IDENTIFICATION OF CELLULAR MARKERS PREDICTING RELAPSES AFTER IMMUNOABLATION AND AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION (ASCT) FOR REFRACTORY SYSTEMIC LUPUS ERYTHEMATOSUS

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Background We recently showed that clinical remissions in systemic lupus erythematosus (SLE) after immunoablation and autologous haematopoietic stem cell transplantation (ASCT) are associated with depletion of the autoreactive immunological memory and the de novo generation of a juvenile and tolerant immune system. Nevertheless, relapses of SLE may occur.

Purpose We further followed the clinical, serological and immunological data of our patients to identify predictive cellular markers for the development of lupus flares after ASCT.

Methods Since 1998 we have longitudinally analysed the immune reconstitution in seven patients with SLE who underwent CD34-ASCT after immunoablation with CYC and ATG. Autoantibody titres were evaluated with indirect immunofluorescence for antinuclear antibodies (ANA) and ELISA, and peripheral T and B lymphocyte subsets were immunophenotyped using multicolour flow cytometry including assessment of TCR Vβ-repertoire on CD4 T cells and Siglec-1 (CD169) on monocytes as surrogate for type I interferon signature.

Results Clinical remissions (SLEDAI ≤ 3) could initially be achieved in all patients associated with the disappearance of anti-dsDNA antibodies, recurrence of thymic-derived CD31+CD45RA+ CD4+ T cells and FoxP3+ Tregs, with a polyclonal TCR Vβ-repertoire, and normalisation of B cell disturbances such as expansion of circulating CD27++ CD20- plasma blasts. While stable long-term clinical remissions could be achieved in patients for up to 11 years after ASCT, three patients suffered a relapse of SLE: p#3 (+18 months), p#4 (+30 months) and p#7 (+36 months). These patients showed recurrence of anti-dsDNA antibodies and ANA (in part with different specificities compared to baseline). Flow cytometric analyses revealed an expansion of memory B cells and circulating plasma blasts and increased coexpression of Siglec-1 on monocytes preceding the flare, and a predominance of CD45RO+ memory T cells with a restricted CD4+ TCR-Vβ repertoire (distinct from pretransplant) and increasing levels of FoxP3+ Tregs that lack surface expression of CD25.

Conclusion Patients with SLE who are at high risk of developing lupus flares after immunoablation and ASCT may be identified by plasma blast expansion, increasing expression levels of Siglec-1 (CD169) on monocytes as a surrogate marker for interferon signature and expansion of CD25- FoxP3+ Tregs. The development of ANA with new specificities and a different oligoclonal TCR Vβ-repertoire compared with pretransplant may illustrate a de novo development of SLE rather than disease reactivation.