Methods: Fifteen severe, refractory SLE patients were included and followed for 2 years. Patients received RTX at week 0 and 2 and BLM at week 4, 6, 8 and then 4-weeks until week 104. Clinical response was assessed by achievement of low-level of disease activity (LLDAS). By using specific antibody assays and high sensi- tivity flowcytometry (HS-FACS), we longitudinally followed, respectively, levels of SLE-specific ANAs and B-cell subsets.

Results: Ten patients (67%) showed a good clinical response after 24 weeks, referred to as ‘responders’. Two of these patients (13%) switched treatment after 24 weeks due to a pregnancy wish and 8 patients (53%) continued study treat- ment throughout the complete 2 years of follow-up. Five patients (33%) discontin- ued treatment due to persistent LN (n=2), major flare (n=2) or relapsing minor flare (n=1), together referred to as ‘non-responders’. Responders achieved LLDAS at a medium of 24 weeks [range 12-36] and remained in LLDAS for 76 weeks [56-92] out of 104 weeks of follow-up. In 7 patients with active LN, 6 attained a complete renal response. In responders, ANAs showed significant and specific reduction throughout 2 years with achievement of seronegative anti-dsDNA immunofluores- cence in 6 out of 6 anti-dsDNA positive patients at baseline while total IgG, anti- titerus and anti-ribellus antibodies remained stable. By using HS-FACS, a median decrease of 97% [99;35] CD19+ B-cell depletion was achieved at 24 weeks. Long-term follow-up showed that B-cell repopulation was inhibited throughout 2 years with a persistent median decrease of 84% [92;22] compared to baseline. Further analysis of B-cell subsets revealed that in the responders, double negative (DN) B cells (CD27-CD4-2) reached maximum depletion at 4 weeks (median 1.091*10^6 cells/liter [range 0.23*10^6-4.31*10^6], which lasted up to week 72 with a median of 1.261*10^6 cells/liter [0.79*10^6-4.11*10^6] at week 72, similar to values at nadir. This was in contrast to non-responders, where maximum deple- tion of DN B-cells was reached at 12 weeks (0.48*10^6 [0.17*10^6-5.86*10^6], after which these cells increased to 2.29*10^6 [0.49*10^6-4.39*10^6] at 24 weeks.

Conclusion: Over 2 years follow-up, RTX+BLM for severe, refractory SLE patients prevented complete B-cell repopulation with persistent and specific reduction of ANAs. Clinical response was observed in 67% of patients and treat- ment discontinuation due to high disease activity was associated with early repo- population of DN B-cells. These data warrant further studies on clinical and immunological benefits of combination treatment RTX+BLM.

REFERENCE:

Trial registration: ClinicalTrials.gov NCT022894848

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that reported the incidence of sustained amennorhoea (defined as at least 12 months of amenorrhoea) during i.v.CYC treatment in patients with ARD, and those that assessed sustained amenorrhoea in patients receiving GnRHa and i.v.CYC, compared to controls receiving i.v.CYC alone.

Results: 1099 articles were identified and their titles and abstracts screened, following which 81 papers were selected for full text review. 31 studies were then identified that addressed the risk of sustained amenorrhoea with i.v.CYC in n=1382 patients with ARD. The majority of these patients had systemic lupus erythematosus (1326 out of 1382 patients, 99.6%). The mean age was 24.9 (range 13-36.1) years. Sustained amenorrhoea occurred in 269 patients (19.5%, range 0-54% depending on age and cumulative cyclophosphamide dose). The rate of sustained amenorrhoea significantly positively correlated with increasing cumulative cyclophosphamide dose, and occurred in patients with a mean age ranging from 13-36.1 years at mean cumulative doses ranging from 1-20.1 g. Further 3 studies assessed ARD patients given i.v.CYC +/- GnRHa, including 56 patients (mean age range 23.9-25.6 years) receiving GnRHa and i.v.CYC, and 37 controls (mean age range 25-29.4 years) given i.v.CYC only. Sustained amenorrhoea occurred in 2/56 (3.6%) patients treated with GnRHa, compared to 15/37 (40.5%) of controls. The pooled odds ratio of sustained amenorrhoea with GnRHa and i.v.CYC compared to i.v.CYC alone was 0.0543 (95%CI 0.0115-0.2578, p=0.0002). The number needed to treat was 2.7 (95%CI 2.0-4.4) and the absolute risk reduction was 97.0% (95%CI 95.6-98.4%).

Conclusion: Although the risk of POI with i.v.CYC was associated with increasing age, it was observed across all age groups and from cumulative doses of 1g or more. GnRHa markedly reduced this risk in ARD, and therefore should be considered for concomitant use with i.v.CYC in all women of child-bearing age with ARD.

REFERENCES: