal fibrosis (chronic damage) and a fulminant clinical course (Cr ≥5.7 mg/dL or DAH), immediate multimodal immunosuppression, including prompt initiation of TPE, to prevent irreversible changes are reasonable.

Duration and discontinuation/number of procedures

Median number of TPE is 7 over a median period of 14 days, up to 12 have been reported to result in further improvement in patients with severe renal failure (Cr ≥5.7 mg/dL or on dialysis) or DAH (deLuna, 2015). Daily therapy should be considered in patients with severe DAH, tapered to every other day as clinical situation improves.

Keywords, ANCA, MPO-ANCA, PR3-ANCA, ANCA associated vasculitis, granulomatosis with polyangiitis; Wegener' granulomatosis, diffuse alveolar hemorrhage, rapidly progressive glomerulonephritis, microscopic polyangiitis, pauci-immune glomerulonephritis, plasma exchange, plasmapheresis, immunoadsorption.

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