Autoimmunity Reviews 15 (2016) 38–49

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Efficacy of plasma exchange and immunoadsorption in systemic lupus erythematosus and antiphospholipid syndrome: A systematic review

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ARTICLE INFO

Article history:
Received 1 August 2015
Accepted 18 August 2015
Available online 28 August 2015

Keywords:
Systemic lupus erythematosus
Immunoadsorption
Plasma exchange
Plasmapheresis
Lupus nephritis
Refractory SLE
Complement
Extracorporeal treatment
Antiphospholipid syndrome

ABSTRACT

Extracorporeal treatments have been used since the 1970s in the management of systemic lupus erythematosus (SLE). A randomised controlled trial comparing the efficacy of standard of care (SOC) combined with plasma exchange against SOC alone in patients with lupus nephritis revealed no difference in terms of renal outcome. Subsequently, initial expectations have been dampened and further experience with plasma exchange is mainly limited to observational studies and single case reports. Beneficial effects have been reported in patients with refractory disease course or in pregnancy with prior complications due to SLE and antiphospholipid syndrome. A more specific form of extracorporeal treatment, immunoadsorption (IAS), has emerged as a valuable option in the treatment of SLE. In line with the plasma exchange experience, IAS seems to have beneficial effects in patients with refractory disease, contraindications to standard immunosuppression or during pregnancy. The mechanism IAS relates to autoantibody removal but for plasma exchange removal of activated complement components, coagulation factors, cytokines and microparticles may also be relevant. Both treatment forms have good safety profiles although reactions to blood product replacement in plasma exchange and procedure related complications such as bleeding or catheter-related infections have occurred. There is a need to more clearly define the clinical utility of plasma exchange and IAS in refractory lupus and APS subgroups.

Contents

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http://dx.doi.org/10.1016/j.autrev.2015.08.010
1568-9972/

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with heterogeneous clinical manifestations and disease course. With the advent of combination glucocorticoid and immunosuppressive therapy, the prognosis of patients has improved [1]. However, those lacking a good response to standard therapy, classified as 'refractory SLE', remain a therapeutic challenge. Definitions of refractory disease are inconsistent: in lupus nephritis, this can comprise progressive deterioration of renal function, persisting nephrotic syndrome and a failure to achieve a partial proteinuric response by 12 months or complete response by 24 months [2]. Such definitions do not exist for other severe or life-threatening disease manifestations, such as refractory cutaneous, neuropsychiatric or haematological SLE. Current guidelines recommend further glucocorticoids, switching between immunosuppressives, e.g. between mycophenolate mofetil, cyclophosphamide and rituximab, and consideration of alternative therapies including plasma exchange (PLEX), immunoadsorption (IAS), or intravenous immunoglobulin (IVIg) [2–4]. A recent survey highlighting different clinical scenarios included PLEX as a treatment option in refractory mononeuritis multiplex or central nervous system vasculitis secondary to SLE only [5].

Extracorporeal treatments such as PLEX and IAS are used in other antibody-mediated disorders, such as myasthenia gravis, idiopathic dilated cardiomyopathy, glomerular disorders (i.e. ANCA-associated vasculitis, focal segmental glomerulosclerosis or anti-GBM disease) and in patients undergoing desensitisation before renal transplantation [6]. An older trial conducted by the Lupus Nephritis Collaborative Study Group (LNCSG) comparing PLEX in combination with cyclophosphamide (CYC) and steroids to standard therapy alone revealed no improvement in patients with severe lupus nephritis in terms of renal outcome [7]. A report by the Lupus Plasmapheresis Study Group (LPSG) indicated long-term remission in 8 of 14 patients undergoing PLEX with subsequent CYC administration ('synchronised' therapy) [8]. Results of their multicentre randomised controlled trial were never communicated. The Dutch Co-operative Study Group compared PLEX in combination with steroids to standard treatment and found no superiority of cytotoxic treatment to PLEX in patients with lupus nephritis [9]. Similar results were corroborated by a small controlled study from Japan [10]. No trials comparing efficacy of IAS either with or without other immunosuppressive measures against a comparator group have been conducted so far. In this review, we focus on principles of PLEX and IAS in SLE and the efficacy of both extracorporeal treatments in clinical trials and observational studies.

2. Methods

2.1. Search strategy

A systematic literature search of the MEDLINE database was conducted, using the key words: "(immunoadsorption OR plasmapheresis) AND (antiphospholipid syndrome OR APS OR catastrophic antiphospholipid syndrome OR CAPS OR lupus nephritis OR LN OR systemic lupus erythematosus OR SLE)".

The search was limited to articles reporting on at least five patients undergoing IAS and ten patients undergoing PLEX. Comments to articles, review articles or reports including mainly patients in remission and comparing different IAS columns were not included. Additional studies were identified by examining the bibliography of the retrieved articles by forward search.

3. Results

3.1. Search results

The systematic search (performed on December 1st, 2014) resulted in 130 records reporting on IAS treatment in SLE, lupus nephritis, antiphospholipid syndrome (APS) or its catastrophic variant. 112 articles were excluded, since these reported on single cases, case series with a total number below five, reviews, non-English publications and one publication comparing different columns [11] in patients with remission and one article could not be assessed in full text [12]. A lack of clinical data and/or publication of *in vitro* results led to the exclusion of another six articles [13–18].

Due to more publications reporting on PLEX treatment in SLE, the arbitrary cut-off for inclusion was set to at least 10 treated patients. We excluded 997 articles due to reporting single cases or case series with fewer than 10 patients, reviews, non-English publications, several non-related case reports/series and two were not accessible in full text [19,20]. Through forward search of the retrieved bibliography we identified another two eligible records. Seven articles were excluded due to not evaluating efficacy of PLEX despite treating at least ten patients [21–24], PLEX treatment in a 'steady' state with no obvious indication to initiate additional immunosuppression [25], *in vitro* experiments [26] and review of the literature [27]. Thus, a total number of 15 articles reporting on PLEX treatment were included.

3.2. Removal of disease-specific antibodies and immunologic alterations following extracorporeal treatment

3.2.1. Plasma exchange

3.2.1.1. Anti-nuclear antibodies and anti-double stranded DNA antibodies. Analysis of an older cohort revealed a decline of both anti-nuclear antibody titre (ANA) from an initial value of 640 (40–2560) to 160 (0–1280) and anti-double stranded DNA (dsDNA) antibody titre from 40 (0–160) to 0 (0–20) after PLEX [28]. After a mean of 11.5 months, another single centre report indicated anti-dsDNA antibody negativity in all patients [29]. In an observational study, anti-dsDNA antibodies decreased from 113 ± 31 to 23 ± 11 U/ml [30], whereas others observed a halving of anti-dsDNA antibodies (48.87 ± 28.9 to 25.7 ± 29.96) in a cohort with lupus nephritis [31]. A prospective randomised controlled trial revealed a similar decrease in anti-dsDNA antibodies in the PLEX-treated arm compared to the comparator group [7]. A four-fold reduction in anti-dsDNA antibodies was reported in patients with lupus nephritis [32]. 'Synchronised' therapy, characterised by PLEX with subsequent administration of CYC to cover a potential antibody rebound,