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Review

Autologous hematopoietic stem cell transplantation in Systemic Lupus Erythematosus and antiphospholipid syndrome: A systematic review

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ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) has been proposed as a therapeutic option for patients with Systemic Lupus Erythematosus (SLE) refractory to standard therapy. This therapeutic approach has been applied to other severe autoimmune diseases refractory to standard therapy with promising results.
Aim: To systematically review the literature and analyze the available evidence on HSCT therapy in patients with SLE and antiphospholipid syndrome (APS), with a focus on therapy efficacy and occurrence of adverse events.
Methods: A detailed literature search, applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation and Ovid Medline 1986 to 2014, has been developed *a priori* to identify articles that reported findings from clinical and laboratory studies that investigated the effect of HCT in patients with SLE.
Results: Twenty-five studies met all inclusion criteria, including a total of 279 SLE patients; of those, 54 patients also fulfilled the classification criteria of APS. The majority of the studies reported an improvement after HSCT in terms of diseases activity control (assessed with SLEDAI, or time-free from diseases) or overall survival. However, one study reported no net benefit of HSCT when compared to immunosuppression alone. One retrospective study reported an overall survival at 5 years of 81% in 28 SLE patients.
Of note, 5 cases (9.3%) of aPL negativization were reported after HSCT in the APS patients. When combining these studies and analyzing these patients with APS, 32 out of 44 (73%) were able to discontinue anticoagulation after HSCT. Our findings also demonstrate a total of 86 infections in the pool of patients (30.8%), 3 of which resulted in the death of the patient (1.3%). We observed an annual incidence of infection of 11.9% with a mean follow up of 36.2 months.
Conclusion: Preliminary results of HSCT as a therapeutic option for SLE appear promising. Further studies are warranted in order to assess the safety of the procedure for both the occurrence of secondary autoimmune disease and the rate of infection. However, the rate of adverse effects confines this option to very selected cases of SLE patients resistant or refractory to standard approaches.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a relapsing intermitting course with periods of flares, alternating periods of remission and by highly heterogeneous clinical manifestations with a multi-systemic involvement [1]. The management of SLE is based on non-steroidal anti-inflammatory drugs, glucocorticoids (GC), hydroxychloroquine (HCQ) and immunosuppressive agents, as well as novel biotechnological therapies [2,3]. Although advances in the treatment of SLE have led to a significant improvement in the prognosis, SLE management remains challenging due to the adverse effects associated with conventional therapies and the occurrence of refractory disease.

Hematopoietic stem cell transplantation (HSCT) has been proposed as an alternative therapeutic option for SLE patients refractory to standard therapy. The initial findings of remission of severe autoimmune disease were described in patients undergoing transplantation for a hematologic disease who also had a coincidental autoimmune disease [4–6]. Following these observations, this therapeutic approach has been applied to other severe autoimmune diseases refractory to standard therapy [7–10] and preliminary results of animal model studies have been promising [11,12]. Although the mechanism of remission of disease induced by HSCT is likely to be due to intensive immune suppression, it may also play a role in modifying the immune system after transplant and thus leading to a prolonged period of remission.

In this systematic review, we aim to analyze the available evidence on HSCT therapy in patients with SLE and antiphospholipid syndrome (APS), focusing on therapy efficacy and occurrence of adverse events.

2. Patients and methods

2.1. Search and study selection

A detailed literature search has been developed *a priori* to identify articles that reported findings from clinical and laboratory studies that investigated the effect of HCT in patients with SLE. Keywords and subject terms included ("lupus vulgaris"[MeSH Terms] OR ("lupus"[All Fields] AND "vulgaris"[All Fields]) OR "lupus vulgaris"[All Fields] OR "lupus"[All Fields]) AND (("transplantation"[Subheading] OR "transplantation"[All Fields] OR "transplantation"[MeSH Terms]) OR (autologous[All Fields] AND ("hematopoietic stem cell transplantation"[MeSH Terms] OR ("hematopoietic"[All Fields] AND "stem"[All Fields] AND "cell"[All Fields] AND "transplantation"[All Fields]) OR "hematopoietic stem cell transplantation"[All Fields] OR ("hematopoietic"[All Fields] AND "cell"[All Fields] AND "transplantation"[All Fields]) OR "hematopoietic cell transplantation"[All Fields])) OR allogenic [All Fields]).

The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation and Ovid Medline 1986 to 2014. References of applicable review articles and included studies were hand searched to identify other relevant studies. No search limits were applied.

All published studies in manuscript form enrolling at least 1 patient with SLE undergoing auto- or allogenic HCT were included. We excluded abstracts not published as full manuscripts. Studies were independently reviewed by 2 authors (AL and AA). Any disagreements were resolved by consensus with other authors (SS, MR, MK).

3. Data collection

Data were collected on study details, patient characteristics, clinical outcomes [overall survival (OS)] and harms [transplantation-related morbidity (TRM), disease relapse, autoantibodies seroconversion]. Methodological quality utilizing a standardized data extraction form (Appendix S1). All data were independently extracted by 2 authors (AL and AA). Extracted data was verified for accuracy by another author (SS). Methodological quality of included cohort studies was assessed using the Newcastle-Ottawa scale modified for single-arm cohort [13].

4. Data analysis and statistical methods

A proportion was calculated for each outcome. When possible, effect estimates from studies similar in terms of study design, included patients, interventions, and outcomes were pooled together. All results are reported as a proportion and a 95% confidence interval (CI). Heterogeneity was tested using the I^2 test. An I^2 above 30% was considered moderate heterogeneity and above 60% was considered high heterogeneity. This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14].

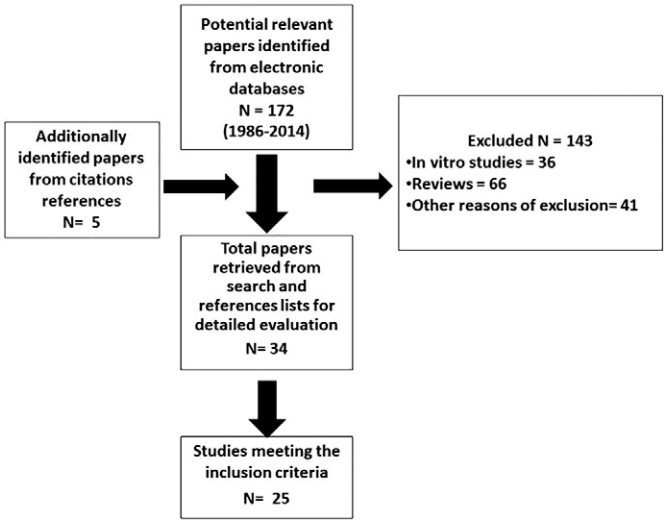

Fig. 1. Study selection process.