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Plasma exchanges for the treatment of severe systemic necrotizing vasculitides in clinical daily practice: Data from the French Vasculitis Study Group

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ABSTRACT

The use of plasma exchanges (PLEX) in systemic necrotizing vasculitides (SNV) still need to be codified. To describe indications, efficacy and safety of PLEX for the treatment of SNV, we conducted a multicenter retrospective study on patients with ANCA-associated vasculitis (AAV) or non-viral polyarteritis nodosa (PAN) treated with PLEX. One hundred and fifty-two patients were included: GPA (n = 87), MPA (n = 56), EGPA (n = 4) and PAN (n = 5). PLEX were used for rapidly progressive glomerulonephritis (RPGN) in 126 cases (86%), alveolar hemorrhage in 64 cases (42%), and severe mononeuritis multiplex in 23 cases (15%). In patients with RPGN, there was a significant improvement in renal function compared to baseline value ($P < 0.0001$), the plateau being reached at month 3 after PLEX initiation, and estimated glomerular filtration rate improved especially as the number of PLEX increased. In patients with alveolar hemorrhage, mechanical ventilation was discontinued in all patients after a median time of 15 days. Patients treated for mononeuritis multiplex showed improvement of severe motor weakness. After a median follow of 22 months, 18 deaths (12%) were recorded, mainly in patients with RPGN and within the first 6 months. Incidence of end-stage renal disease and/or death was similar between groups of different baseline renal function, but was increased in MPO-ANCA compared to PR3-ANCA. Adverse events

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attributable to PLEX were recorded in 63%. No death occurred during PLEX. This large series describes indications, efficacy and safety of PLEX in daily practice. Randomized controlled studies are ongoing to define optimal indications, PLEX regimen and concomitant medications.

1. Introduction

The therapeutic management of systemic necrotizing vasculitides has dramatically improved during the last decades [1–3]. Prospective randomized trials have defined the standard of care for inducing remission, with an association of corticosteroids and immunosuppressive or immunomodulatory agents, according to disease severity [4–9].

Plasma exchanges (PLEX) were further included in regimens to treat vasculitides in certain conditions, including vasculitides secondary to virus infections and those associated with antineutrophil cytoplasmic antibodies (ANCA) and severe renal failure [10]. In hepatitis B virus (HBV)-related polyarteritis nodosa (PAN), antiviral agents combined with PLEX and short-term corticosteroids effectively leads to recovery from vasculitis [11]. In ANCA-associated vasculitides (AAV), prospective studies have shown that PLEX do not improve overall survival [12–14], but the MEPEX trial has demonstrated that PLEX in combination with prednisone and cyclophosphamide improved the rate of renal recovery in patients with serum creatinine level >500 μmol/L, when compared with intravenous methylprednisolone [15]. Nevertheless, although short-term results with PLEX were encouraging, the benefit on end-stage renal disease (ESRD) or death rates remained unclear after long-term follow-up [16,17].

These data raise the question of whether PLEX should be initiated in less severe patients to achieve the best therapeutic response, and what the optimal PLEX dosing and type of concomitant medications should be [17]. Small studies have showed a beneficial effect of PLEX in AAV patients with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 [18,19]. In addition, studies have to date focused on the use of PLEX in rapidly progressive glomerulonephritis (RPGN), but other indications have received less attention. Along this line, the indications of PLEX in systemic necrotizing vasculitides still need to be codified, and the current international prospective PEXIVAS trial will answer some important questions [20].

To provide additional findings on the long-term follow-up of vasculitis patients receiving PLEX, rarely described in the literature, we conducted a retrospective study to evaluate indications, efficacy and safety of PLEX in daily practice for the treatment of systemic necrotizing vasculitides.

2. Patients and methods

2.1. Patients

We performed a nationwide retrospective multicenter study from June 2014 to January 2015 on behalf of the French Vasculitis Study Group, which collected data from 16 departments of Internal Medicine and Nephrology. Patients having received PLEX for active disease, and meeting the American College of Rheumatology 1990 criteria [21–23] and/or the European Medicines Agency algorithm [24] and/or the definitions from the 2015 Chapel Hill Consensus Conference [25] for non-HBV PAN and AAV, i.e. granulomatosis with polyangiitis (GPA) (Wegener's), microscopic polyangiitis (MPA) or eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss), were included. Exclusion criteria were positive serum anti-glomerular basal membrane antibodies or positive serum cryoglobulinemia, presence of immune deposits on immunofluorescence study of kidney biopsy, and presence of concomitant HBV, hepatitis C virus and human immunodeficiency virus infections. This study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles, and was approved by the local Institutional Review Board.

2.2. Clinical and laboratory assessment

Charts of patients were collected by physicians in charge of the patients. For each patient, clinical and biological data were recorded from the initial evaluation throughout follow-up at months 3, 6, 9, 12, 18 and 24 after PLEX onset, and at last visit. Laboratory assessment included C-reactive protein level (CRP), ANCA status and specificity determined by indirect immunofluorescence and enzyme immunoassays and/or immunodot assay, respectively, renal function as estimated by eGFR using the Modification of Diet in Renal Disease Study equation [26]. For anuric patients, and those who required renal replacement therapy, eGFR was arbitrarily fixed at 0 mL/min/1.73 m^2. Motor weakness was evaluated according to Medical Research Council scale and was considered to be severe for score <3/5. The 1996 Five Factor Score [4] was used to determine patients' prognosis. The BVAS [27] was used to assess disease activity, and the Vasculitis Damage Index [28] to assess damage at baseline and during follow-up. PLEX procedure was evaluated, and adverse events attributable to PLEX were recorded.

2.3. Response to therapy

Therapeutic responses were evaluated after 3, 6, 9, 12, 18 and 24 months and at last visit after PLEX onset, based on the patient's treating physicians' reports, BVAS and laboratory results. Response to therapy was defined according to EULAR recommendations [29]. Relapse of AAV was defined as the re-occurrence or new onset of disease attributable to active vasculitis. Renal response assessment was based on the evolution of eGFR and the occurrence of ESRD. ESRD was defined as the need for permanent renal replacement therapy as determined by permanent dialysis dependence or receipt of a renal transplant. We also recorded the occurrence of death from any cause, and the composite outcome of both the occurrence of ESRD and death.

2.4. Statistical analyses

Data are presented as mean (standard deviation) or as median (range) as appropriate for continuous variables and number (%) for qualitative variables. Fisher's exact test was used to compare qualitative variables and the non-parametric Mann–Whitney U-test was used to compare continuous variables. Cumulative incidence curves of ESRD, death or both were plotted and analyzed with the log-rank test. $P < 0.05$ was considered statistically significant. Statistical analyses were computed with GraphPad Prism version 4.0 and Instat version 3.0 for Windows (GraphPad Software, La Jolla, CA, USA).