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 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 disease 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.

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Keywords:
Autologous hematopoietic stem cell transplantation
Systemic lupus erythematosus
Antiphospholipid syndrome
Anticardiolipin
Lupus anticoagulant
Thrombosis

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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”[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 stem cell transplantation”[All Fields])) OR allogenic [All Fields]).

The search strategy was applied to Ovid MEDLINE, In-Pro cess 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].
### Table 1
Demographic and pre-transplant clinical characteristics of SLE patients.

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Controls (if any)</th>
<th>Female (n.)</th>
<th>Age (mean)</th>
<th>Transplant details (type)</th>
<th>Indication for transplant</th>
<th>Treatment for ablation</th>
<th>Treatment for after transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traynor et al. [15]</td>
<td>2000</td>
<td>Phase 1 study</td>
<td>7</td>
<td>0 NR</td>
<td>27</td>
<td>Autologous HSCT</td>
<td>Refractory SLE</td>
<td>CYC (200 mg/kg), MTP (1 g), and ATG (90 mg/kg)</td>
<td>3 patients were tapered to 5 mg PDN daily and the other 4 patients had their medication discontinued.</td>
<td></td>
</tr>
<tr>
<td>Loh et al. [16]</td>
<td>2007</td>
<td>RS</td>
<td>55 (13 pts. with significant cardiac abnormalities)</td>
<td>0</td>
<td>12 of the 13 with cardiac abnormalities</td>
<td>39.3 (median age of the 13 with cardiac abnormalities)</td>
<td>Autologous HSCT</td>
<td>Of the 13: nephritis (n = 7), cerebritis (n = 8), refractory cytopenia (n = 4), APS (n = 8), pulmonary involvement (n = 7), serositis (n = 4) and cardiac dysfunction (n = 2)</td>
<td>IV CYC + ATG/alemtuzumab</td>
<td>NR</td>
</tr>
<tr>
<td>Vanikar et al. [17]</td>
<td>2007</td>
<td>RS</td>
<td>27</td>
<td>0 NR</td>
<td>24</td>
<td>24.2</td>
<td>Allogeneic HSCT</td>
<td>NR</td>
<td>CYC, PDN, ATG</td>
<td>NR</td>
</tr>
<tr>
<td>Guandalini et al. [18]</td>
<td>2007</td>
<td>RS</td>
<td>5</td>
<td>0 NR</td>
<td>24</td>
<td>Autologous BMT/HSCT</td>
<td>NR</td>
<td>BEAM + ATG</td>
<td>No patient is taking over 5 mg of prednisone following transplant</td>
<td></td>
</tr>
<tr>
<td>Carrion et al. [19]</td>
<td>2010</td>
<td>RS</td>
<td>2</td>
<td>0 NR</td>
<td>22</td>
<td>Auto-mesenchymal stem cell transplant</td>
<td>Severe SLE</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Meng et al. [20]</td>
<td>2011</td>
<td>RS</td>
<td>11</td>
<td>NR</td>
<td>39^</td>
<td>29</td>
<td>Autologous HSCT</td>
<td>Refractory SLE</td>
<td>CYC/ATG regimen</td>
<td>NR</td>
</tr>
<tr>
<td>Song et al. [21]</td>
<td>2011</td>
<td>RS</td>
<td>17</td>
<td>NR</td>
<td>14</td>
<td>23</td>
<td>Autologous HSCT</td>
<td>Severe SLE*</td>
<td>CYC/ATG regimen</td>
<td>Glucocorticoids discontinued at 6 (12) or 12 months (4) except one patient who continuously takes prednisone 5 mg/day.</td>
</tr>
<tr>
<td>Pasquini et al. [22]</td>
<td>2012</td>
<td>RS</td>
<td>27</td>
<td>0 NR</td>
<td>25</td>
<td>Autologous or Allogeneic HSCT</td>
<td>NR</td>
<td>CYC/ATG regimen</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Alchi et al. [23]</td>
<td>2013</td>
<td>RS</td>
<td>28</td>
<td>0 NR</td>
<td>29</td>
<td>Autologous HSCT</td>
<td>Refractory SLE</td>
<td>Low or intermediate intensity CYC/ATG regimen</td>
<td>12 patients had an immunosuppressive drug (Cy or MMF) or biological agent introduced after HSCT. PDN was withdrawn in 4/26 and the 22/26 remaining patients were receiving PDN in doses of 3–100 mg daily at time of last follow-up.</td>
<td></td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Controls (if any)</th>
<th>Female (n.)</th>
<th>Age (mean)</th>
<th>Transplant details (type)</th>
<th>Indication for transplant</th>
<th>Treatment for ablation</th>
<th>Treatment for after transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euler et al. [24]</td>
<td>1996</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>28</td>
<td>Autologous HSCT</td>
<td>Severe SLE and non-Hodgkin lymphoma</td>
<td>BEAM regimen</td>
<td>NR</td>
</tr>
<tr>
<td>Snowden et al. [25]</td>
<td>1997</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>NR</td>
<td>Autologous HSCT</td>
<td>Non-Hodgkin lymphoma</td>
<td>CBV regimen</td>
<td>PDN was reduced 1 mg every 3 weeks and then discontinued. Three years later steroid treatment was re-started for thrombocytopenia</td>
</tr>
<tr>
<td>Marmont et al. [26]</td>
<td>1997</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>46</td>
<td>Autologous HSCT</td>
<td>Severe refractory SLE</td>
<td>15 mg/kg Thiotepa/100 mg CYC</td>
<td>Seven months after transplant corticosteroid requirement is 10 mg/daily</td>
</tr>
<tr>
<td>Burt et al. [27]</td>
<td>1998</td>
<td>CR</td>
<td>2</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>Autologous HSCT</td>
<td>Acute renal failure and recurrent alveolar hemorrhage</td>
<td>Cymethyl-prednisolone/ATG regimen</td>
<td>One patient - no treatment, other patient - tapering of steroids PDN reduced from 50 mg to 12.5 mg</td>
</tr>
<tr>
<td>Fouillard et al. [28]</td>
<td>1999</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>35</td>
<td>Autologous HSCT</td>
<td>Severe and progressive SLE</td>
<td>BEAM regimen</td>
<td></td>
</tr>
<tr>
<td>Brunner et al. [29]</td>
<td>2002</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>18</td>
<td>Autologous HSCT</td>
<td>Refractory SLE with pulmonary impairment</td>
<td>CYC/ATG regimen</td>
<td>NR</td>
</tr>
<tr>
<td>Lisukov et al. [30]</td>
<td>2004</td>
<td>CR</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>22</td>
<td>Autologous HSCT</td>
<td>Severe refractory SLE</td>
<td>BEAM + ATG (n = 2), melphalan + etoposide (n = 2) and CYC/ATG (n = 2)</td>
<td>Patient 1 - oral PDN withdrawn after 10 months of BMT, patient 2 - maintenance therapy of Cy 100 mg/day, low dose corticosteroids (10–7.5 mg/day) and AZA 50 mg/day, patient 3 - none mentioned PDN 5 mg daily</td>
</tr>
<tr>
<td>Talaulikar et al. [31]</td>
<td>2005</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>39</td>
<td>Autologous HSCT</td>
<td>Refractory SLE</td>
<td>CYC/ATG regimen</td>
<td></td>
</tr>
<tr>
<td>Marmont et al. [32]</td>
<td>2006</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>Autologous HSCT</td>
<td>Diffuse global lupus nephritis and refractory nephrotic syndrome with high proteinuria</td>
<td>Thiotaepa 10 mg/kg followed by CYC100mg/kg</td>
<td>5 mg of PDN every other day</td>
</tr>
<tr>
<td>Alexander et al. [33]</td>
<td>2013</td>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>Autologous HSCT</td>
<td>Severe refractory SLE</td>
<td>CYC/ATG regimen</td>
<td>Immunosuppressive drugs withdrawn</td>
</tr>
</tbody>
</table>

NR, not reported; RS, retrospective study; CR, case report; *SLE patients receiving immunosuppression therapy not transplant; CYC, cyclophosphamide; MTP, methylprednisolone; PDN, prednisolone; HSCT, hematopoietic stem cell transplantation; BMT, bone marrow transplantation; *SLE patients with transfusion-dependent cytopenias, severe pericarditis, lung/CNS involvement or tx-resistant glomerulonephritis; ATG, anti-thymocyte globulin; BEAM, BCNU – carmustine, etoposide, Ara-C – cytarabine, melphalan; CBV, cyclophosphamide, BCNU (carmustine), and VP-16 (etoposide); Cy, cyclosporine; MMF, mycophenolate; AZA, azathioprine;
5. Results

5.1. Search results and characteristics of included studies

The search identified 2088 studies and 25 met all inclusion criteria [15–39]. The study selection process is reported in Fig. 1. The use of allogenic/auto-HSCT as rescue therapy for SLE/SAPS was assessed using data from 2 prospective [15,36], 10 retrospective studies [16–23, 34] and 13 case reports [24–33,35,37–39], for a total of 279 SLE patients. Of those, 54 patients also fulfilled the criteria of APS. The demographic and pre-transplant clinical characteristics of the patients of included studies are reported in Tables 1 and 2 for patients with SLE and for SLE and APS, respectively.

5.2. Control of disease activity

Three out of 12 studies (2 prospective and 10 retrospective) assessed SLE activity with SLE Disease Activity Index (SLEDAI) [15,18,20], Traynor and colleagues [15] reported that following HSCT a gradual, but marked, improvement in their cohort (from 90 of cumulative SLEDAI index to 9 after transplant. Whereas an

difference between the two groups.

Four studies reported the disease-free survival in their cohort of patients [17,21,23,34]. Vanikar et al. [17] reported a disease-free interval of 7.35 months; Alchi et al. [23] showed a 5 year disease-free survival of 29%; Song et al. [21] reported a progression-free survival of 64.7% (significantly higher than the control group), and finally Burt et al. [34] described a 50% disease-free survival at 5 years.

5.3. aPL profile changes after HSCT

It is worth noting that studies that included SLE patients with APS (SAPS), reported 4 cases (7.4%) of aPL neutralization after transplant and one study reported one case (1.9%) of aPL neutralization after transplant in the first 6 months of follow-up. Statkute et al. [37] stated that 14 out of 22 SAPS patients were able to discontinue anticoagulation, while Burt et al. [34] described 18 out of 22 SAPS patients that were able to stop anticoagulation therapy after transplant. No APS-related recurrences were described during the follow up (range = 8–29 months).

5.4. Overall-survival and mortality

One retrospective study out of 12 total studies [23] reported the 5 years overall survival outcome. Alchi et al. [23] reported that in their 28 SLE patients the OS was 81% (5 patients died in 2 years after treatment, 3 deaths were caused by infections, 1 progressive SLE and 1 caused by autoimmune haemolytic anaemia).

Burt et al. observed in 50 SLE patients a disease-free survival at 5 years of 50% (2 patients died after mobilization: one active lupus and one from mucormycosis) [34].

Song et al. [21], reported that in their study of 17 SLE patients there were 2 deaths during the follow up period of 89 months.

Paquini et al. [22], with a cohort of 27 SLE patients, reported 8 deaths in a follow up period of 31 months and lastly Loh et al. [16] reported 3 deaths (2 SLE progression and the third following an accident). Furthermore, a case report described the death of all three of these patients due to transplant related complications during the follow up of 60 months [30].

Twenty studies did not report deaths during their follow-up period (range = 7–70 months).

When pooling together these studies, we observed an overall mortality of 8.3% with a mean follow-up of 36.2 months.

The heterogeneity between studies was high ($I^2 = 87\%$).

The results describing outcomes, mortality and post-transplant clinical characteristics of the patients included in the analysis are summarized in Tables 3 and 4.

5.5. Adverse events (AEs)

In the 25 studies included, we observed a total of 86 infections (30.8%), 3 of which resulted in the death of the patient (1.3%). When pooling together the results from the studies analysed, there was an annual incidence of infections of 11.9% with a mean follow up of 36.2 months. Other adverse events included one case of allergic reaction to cyclophosphamide (0.4%), one case of fever related to G-CSF (0.4%), one Epstein Barr–associated lymphoproliferative disorder, one case of angioedema (0.4%), one case of factor VIII inhibitor hemorrhage (0.4%), two cases of secondary autoimmune diseases (0.7%) (one case of autoimmune hemolytic anaemia that caused the death of the patient and one acquired haemophilia), three cases of bone pain (1.1%), three cases of mucositis (1.1%), three cases of (1.1%) enteropathy and finally three cases of severe hemorrhage (1.1%).

Table 2

Demographic and pre-transplant clinical characteristics of SAPS patients.

<table>
<thead>
<tr>
<th>First author</th>
<th>Study design</th>
<th>Age (mean)</th>
<th>SAPS Indication for transplant</th>
<th>Treatment for after transplant</th>
<th>Anticoagulation before transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burt (2006) [34]</td>
<td>RC 50</td>
<td>43 30 22</td>
<td>Refractory SLE and either organ- or life-threatening visceral involvement</td>
<td>NR</td>
<td>Y</td>
</tr>
<tr>
<td>Hashimoto (2004) [35]</td>
<td>CR 1</td>
<td>1 27 1</td>
<td>Progressive myocardial damage caused by APS despite treatment</td>
<td>Low-dose corticosteroids</td>
<td>N</td>
</tr>
<tr>
<td>Rosen (2000) [36]</td>
<td>Phase 1/2 study 3</td>
<td>2 37 1</td>
<td>Refractory SLE</td>
<td>Reduced steroid therapy (APS patient still on warfarin)</td>
<td>Y</td>
</tr>
<tr>
<td>Statkute/Burt (2005) [37]</td>
<td>RC 28</td>
<td>25 29 28</td>
<td>Glomerulonephritis, involvement of the lung or CNS, transfusion-dependent autoimmune cytopenias, or APS</td>
<td>8/22 remained on anti-coagulation, 11/28 on immunosuppression and 8/11 discontinued this within 13 months</td>
<td>Y</td>
</tr>
<tr>
<td>Tysberg (2000) [38]</td>
<td>CR 1</td>
<td>1 16 1</td>
<td>CNS lupus</td>
<td>Cyclosporin A, low dose corticosteroids, azathioprine</td>
<td>Y</td>
</tr>
<tr>
<td>Musso (1999) [39]</td>
<td>CR 1</td>
<td>1 19 1</td>
<td>SLE complicated by Evans’ syndrome, severe hypercorticism and anemorhoea</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*8 with probable APS, 16 patients were positive for LAC, 20 for anticardiolipin antibodies; **3 patients were positive for anticardiolipin antibodies.
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Outcomes</th>
<th>Infections</th>
<th>Deaths</th>
<th>Other adverse events</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traynor et al. [15]</td>
<td>2002</td>
<td>All patients demonstrated a gradual, but marked, improvement. The SLEDAI score has declined to &lt;5 in 12 patients. Complement and anti–double-stranded DNA levels have normalized and marked improvements in end organ function have occurred in all subjects</td>
<td>10 different infections reported</td>
<td>NR</td>
<td>NR</td>
<td>36</td>
</tr>
<tr>
<td>Loh et al. [16]</td>
<td>2007</td>
<td>No transplant-related or cardiac deaths occurred among the 13 patients. Significant non-haematological toxicities included fluid overload, infection and engraftment syndrome. All patients with impaired LVEF remained stable or improved while 3 with symptomatic mitral valve disease similarly improved.</td>
<td>NR</td>
<td>3*</td>
<td>NR</td>
<td>24</td>
</tr>
<tr>
<td>Vanikar et al. [17]</td>
<td>2007</td>
<td>Average disease-free interval was 7.35 months and serology improved</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>57</td>
</tr>
<tr>
<td>Guandalini et al. [18]</td>
<td>2007</td>
<td>All had a complete remission following transplant, but there were two relapses. However these both responded to Rituximab. The cumulative SLEDAI index dropped from 90 pre-transplant to 9 post-transplant.</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Carrion et al. [19]</td>
<td>2010</td>
<td>HSCT induces an increase of circulating T-reg cells that was not associated with clinical benefit</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>3,5</td>
</tr>
<tr>
<td>Meng et al. [20]</td>
<td>2011</td>
<td>SLEDAI scores after treatment either by transplantation or by immunosuppressive therapy decreased dramatically when compared to that before treatment, although there was no significant difference between the two groups. However, the rate of maternal HTN and lupus nephritis of mother was greatly reduced in autologous peripheral blood stem cell transplanted group compared to non-transplanted group. Additionally, the outcome of lupus flare activity of the mother after delivery is significantly better in transplanted group.</td>
<td>9% of transplanted group and 13% of non-transplanted group</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Song et al. [21]</td>
<td>2011</td>
<td>Progression-free survival of patients in auto-HSCT group was 64.7% (significantly higher than control group), one female patient experienced a relapse after a spinal TB infection</td>
<td>8</td>
<td>2**</td>
<td>4 (allergic reaction to cyclophosphamide - 1, fever related to G-CSF - 3 and bone pain - 4)</td>
<td>89</td>
</tr>
<tr>
<td>Pasquini et al. [22]</td>
<td>2012</td>
<td>6 deaths</td>
<td>NR</td>
<td>8***</td>
<td>NR</td>
<td>31</td>
</tr>
<tr>
<td>Alchi et al. [23]</td>
<td>2013</td>
<td>5 year overall survival was 81% (±8%), disease-free survival was 29% (±9%), relapse incidence 56% (±11%)</td>
<td>15</td>
<td>5 in 2 years after treatment (3 caused by infection, 1 progressive SLE, 1 secondary autoimmune disease)</td>
<td>31 severe or life-threatening AE (15 infections, one developed Epstein Barr-associated lymphoproliferative disorder, 2 developed secondary autoimmune disease, one autoimmune haemolytic anaemia, 1 acquired haemophilia, 2 CV events)</td>
<td>38</td>
</tr>
<tr>
<td>Eular et al. [24]</td>
<td>1996</td>
<td>Complete remission of NHL and SLE but serological SLE symptoms persisted. On day 352 after transplant, patient showed signs of relapsing SLE, eventually developing severe thrombocytopenia which eventually led to a fatal intracerebral hemorrhage on day 378</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td>Snowden et al. [25]</td>
<td>1997</td>
<td>Patient went into clinical and serological remission following transplant, however 3 years later the patient presented with thrombocytopenia (ITP), which had not</td>
<td>2 (oral herpes simplex, Pneumocystis jirovecii 5 months after transplant)</td>
<td>0</td>
<td>Angular cheilitis</td>
<td>36</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Outcomes</th>
<th>Infections</th>
<th>Deaths</th>
<th>Other adverse events</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marmont et al. [26]</td>
<td>1997</td>
<td>Patient obtained good partial remission, reduction in steroid requirement, and a persistent normalization of ANA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Burt et al. [27]</td>
<td>1998</td>
<td>First patient is off all immunosuppressants for the first time in 13 years, second patient - hemoptysis and pulmonary infiltrates have resolved and steroids are gradually being tapered off.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Fouillard et al. [28]</td>
<td>1999</td>
<td>One year later, the patient is in clinical remission. ANA and anti-SSA antibodies were undetectable at 1 and 6 months after intensification, but reappeared at low levels at 9 months.</td>
<td>None during tx but once discharged the patient developed herpes simplex virus on day 90</td>
<td>0</td>
<td>Grade B mucositis</td>
<td>12</td>
</tr>
<tr>
<td>Brunner et al. [29]</td>
<td>2002</td>
<td>21 months after the patient was still in clinical remission, with no signs of SLE-related disease activity and without any immunosuppressive medications. Her pulmonary function has also returned to normal.</td>
<td>Pseudomonas aeruginosa</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Lisukov et al. [30]</td>
<td>2004</td>
<td>3 patients died on days 11, 22 and 63 due to transplant related complications, complete remission of SLE in 2 patients after 6 months, other patient (with neuropsychiatric lupus) had neurological improvement but serological SLE symptoms persist (elevated ANA, anti-dsDNA and antinuclear and antihistone antibodies) and SLEDAI 2 - partial improvement</td>
<td>4 (pneumonia × 2, CMV × 1, genital herpes × 1)</td>
<td>3</td>
<td>Mucositis × 3, enteropathy × 3, severe hemorrhage × 2, sepsis × 3</td>
<td>(60 and 6 months for 2 patients - complete remission and 42 months for the patient with a partial response)</td>
</tr>
<tr>
<td>Talaulikar et al. [31]</td>
<td>2005</td>
<td>At 12 months post-transplantation, the patient remains asymptomatic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Marmont et al. [32]</td>
<td>2006</td>
<td>Proteinuria dropped almost immediately, serology (anti-dsDNA, ANA, LAC) became negative within 2 months and 5 years on the patient is well and active.</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>60</td>
</tr>
<tr>
<td>Alexander et al. [33]</td>
<td>2013</td>
<td>Clinical remission was achieved for SLE within 3 months after HSCT and anti-dsDNA antibodies disappeared despite immunosuppressive drug withdrawal</td>
<td>NR</td>
<td>0</td>
<td>8 months after HSCT, the patient presented with spontaneous joint and skin bleeding and was diagnosed with factor VIII (FVIII) inhibitor haemophilia</td>
<td>8</td>
</tr>
</tbody>
</table>

*Three patients died; two from SLE progression/relapse at 11.5 months and 19 months post-transplant, respectively and the third following an accident at 8 months; **severe pneumonia - 33 months after and heart failure - 64 months after; ***6 from infestations, 1 from active SLE and 1 from graft failure.

6. Discussion

Conventional treatments for SLE are typically directed against the adaptive immune response by limiting T and B cell activation, and/or lowering auto-antibody production. The rationale behind HSCT therapy in SLE is based on an initial phase of intensive immunosuppression to ablate the auto-reactive lymphocytes. The second phase is represented in SLE is based on an initial phase of intensive immune-suppression to lowering auto-antibody production. The rationale behind HSCT therapy is to ablate the immune system to the point of marrow suppression, and the related adverse events can't be underestimated.

Interestingly in the studies analysed, antibody negativization occurred in some of patients both for anti-DNA antibodies and antiphospholipid antibodies (aPL). Conversely, aPL negativization following immunosuppression therapy have been only occasionally described [40]. Besides, it is important to note that out of 44 APS reported cases for whom detailed therapy was provided, >70% were able to discontinue anticoagulation after HSCT [34,36–38].

There are several limitations to the studies analysed: low number of patients of the studies included, potential publication bias with studies reporting only positive outcomes, heterogeneity in clinical presentation, and applied protocols of both immunosuppression and HSCT. It is also important to note a high number of infections and adverse events occurred in patients that underwent the protocol of high dose immune suppression regimen followed by HSCT. In fact, the protocol of intense immunosuppression applied to the treatment is intended to ablate the immune system to the point of marrow suppression, and the related adverse events can't be underestimated.

A further obstacle to this therapy, as described by Daikeler and colleagues [41], is the development of secondary autoimmune diseases that may occur after HSCT. In this retrospective study, after autologous HSCT for primary autoimmune diseases, 29 of 347 patients analysed,
developed at least one secondary autoimmune disease in the follow up period, and after allogeneic HSCT, 3 of 16 patients. Even though in our analysis only two cases of secondary autoimmune disease were described, Daikeler et al. identified, after multivariate analysis, an initial diagnosis of SLE (P = 0.019; hazard ratio = 3.21; 95% confidence interval, 1.21–8.48) as a significant risk factor for developing a secondary autoimmune disease after HSCT.

7. Conclusion

Despite the limitations of the studies analysed, the preliminary results of intense immunosuppression and HSCT seem promising. Further studies are warranted in order to assess the safety of the procedure both for occurrence of secondary autoimmune diseases and rate of infections. Prior to considering HRCT as a novel and viable therapeutic option, randomized prospective trials are advised in order to determine the efficacy of HSCT alone and its contribution in inducing remission in SLE and APS patients.

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Disclosure of conflicts of interest

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References


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