Plasma exchange for systemic lupus erythematosus

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Received 18 December 2004; accepted 5 January 2007

Abstract

Efficacy of plasma exchange in patients with systemic lupus erythematosus has not been supported by the results of the first non-controlled and retrospective studies. Nonetheless, they remain relevant for some selected patients with life-threatening manifestations and/or severe therapy-resistant manifestations. They can be used as an adjuvant therapy in combination with corticosteroids and, when required, other immunosuppressant(s) for refractory renal disease, alveolar hemorrhage, some neuropsychiatric manifestations, thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome, hyperviscosity syndrome or symptomatic cryoglobulinemia. The use of newer technologies, like immunoadsorption, possibly in combination with recent biologics, might, in the future, offer some new perspectives for extracorporeal therapy of systemic lupus erythematosus.

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Keywords: Plasma exchange; Plasmapheresis; Immunoadsorption; Systemic lupus erythematosus; Lupus nephritis

0. Introduction

Circulating immune complexes, autoantibodies, such as anti-double-stranded (ds) DNA or anti-SSA, and other immune reactants (e.g., complement components, cytokines) have been implicated in the pathogenesis of systemic lupus erythematosus (SLE). Therefore, it sounded rational to use plasma exchange (PE) to remove them from SLE patients. Indeed, SLE was the second most common indication for PE in the early 80s, just before the first non-controlled [1] and/or retrospective trials [2,3] failed to confirm their benefit. However, PE are and will probably remain, at least for several more decades, of relevance for some selected SLE patients, with acute life-threatening manifestations, severe therapy-refractory disease and/or other rare and severe complications of SLE [4], in combination with corticosteroids and other immunosuppressant drug(s).

1. Conflicting and disappointing results of the first trials evaluating PE in SLE patients

Results of non-controlled studies [2,5,1,6] were quite disappointing. Most importantly, they demonstrated that PE alone were not able to replace or circumvent cytotoxic agents, partly because of the classical and so-called antibody rebound, which may occur after stopping PE [1,3]. The results of the first published randomized studies also revealed that PE had no beneficial effect in mild forms of SLE,
Subsequent prospective studies provided complementary information on the potential indications of PE in SLE. The first one, conducted by Lewis et al. [9], concerned SLE patients with stage III, IV or V glomerulonephritis (mean creatininemia, 180 ± 115 μmol/l). All patients received a standard therapy consisting of corticosteroids and oral cyclophosphamide for 8 weeks, alone (n = 46) or in association with PE (n = 40), three times/week for 4 weeks. Mortality rates were comparable in the two arms (13% of the standard-therapy patients died, compared to 20% of those also receiving PE), as were the numbers of patients who developed renal failure (17% versus 25%, respectively) and achieved remission of their renal disease (28% and 30%, respectively). Serum creatinine and proteinuria decreased similarly in both groups, but the serum levels of anti-ds DNA antibodies and cryoglobulins decreased more rapidly in the PE group [9]. The Lupus Plasmapheresis Study Group considered PE immunological potentiators of cyclophosphamide for the treatment for SLE, based on the benefit suggested earlier in an open study on 14 SLE patients treated using a synchronization strategy [10]. Practically, cyclophosphamide was infused daily for 3 days only after three consecutive days of daily PE and started 6 h after the third PE, before switching to oral cyclophosphamide, in combination with corticosteroids from day 5 onwards. That strategy relied on the fact that when no cytotoxic agents are combined, PE are responsible for antibody depletion, which is followed by a subsequent increased and compensatory activity of pathogenic B-lymphocyte clones. Furthermore, it has been hypothesized that these B-cell clones might be more accessible and vulnerable to cytotoxic drugs when administered just when rebound occurs, rather than concomitantly with PE [10]. Hence, they prospectively tested this synchronization approach in a large multicenter trial including patients with severe SLE – nephritis, central nervous system, leukocytoclastic vasculitis, cardiopulmonary involvement and/or hematological anomalies – by comparing 6 months of such cycles, i.e. a daily PE for three consecutive days preceding each cyclophosphamide pulse, versus a traditional monthly cyclophosphamide pulse for 6 months [11,9,12]. Efficacy was evaluated using different SLE-activity scores or parameters, but the preliminary results [13,12] failed to show any difference between these two regimens after 1 year of follow-up. Even though results of that study have not been published in extenso, for the 18 SLE patients with class III or IV glomerulonephritis (nine in each arm), it appeared that anti-ds DNA antibodies decreased more significantly in those treated with the synchronization strategy, whereas none of the other considered parameters differed significantly [14]. Two patients in each group evolved to end-stage renal disease and three achieved renal disease remission at 2 years.

2. Most pertinent and remaining indications for PE in SLE patients

The disappointing results of those studies led to the dramatically decreased use of PE to treat SLE patients. However, data from the registry established by the French Society for Hemapheresis (cf. article by JF Korach in the Journal) showed that, over the past 5 years, a stable number of 10–20 SLE patients have been treated with PE every year, accounting for 2% of all the patients undergoing PE for different indications (around 1000 in 2003) [15]. In other international apheresis registries, SLE patients represent a similar percentage of patients treated with PE: 3.1% in 2001 in Sweden [16] and less than 0.5% in 1997 in Canada [17]. Indeed, and as supported by those registry data, PE remain useful in a small selected number of patients with specific indications, detailed below. In their retrospective study of 22 SLE children, Wright et al. [18] concluded that like in adults, PE might be particularly relevant as an adjunctive therapy for severe acute manifestations or disease refractory to standard regimens. Prospective trials to precisely evaluate the contribution of PE in these subgroups of patients are now hardly feasible, mostly because of the rarity of these patients and because other and/or second-line treatments have become available since the 80s, e.g., mycophenolate mofetil. Notably, PE safety should no longer be a matter of real concern, at least in qualified and trained hands. Indeed, PE side effects now occur in less than 3% of the patients [15,19]. Hypocalcemia remains the most frequent adverse event (0.8% of the patients), followed by allergic reactions (0.5%). Severe infections and deaths rarely occur, with respective rates of 0.01% and 0.007%, when peripheral venous access is used rather than central venous access, the latter carrying a slightly higher infectious risk [15].
2.1. Severe SLE renal disease and/or SLE nephropathy resistant to conventional treatments

Therapy for severe SLE renal disease has to include corticosteroids and a cytotoxic agent, usually cyclophosphamide or mycophenolate mofetil for induction therapy, then azathioprine or mycophenolate mofetil for maintenance therapy. Adjunction of PE early during this standard regimen may further improve renal recovery [9]. However, the precise definition and characteristics of those patients with severe SLE renal disease who might benefit from PE have not been clearly identified. Indeed, no clear-cut threshold of creatininemia has been identified above which PE may have beneficial adjuvant effects in patients with class III, IV or V glomerulonephritis.

2.2. Diffuse alveolar hemorrhage

Alveolar hemorrhage is uncommon in SLE, occurring in less than 2% of the patients. However, it may be a life-threatening complication, associated a high mortality rate of 53–86% [20]. PE were proven effective for alveolar hemorrhage in similar conditions, such as Goodpasture’s syndrome, and, although less evidence-based, in some vasculitis-related lung capillaritides [21,22]. Even though they did not appear to improve survival in a study on 15 SLE patients [20], PE have been considered effective in numerous case reports to date [23,24].

2.3. Neurolupus and neuropsychiatric SLE

The frequency of neuropsychiatric manifestations during SLE varies between 14% and 75% [25,26]. They are among the leading causes of mortality due to SLE, with 10-year survival rates, in the earlier studies on SLE patients, declining from 83% to 50% when the central nervous system was involved [27]. Some of those SLE patients with different severe central nervous system manifestations [28,29], neuropsychiatric symptoms, such as psychosis [30] or catatonia [31], acute myelopathy [32], or neuromyelitis optica [33], have been successfully treated with adjunctive PE. Guillain–Barré syndrome [34,35] or acute peripheral neuropathies [36] have also been described in a few SLE patients with variable responses to PE, as for multifocal motor neuropathy, another supposedly immune-mediated neuropathy, for which they are rarely effective [37]. Conversely, it should be kept in mind that PE are not indicated for other potential cerebral manifestations of SLE like ischemic stroke or thrombophlebitis, for which traditional and effective anticoagulation is required.

2.4. SLE myocarditis

Though now uncommon and occurring in far less than 10% of SLE patients, myocarditis may be life-threatening and has no adequate specific therapy available to date. There are some anecdotal case reports of severe acute myocarditis unsatisfactorily treated with PE in combination with immunosuppressants, but few promising responses were obtained using immunoabsorption techniques [38].

2.5. Thrombotic thrombocytopenic purpura (TTP)

TTP is one of the thrombotic microangiopathic hemolytic anemias (TMHA), which are characterized by thrombocytopenia, microangiopathic hemolytic anemia with negative Coombs’ test and variable fever, neurological signs and/or glomerulonephritis [39]. TTP may occur in 0.5–22.5% of SLE patients [40], mostly younger patients in whom reported frequencies reached 35–50% [41]. As with TTP not related to SLE [17], the combination of PE with corticosteroids, cyclophosphamide, intravenous immunoglobulins and anticoagulation is now considered the standard regimen [42]. In some, but not all, TTP patients, antiphospholipid antibodies (aPL) are detected. In the study conducted by Espinosa et al. [39], 70% of the patients with TMHA and aPL (not exclusively SLE patients) improved when PE were associated with other treatments (corticosteroids, immunosuppressants...) compared to 34% without PE. Indeed, SLE patients with TTP and aPL or lupus anticoagulant are probably the best candidates for PE, and perhaps also for B lymphocyte-depleting agents, such as monoclonal anti-CD20 antibodies [43]. TTP can be life-threatening, but its attributed mortality is now only 10–20%, since PE use has become widespread.

2.6. Catastrophic antiphospholipid syndrome (CAPS)

CAPS is characterized by the presence of aPL and the involvement of at least three organs [44,39]. Up to 50% of SLE patients may have circulating aPL [45], but CAPS occurs in less than 1% of all the patients with primary or secondary antiphospholipid
syndrome. On the other hand, SLE patients account for 46% of all CAPS cases [46], compared to 41% for patients with primary antiphospholipid syndrome [39]. CAPS carries a 50% mortality rate, warranting rapid diagnosis, with immediate initiation of effective treatment, which may optimally combine anticoagulation, corticosteroids, cyclophosphamide, intravenous immunoglobulins and repeated PE (with or without fresh-frozen plasma as the replacement fluid), in conjunction with the treatment of any triggering and/or precipitating factors (e.g., with antibiotics for infection or surgery for limb gangrene) [44,47]. In a series of 80 CAPS episodes collected by Asherson et al. [46], independently of the combined treatments, ‘only’ 33% of the patients treated with PE survived compared to 61% without PE, but this difference was not significant. Moreover, 40% recovered after receiving anticoagulants, corticosteroids and PE versus 67% given anticoagulants, corticosteroids and intravenous immunoglobulins (this difference also was not significant). However, that retrospective study was not intended to evaluate PE efficacy and only 20% of the included patients were treated with PE. Conversely, in a case report by the same group [47], adjunctive and repeated PE were the only means to halt CAPS and maintain the response over 3 years.

2.7. Hyperviscosity syndrome

Hyperviscosity syndrome is a very rare complication of SLE, resulting from increased serum concentrations of polyclonal immunoglobulins and immune complexes. Serum viscosity usually decreases remarkably well when PE are combined with corticosteroids [48] and cyclophosphamide [49].

2.8. Cryoglobulinemia

Circulating cryoglobulins can be detected in some SLE patients. In the study by Garcia-Carrasco et al. [50], mixed cryoglobulinemia was found in up to one-quarter of SLE patients, in association with hepatitis C virus infection in 21% of them. The clinical impact of these cryoglobulins was generally mild, and only cutaneous vasculitis appeared significantly more frequently (39% versus 16%) [50]. PE were shown to be effective against essential mixed cryoglobulinemia [51] and may therefore also be prescribed for SLE patients with symptomatic cryoglobulinemia [4]. Their indications and potential benefits in the latter setting will be difficult to confirm further, as large studies may no longer be feasible because of the rarity of this condition.

2.9. Prevention of congenital complete heart block in anti-Ro (SSA) syndrome

Once fetal heart block is detected, any therapeutic intervention is probably too late and insertion of a pace-maker may become mandatory. PE or immunoadsorption, when applied during pregnancy, have been reported to effectively prevent congenital heart block in some infants born to mothers, some of whom had previous fetuses who died from congenital complete heart block [52]. In a Japanese cohort of 15 SLE anti-SSA/Ro- and SSB/La-positive pregnant women, weekly PE led to significant decreases of their antibody titers and to the delivery of healthy babies for 14 women [53]. However, the exact place, if indeed they even have one, and schedule of PE in this indication remain to be determined. Prophylaxis itself (mainly with corticosteroids) during pregnancy is still being debated and, to date, is not systematically recommended, even to prevent the recurrence of congenital heart block in a subsequent fetus. Moreover, PE certainly represents a too cumbersome procedure for these pregnant women. Hence, in our opinion, anti-Ro syndrome is currently not an indication of PE.

2.10. SLE-related vasculitis

Vasculitis can be observed as a complication in some SLE patients, mainly with features restrained to only cutaneous leukocytoclastic vasculitis. Definitely, PE does not have any indications in such mild cases. However, they have recently been reported to provide rapid benefit when added to standard immunosuppressive therapy in some SLE patients with retinal vasculitis [54].

3. What could be the future for PE in SLE?

On the one hand, results of all the trials evaluating the efficacy of PE in the management of SLE patients, mentioned above, have narrowed their indications to some specific conditions. On the other hand, PE now have to confront new competitors, i.e., biologics targeting cytokines or lymphocyte sub-populations (e.g., monoclonal anti-CD20 rituximab) [55,56]. Hence, the future of PE may rely on technical improvements, mainly immunoadsorption, and a better understanding of their mechanism(s), which
might also help clinicians to choose to include them in a standard regimen and/or combine them with new biologics [57], in addition to scheduling each PE more pertinently with regards to the other agents being used. The timing of PE sessions and their duration depends, in part, on the severity of the disease and physicians’ habits. Briefly, we recommend three sessions/week for 3 weeks followed by two sessions/week for 2–3 weeks then one session/week over a prolonged period. However, the most severely affected patients might require daily or even twice daily PE until improvement is noted, while they may be discontinued earlier, e.g., after 2 or 3 weeks, once the primary therapeutic objectives have been reached. Conversely, PE may have to be continued for years when they appear to be the only effective treatment [47].

Immunoabsorption is a promising technique of extracorporeal therapy, like PE, that has gained popularity, especially in some European countries [58,59,38,57]. It aims at more selectively clearing immunoglobulins or a specific antibody and has theoretical advantages by avoiding or, at least, limiting albumin and plasma replacement. It was feared, and sometimes proven, that the first membranes used for this new PE technology activated complement components and heightened risks of hemolysis and infections. Current membranes (dextran sulfate, protein A – silica or – sepharose, tryptophan, phenylalanine, and Ig – Therasorb columns) seem able to avoid these adverse phenomena [58,59] and even prevent the rebound effect observed with conventional PE, at least when adsorbed immunoglobulins are replaced with low doses of human intravenous polyvalent immunoglobulins [59]. Successful treatment of many patients with severe forms of SLE with immunoabsorption in combination with conventional treatments or biologics has already been reported [38,57,60]. According to a recently published open study, among the 16 patients included with severe SLE and renal disease treated with immunoglobulin G immunoabsorption technology (Ig – Therasorb columns) [61], 14 responded within 3 months and 11 opted for continuation of this therapy. Proteinuria was significantly decreased at 3 and 12 months as were anti-ds DNA antibodies, and SLEDAI and ECLAM SLE-activity scores. Further controlled trials are needed to clarify the future of immunoabsorption in SLE, as are cost–benefit analyses in comparison with traditional PE, because its relatively high cost at present is a commonly reported limitation for its use.

References


