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# **Autologous Hematopoietic Stem Cell Transplantation in Systemic Lupus Erythematosus and Antiphospholipid Syndrome: a systematic review.**

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**Running title:** HSCT in SLE and APS

**Keywords:** autologous hematopoietic stem cell transplantation, systemic lupus erythematosus, antiphospholipid syndrome, anticardiolipin, lupus anticoagulant, thrombosis

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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**

25 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.

### **Highlights**

- Hematopoietic stem cell transplantation (HSCT) has been proposed with promising results as a therapeutic option for patients with severe autoimmune diseases refractory to standard therapy.
- The rate of adverse effects confines HSCT to very selected cases of patients with Systemic Lupus Erythematosus resistant or refractory to standard approaches.

## 1.1 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.

## 2.1 Patients and Methods

### 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. Key words 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).

## **2.2 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 1). 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].

## **2.3 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].

### **3.1 Results**

#### **3.2 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 Figure 1. The use of allogenic/auto-HCT 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.

#### **3.3 Control of disease activity**

3 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 (<5 of SLEDAI in 12 patients). Gualandi et al. [18] demonstrated that 5 SLE patients had a decrease from 90 of cumulative SLEDAI index to 9 after transplant. Whereas another study [20] reported an overall decrease of SLEDAI after either immunosuppression alone or followed by transplant, with no statistical difference between the two groups.

4 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.

#### **3.4 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 negativization after transplant and one study reported one case (1.9%) of aPL negativization 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).

### **3.5 Overall-survival and mortality**

One retrospective study out of twelve 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 and one from mucormycosis).

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 Table 3 and 4.

### **3.6 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 analyzed, 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 angular cheilitis (0.4%), one case of factor VIII inhibitor hemorrhage (0.4%), two cases of secondary autoimmune diseases (0.7%) (one case of autoimmune hemolytic anemia that caused the death of the patient and one acquired hemophilia), 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%).

### **4.1 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 immune-suppression to ablate the auto-reactive lymphocytes. The second phase is represented by a repopulation of the immune system by transplant with either autologous or allogeneic hematopoietic CD34+ progenitors cells, rescuing the patient from severe cytopenia and/or hematopoietic failure. It has been hypothesized that HSCT might permanently alter the immune system composition by losing T cell-mediated immune memory[4,9]. Although preliminary results described in the literature are promising, it is not clear whether HSCT alone with no intensive immunosuppression regimen could potentially induce remission in SLE patients. Currently, there is only one prospective phase I study that has investigated the safety and efficacy of immune suppression and HSCT in the treatment of SLE [15]. Although all patients included in the study demonstrated a gradual, but marked improvement (both in terms of clinical and laboratory parameters) it is important to note that phase I studies are not powered to determine efficacy of new experimental therapies.

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, more than 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) is significant risk factor for developing a secondary autoimmune disease after HSCT.

## **5.1 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 infection. 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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First Author	Year	Study design	Number of Patients	Controls (if any)	Female (n.)	age (mean)	transplant details (type)	Indication for transplant	Treatment for ablation	Treatment for after transplant
<b>Phase 1 trial</b>										
Traynor et al. [15]	2000	Phase 1 study	7	0	NR	27	Autologous HSCT	refractory SLE	CYC (200mg/kg), MTP (1g), and ATG (90mg/kg)	3 patients were tapered to 5mg PDN daily and the other 4 patients had their medication discontinued.
<b>Retrospective studies</b>										
Loh et al. [16]	2007	RS	55 (13 pts with significant cardiac abnormalities)	0	12 of the 13 with cardiac abnormalities	39.3 (median age of the 13 with cardiac abnormalities)	Autologous HSCT	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)	IV CYC + ATG/alemtuzumab	NR
Vanikar et al. [17]	2007	RS	27	0	24	24,2	Allogeneic HSCT	NR	CYC, PDN, ATG	NR
Gualandi et al. [18]	2007	RS	5	0	NR	NR	Autologous BMT/HSCT	NR	BEAM + ATG	No patient is taking over 5 mg of prednisone following transplant'
Carrion et al. [19]	2010	RS	2	0	2	22	auto-mesenchymal stem cell transplant	severe SLE	NR	NR
Meng et al. [20]	2011	RS	11	39^	(all - as paper focuses on pregnancy outcomes)	29	Autologous HSCT	refractory SLE	CYC/ATG regimen	NR
Song et al. [21]	2011	RS	17	20	14	23	Autologous HSCT	severe SLE*	CYC/ATG regimen	Glucocorticoids discontinued at 6 (12) or 12 months (4) except one patient who continuously takes prednisone 5mg/day.
Pasquini et al. [22]	2012	RS	27	0	NR	NR	Autologous or Allogeneic HSCT	NR	CYC/ATG regimen	NR
Alchi et al. [23]	2013	RS	28	0	25	29	Autologous HSCT	refractory SLE	low or intermediate intensity CYC/ATG regimen	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.
<b>Case reports</b>										

Euler et al. [24]	1996	CR	1	0	1	28	Autologous HSCT	Severe SLE and non-Hodgkin lymphoma	BEAM regimen	NR
Snowden et al. [25]	1997	CR	1	0	1	NR	Autologous HSCT	non-Hodgkin lymphoma	CBV regimen	PDN was reduced 1mg every 3 weeks and then discontinued. Three years later steroid treatment was re-started for thrombocytopenia
Marmont et al. [26]	1997	CR	1	0	1	46	Autologous HSCT	severe refractory SLE	15mg/kg Thiotepa / 100mg CYC	seven months after transplant corticosteroid requirement is 10mg/daily
Burt et al. [27]	1998	CR	2	0	NR	NR	Autologous HSCT	acute renal failure and recurrent alveolar hemorrhage	Cymethyl-prednisolone/ATG regimen	One patient - no treatment, other patient - tapering of steroids
Fouillard et al. [28]	1999	CR	1	0	1	35	Autologous HSCT	severe and progressive SLE	BEAM regimen	PDN reduced from 50mg to 12.5mg
Brunner et al. [29]	2002	CR	1	0	1	18	Autologous HSCT	refractory SLE with pulmonary impairment	CYC/ATG regimen	NR
Lisukov et al. [30]	2004	CR	6	0	6	22	Autologous HSCT	severe refractory SLE	BEAM + ATG (n=2), melphalan + etoposid (n=2) and CYC/ATG (n=2)	Patient 1 - oral PDN withdrawn after 10 months of BMT, patient 2 - maintenance therapy of Cy 100mg/day, low dose corticosteroids (10-7.5mg/day) and AZA 50mg/day, patient 3- none mentioned)
Talaulikar et al. [31]	2005	CR	1	0	1	39	Autologous HSCT	refractory SLE	CYC/ATG regimen	PDN 5mg daily
Marmont et al. [32]	2006	CR	1	0	0	26	Autologous HSCT	Diffuse global lupus nephritis and refractory nephrotic syndrome with high proteinuria	Thiotepa 10mg/kg followed by CYC100mg/kg	5mg of PDN every other day
Alexander et al. [33]	2013	CR	1	0	0	21	Autologous HSCT	severe refractory SLE	CYC/ATG regimen	immunosuppressive drugs withdrawn

**Table 1.** Demographic and pre-transplant clinical characteristics of SLE patients

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, BiCNU– carmustine, Etoposide, Ara-C – cytarabine, Melphalan; CBV, cyclophosphamide, BCNU (carmustine), and VP-16 (etoposide); Cy, cyclosporine; MMF, mycophenolate; AZA, azathioprine;

First Author	Study design	N #	F	age (mean)	SAPS	Indication for transplant (all receiving Autologous HSCT with CYC/ATG regimen for ablation)	Treatment for after transplant	anticoagulation before transplant (Y/N)
Burt (2006) [34]	RC	50	43	30	22	refractory SLE and either organ- or life-threatening visceral involvement	NR	Y
Hashimoto (2004) [35]	CR	1	1	27	1	progressive myocardial damage caused by APS despite treatment	low-dose corticosteroids	N
Rosen (2000) [36]	Phase 1/2 study	3	2	37	1	refractory SLE	reduced steroid therapy (APS patient still on warfarin)	Y
Statkute / Burt (2005) [37]	RC	28	25	29	28	glomerulonephritis, involvement of the lung or CNS, transfusion-dependent autoimmune cytopenias, or APS	8/22 remained on anti-coagulation, 11/28 on immunosuppression and 8/11 discontinued this within 13 months	Y
Trysberg (2000) [38]	CR	1	1	16	1	CNS lupus	Cyclosporin A, low dose corticosteroids, azathioprine	Y
Musso (1999) [39]	CR	1	1	19	1	SLE complicated by Evans' syndrome, severe hypercorticism and amenorrhoea	NR	NR

**Table 2.** Demographic and pre-transplant clinical characteristics of SAPS patients

*\*8 with probable APS, 16 patients were positive for LAC, 20 for anticardiolin antibodies; \*\*3 patients were positive for anticardiolin antibodies*

First Author	Year	Outcomes	Infections	Deaths	other adverse events	Follow-up (months)
<b>Phase I trial</b>						
Traynor et al. [15]	2002	All patients demonstrated a gradual, but marked, improvement. The SLEDAI score has declined to <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	10 different infections reported	NR	NR	36
<b>Retrospective studies</b>						
Loh et al. [16]	2007	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.	NR	3*	NR	24
Vanikar et al. [17]	2007	Average disease-free interval was 7.35 months and serology improved	NR	NR	NR	57
Gualand i et al. [18]	2007	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.	NR	NR	NR	NR
Carrion et al. [19]	2010	??? - Induces an increase of circulating T-reg cells that was not associated with clinical benefit	NR	0	NR	3,5
Meng et al. [20]	2011	SLESAI 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.	9% of transplanted group and 13% of non-transplanted group	NR	NR	NR
Song et al. [21]	2011	progression-free survival of patients in auto-SCT group was 64.7% (significantly higher than control group), one female patient experienced a relapse after a spinal TB infection	8	2**	4 (allergic reaction to cyclophosphamide - 1, fever related to G-CSF - 3 and bone pain -4 )	89
Pasquini et al. [22]	2012	6 deaths	NR	8***	NR	31
Alchi et al. [23]	2013	5 year overall survival was 81% (+/-8%), disease-free survival was 29% (+/-9%), relapse incidence 56% (+/-11%)	15	5 in 2 years after treatment (3 caused by infection, 1	31 severe or life-threatening AE (15 infections, one developed Epstein Barr-associated lympho	38

				progressive SLE, 1 secondary autoimmune disease)	proliferative disorder, 2 developed secondary autoimmune disease, one autoimmune haemolytic anaemia, 1 acquired haemophilia, 2 CV events)	
<b>Case report</b>						
Eular et al. [24]	1996	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	NR	1	NR	12
Snowden et al. [25]	1997	Patient went into clinical and serological remission following transplant, however 3 years later the patient presented with thrombocytopenia (ITP), which had not previously been a feature of the SKE, necessitating reintroduction of steroid immunosuppression.	2 (oral herpes simplex, pneumocystis jirovecii 5 months after transplant)	0	angular cheilitis	36
Marmont et al. [26]	1997	Patient obtained good partial remission, reduction in steroid requirement, and a persistent negativisation of ANA	0	0	0	7
Burt et al. [27]	1998	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.	0	0	0	11
Fouillard et al. [28]	1999	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.	None during tx but once discharged the patient developed herpes simplex virus on day 90	0	grade II mucositis	12
Brunner et al. [29]	2002	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.	Pseudomonas aeruginosa	0	0	21
Lisukov et al. [30]	2004	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 CNS lupus) had neurological improvement but serological SLE symptoms persist (elevated ANA, anti-dsDNA and anticardiolipin antibodies) and SLEDAI 2 - partial improvement	4 (pneumonia x2, CMV x1, genital herpes x1)	3	mucositis x3, enteropathy x3, severe haemorrhage x2, sepsis x3	(60 and 6 months for 2 patients - complete remission)

						on and 42 months for the patient with a partial response)
Talaulikar et al. [31]	2005	at 12 months post-transplantation, the patient remains asymptomatic	0	0	0	12
Marmont et al. [32]	2006	Proteinuria dropped almost immediately, serology (anti-dsDNA, ANA, LAC) became negative within 2 months and 5 years on the patient is well and active..	NR	0	NR	60
Alexander et al. [33]	2013	Clinical remission was achieved for SLE within 3 months after HSCT and anti-dsDNA antibodies disappeared despite immunosuppressive drug withdrawal	NR	0	8 months after HSCT, the patient presented with spontaneous joint and skin bleeding and was diagnosed with factor VIII (FVIII) inhibitor haemophilia	8

**Table 3.** Outcomes, mortality and post-transplant clinical characteristics of SLE patients

*\* 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 infections, 1 from active SLE and 1 from graft failure.*

First Author	Outcomes	Infections	Deaths	Follo w-up (mon ths)	aPL negativizati on after transplant	Patient anticoagulated after trasplant
Burt (2006) [34]	50% survived disease-free at 5 years, 84% survived at 5 years	27 infections during treatment, post-discharge (flu)	2 patients died after mobilization (one from mucormyosis and another from active lupus), treatment-related mortality was 2% (1/50)	29	NR	4 (18 were able to discontinue anticoagulation)
Hashimoto (2004) [35]	Improved clinical symptoms of APS	0	0	21	1	0
Rosen (2000) [36]	patients in remission, disease-related autoantibody titres declined to within the normal range. Corticosteroid therapy was gradually reduced in all patients.	0	0	19	all 3 became negative	1
Statkute / Burt (2005) [36]	21/28 entered remission of SLE, 9/28 were able to discontinue all immunospressive medications from immediately to 13 months after transplantation and stayed in remission from 12 to 66 months since stopping immunosuppression.	9 bacterial infection, 2 fungal, 3 viral	0			1
Trysberg (2000) [38]	regression of lesions in the brain and spinal cord	0	0	18 months	negative in first 6 months	1
Musso (1999) [39]	patient alive and well, with normal blood counts and persistent low-titre direct anti-globulin and ANA tests. Anti-dsDNA, LCA and aCL tests are all negative. No further treatment given.	1 (Pseudomonas spp.)	0	8	negative	0

**Table 4.** Outcomes, mortality and post-transplant clinical characteristics of SAPS patients

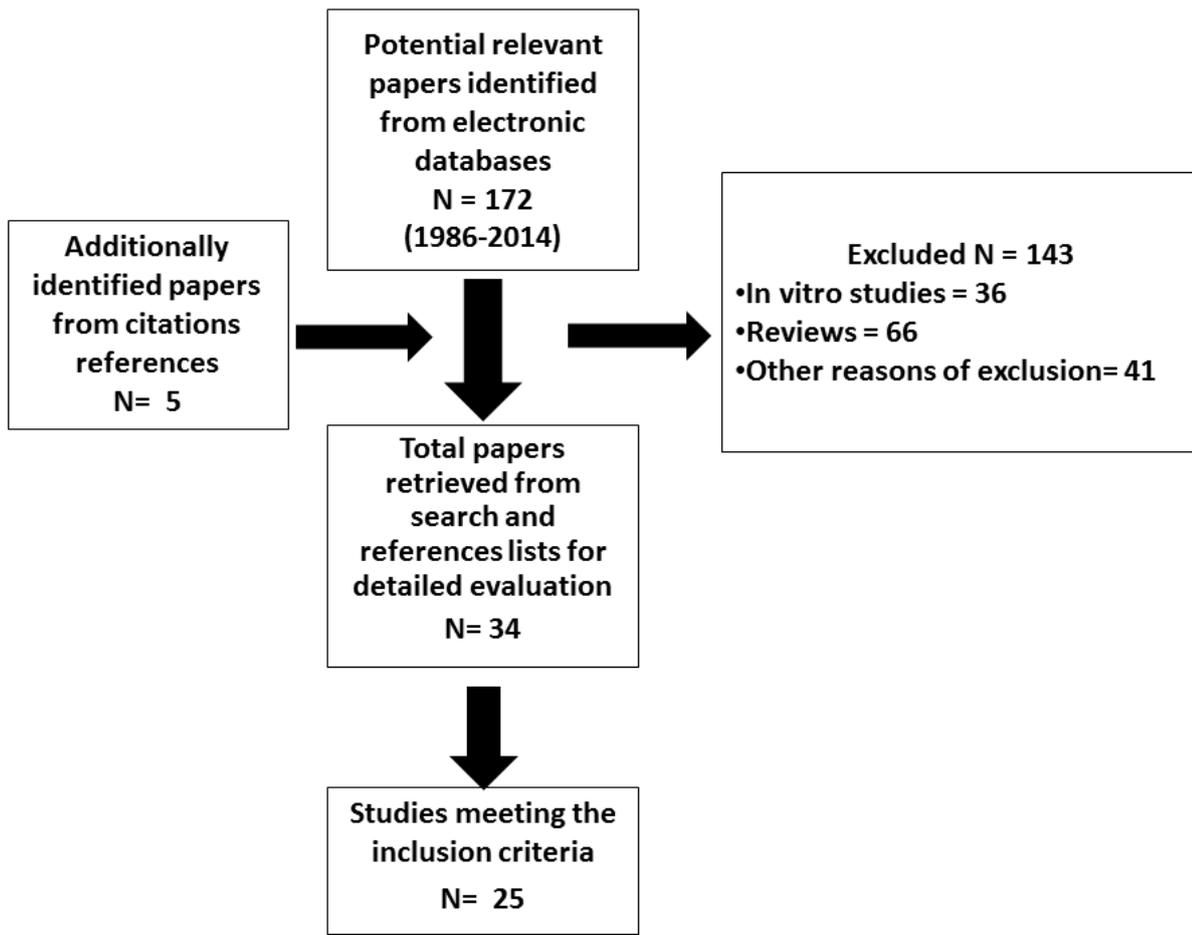


Figure 1. Study selection process