Editorial

Autologous haematopoietic stem cell transplantation for systemic lupus erythematosus: time for a paradigm shift?

T. Alexander and F. Hiepe

Charité – University Medicine Berlin, Germany.

Tobias Alexander, MD
*Falk Hiepe, MD**

**on behalf of the Autoimmune Disease Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT).*

Please address correspondence to:
Dr Tobias Alexander,
Department of Rheumatology and Clinical Immunology,
Charité – University Medicine Berlin,
10117 Berlin, Germany.
E-mail: tobias.alexander@charite.de

Received and accepted May 19, 2017.

Clin Exp Rheumatol 2017; 35: 359-361.

Key words: SLE, autologous haematopoietic stem cell transplantation

Competing interests: none declared.

Systemic lupus erythematosus (SLE) is a prototypical systemic autoimmune disease (AD) with heterogeneous clinical manifestations, which develops in genetically predisposed persons upon certain environmental triggers. The prevalence ranges form 20–150 cases per 100,000, predominantly affecting females (>85%) with higher frequency among people of African origin (1). A hallmark of SLE is a loss of self-tolerance that permits activation of autoreactive lymphocytes, which, amplified by type-I interferon activity, propagate chronic autoimmune responses in a self-perpetuating process, leading to autoantibody production, immune complex deposition, complement activation and end-organ failure (2). Over recent decades, survival rates have substantially improved with an estimated 5-year survival of over 90% and 15 to 20 years survival rates of around 80% (3). The major cause of morbidity and mortality is lupus nephritis (LN), which affects over half of all SLE patients. Although introduction of cyclophosphamide (CY) and mycophenolate mofetil (MMF) as standard-of-care substantially improved outcomes, such chronic immunosuppression is still associated with significant morbidity and unacceptably high progression rates. It is estimated that 35% of LN patients suffer at least one episode of renal relapse and 5% to 20% develop end-stage renal disease (4). Novel targeted cellular therapies or specific immunomodulators have demonstrated promising results, but failed to meet their primary endpoints in randomised controlled trials (RTCs) (5).

Supported by preclinical models, high-dose immunosuppression followed by transplantation of autologous haematopoietic stem cells (ASCT) has been utilised in severely affected patients with several ADs. Since its first application in 1997 (6), 115 ASCT for SLE have been reported to the European Society for Blood and Marrow Transplantation (EBMT) registry to date (March 2017). The two largest experiences so far come from the EBMT data registry (n=85; mean follow-up 25 months, range: 2–123 months) (7) and from the single centre pilot trial by Northwestern University (n=50; mean follow-up: 29 months, range: 6–90 months) (8). The probability of five-year disease free survival was 50% in both studies, similar to results from smaller pilot studies (reviewed in (9)). Meanwhile, mechanistic studies have provided the proof-of-concept that ASCT not solely acts as prolonged immunosuppression, but rather rewires an autoreactive immune system into a self-tolerant state. This is achieved by two major principles: i) vast eradication of the autoreactive immunologic memory by an immunoablative regimen and ii) fundamental reconfiguration of the adaptive immune system (10). This notion is reflected by a significant decrease or even disappearance of autoantibody levels (including anti-dsDNA, anti-phospholipid and antinuclear antibodies), where state-of-the-art chronic immunosuppression had been ineffective. In addition, in-depth analyses of the regenerating adaptive immune system confirmed the previously described normalisation of the restricted T cell repertoire (11) and demonstrated recurrence of newly generated $Foxp3^+$ $Helios^+$ regulatory T cells to the range seen in young healthy controls, mediated by sustained thymic reactivation (12). In addition, a dramatic shift in B cell subpopulations from memory to a naïve B cell dominance after ASCT was confirmed with normalisation of circulating plasmablast expansion, a hallmark of lupus immunopathology (11).

In this issue of Clinical and Experimental Rheumatology (CER), two studies on ASCT for refractory SLE are

presented from two Chinese centres, comprising data of 46 patients. In the first study, Leng and colleagues from the Medical College Hospital Bejing reported outcomes of 24 SLE patients after receiving a CD34-selected ASCT, collected from CY and granulocyte-colony stimulating factor (G-CSF) mobilised peripheral blood and conditioning with CY and anti-thymocyte globulin (ATG). All patients had visceral involvement and were refractory to various immunosuppressive / modulatory treatments including CY, CsA, AZA, MTX, MMF, HCQ, and IVIG. With a median follow-up of 120 months (range 8–180 months), both overall survival (OS) and progression-free survival (PFS) were 86% at 10 years, while transplant-related mortality (TRM) was 4% due to one fatal CMV infection (1/24 patients). Remarkably, responding patients had no signs of clinical or serologic disease activity, reflected by a median SLE Disease Activity Index (SLEDAI) of 0 despite discontinuation of chronic immunosuppression; only antimalarials were maintained in the majority (~60%) of patients. The level of antinuclear antibodies and anti-dsDNA antibodies completely normalised and proteinuria significantly improved in 15 patients with LN form a median of 4 g/day to 0 g/day at 10 years post-transplantation.

In the second study presented in this issue of CER, Cao and colleagues from Nanfang Medical University reported data on 22 lupus patients after receiving a CD34-selected ASCT following a CY and rabbit ATG based immunoablative regimen. All patients had LN and other visceral manifestations (neurological involvement, lung disease or haemolytic anaemia) and failed previous therapy with glucocorticoids and intravenous CY for at least 6 months. With a median follow-up of 113 months (range 51–147 months), OS and PFS at 5 years post-transplantation were 95.2% and 67.9%, respectively. Most frequent adverse events were viral reactivations, affecting 22 from 24 patients, particularly with CMV (59%), but no TRM was observed. Complement factors normalised and levels of ANA and anti-dsDNA antibodies significantly decreased. Most importantly, LN was controlled in the majority of patients, reflected by a significantly decrease of proteinuria to almost normal levels at 100 days post-transplantation and a marked reduction of immune complex depositions in renal re-biopsies performed in 6 out of 22 patients at 12 to 95 months post-transplantation.

Overall, both studies not only confirmed previous results from phase I/II clinical trials, they also added important new aspects to the field. First, clinical outcomes in both studies are substantially improved compared to results from pre-existing case series, where the probability of progression-free survival was only about 50% at 5 years. The reported PFS of 86% at 10 years by Leng and colleagues is outstanding, considering that all patients had failed previous state-of-the-art immunosuppression.

The relatively low relapse incidence may be related to the use of anti-malarials as maintenance in the majority of patients (~60%), which may have a role in preventing disease reactivation in the genetically predisposed population. Second, both studies have long follow-up periods, and the 10-year follow-up in the study presented by Leng *et al*. is the longest reported ever after ASCT for SLE. These data demonstrate that, once achieved, clinical remissions may be sustained for many years post-transplantation even in the absence of chronic immunosuppression, further highlighting the curative potential of this treatment. Third, by performing kidney re-biopsies, Cao and colleagues demonstrated that immune-complex mediated immune responses are dampened at the site of inflammation after ASCT, suggesting that a complete disruption of chronic autoimmune responses is essential to restore organ functions in lupus. Finally, the combined TRM of 2% across both studies (1/46 patients) supports an improvement compared to previous single centre data from the Northwestern University study (TRM 4%) and the first multicentre EBMT analysis (TRM 12%). This may be the result of better patient selection, centre effect, transplantation early in the disease course (as performed in the study by Cao *et al*.) and improved pre-emptive anti-infectious and other supportive therapies. Nevertheless, some caution is still required as both studies have methodological limitations, such as lack of defined inclusion criteria, use of heterogeneous regimens for mobilisation and conditioning as well as post-transplant therapies, missing data regarding organ-specific disease activities indices and incomplete datasets regarding serologic responses during follow-up.

Early in its evolution, ASCT has been considered as salvage therapy in severely affected patients, applied at the very end of the line of immunosuppressive and/or experimental biologic therapies, such as rituximab. In view of the remarkable outcomes provided by both studies in this issue of CER, the question may be raised whether ASCT could not applied at earlier time-points or even replace state-of-the-art immunosuppression in the future. Current treat-to-target (T2T) recommendations in lupus propose to aim for remission or when remission cannot be achieved, the lowest possible disease activity (13). However, in real life, agents readily available to achieve this goal are limited. For example, in LN patients failing either CY or MMF treatment, recommendations from the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) suggest switching from CY to MMF (or *vice versa*) or the addition of rituximab (either as add-on treatment or as monotherapy), despite limited evidence from controlled studies (14).

Compared to continued insufficient or failed chronic immunosuppression, early use of ASCT has the potential to protect against organ-failure and toxicity-related morbidity (such as cardiovascular events, infections and secondary malignancy), improve quality of life and reduce socioeconomic costs. But is the time right for such paradigm shift in lupus treatment? Several issues have to be considered before ASCT is accepted into routine clinical practice. First, the encouraging results of phase I/II trials have to be weighed against the increased risk of short-term mortality

associated with ASCT. Although TRM and PFS have gradually improved over the past 20 years due to greater centre experience, better patient selection and supportive care, the risk/benefit ratio can only be estimated in RCTs. The only controlled study for ASCT in lupus is currently performed in a multicentre investigator-initiated trial in Germany (NCT 00750971), comparing ASCT with best available standard of care (SOC), including rituximab. Second, there is still no consensus on appropriate candidates for ASCT. Ideally, relatively young patients with increased risk of lupus-related mortality and potentially reversible organ damage should be selected. However, despite the current evolution of precision medicine, reliable prognostic factors for the early identification of poor-prognosis patients are still lacking. Finally, the optimal timepoint for transplantation in the treatment course needs to be defined. Expert consensus recommendations suggest that candidates for ASCT would reasonably include those with sustained or relapsed active BILAG category A remaining steroid dependent after at least 6 months of the best standard therapy, using MMF or CY with or without anti-CD20 and other MoAbs, with documented evidence of visceral involvement or refractory SLE (15, 16).

The future of ASCT for lupus and other severe autoimmune diseases highly depends on the "dynamics" of available alternative treatment options, including novel biologic targeted therapies. However, these therapeutic approaches do not eradicate the autoreactive immunological memory as a driver of chronic inflammation. The unique advantage of ASCT is the almost complete ablation of the autoreactive memory as a precondition for the resetting of the immune system becoming tolerant to self that can provide sustained remissions in the absence of chronic immunotherapy potentially providing cure (11, 17, 18). Overall, the ultimate benefit of ASCT will only be determined after decades of follow-up when the upfront increase in mortality can be balanced against any long-term benefit in mortality and co-morbidities. Moving forward, further efforts are needed to drive this approach into routine clinical care. Where possible, patients should be treated in prospective clinical trials in experienced transplant centres with close interdisciplinary working between rheumatology and haematology. Conditioning regimens, graft selection and maintenance therapies should be optimised. In addition, comprehensive data reporting, harmonisation and exploitation of existing biobanking infrastructure (19), education at individual centre and network level, and health economic evaluations along with evidence-based recommendations coordinated by national and European societies will all help to determine the future place of ASCT in the treatment algorithm for SLE.

References

1. TSOKOS GC: Systemic lupus erythematosus. *N Engl J Med* 2011; 365: 2110-21.
2. WAHREN-HERLENIUS M, DORNER T: Immunopathogenic mechanisms of systemic autoimmune disease. *Lancet* 2013; 382: 819-31.
3. PONS-ESTEL GJ, ALARCON GS, SCOFIELD L, REINLIB L, COOPER GS: Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum* 2010; 39: 257-68.
4. BORCHERS AT, NAGUWA SM, SHOENFELD Y, GERSHWIN ME: The geoepidemiology of systemic lupus erythematosus. *Autoimmun Rev* 2010; 9: A277-87.
5. MOK CC: Biological and targeted therapies of systemic lupus erythematosus: evidence and the state of the art. *Expert Rev Clin Immunol* 2017 May: 1-16 [Epub ahead of print].
6. MARMONT AM, VAN LINT MT, GUALANDI F, BACIGALUPO A: Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. *Lupus* 1997; 6: 545-8.
7. JAYNE D, PASSWEG J, MARMONT A *et al*.: Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* 2004; 13: 168-76.
8. BURT RK, TRAYNOR A, STATKUTE L *et al*.: Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* 2006; 295: 527-35.
9. ALEXANDER T, ARNOLD R, HIEPE F: [Autologous hematopoietic stem cell transplantation in systemic lupus erythematosus]. *Z Rheumatol* 2016; 75: 770-9.
10. ALEXANDER T, ARNOLD R, HIEPE F, RADBRUCH A: Resetting the immune system with immunoablation and autologous haematopoietic stem cell transplantation in autoimmune diseases. *Clin Exp Rheumatol* 2016; 34: 53-7.
11. ALEXANDER T, THIEL A, ROSEN O *et al*.: Depletion of autoreactive immunologic memory followed by autologous hematopoietic stem cell transplantation in patients with refractory SLE induces long-term remission through de novo generation of a juvenile and tolerant immune system. *Blood* 2009; 113: 214-23.
12. ALEXANDER T, SATTLER A, TEMPLIN L *et al*.: 2013. Foxp3+ Helios+ regulatory T cells are expanded in active systemic lupus erythematosus. *Ann Rheum Dis* 2013; 72: 1549-58.
13. VAN VOLLENHOVEN RF, MOSCA M, BERTSIAS G *et al*.: Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014; 73: 958-67.
14. BERTSIAS GK, TEKTONIDOU M, AMOURA Z *et al*.: Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR / ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; 71: 1771-82.
15. ILLEI GG, CERVERA R, BURT RK *et al*.: Current state and future directions of autologous hematopoietic stem cell transplantation in systemic lupus erythematosus. *Ann Rheum Dis* 2011; 70: 2071-4.
16. SNOWDEN JA, SACCARDI R, ALLEZ M *et al*.: Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012; 47: 770-90.
17. HIEPE F, DORNER T, HAUSER AE, HOYER BF, MEI H, RADBRUCH A: Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. *Nat Rev Rheumatol* 2011; 7: 170-8.
18. SWART JF, DELEMARRE EM, VAN WIJK F *et al*.: Haematopoietic stem cell transplantation for autoimmune diseases. *Nat Rev Rheumatol* 2017; 13: 244-56.
19. ALEXANDER T, BONDANZA A, MURARO P *et al*.: SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking. *Bone Marrow Transplant* 2015; 50: 173-80.