Medical or Research Professionals/Clinicians

Topic area: Clinical topics by disease

Topic: 14. Rheumatoid arthritis - other biologic treatment

EULAR16-4019

IMMUNE RECONSTITUTION 20 YEARS AFTER TREATMENT WITH ALEMTUZUMAB IN A RHEUMATOID ARTHRITIS COHORT: IMPLICATIONS FOR LYMPHOCYTE DEPLETING THERAPIES

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My abstract has been or will be presented at a scientific meeting during a 12 months period prior to EULAR 2016: No

Is the first author applying for a travel bursary and/or an award for undergraduate medical students?: No

Background: Alemtuzumab, an anti-CD52 monoclonal antibody, was administered (cumulative dose range 1-420mg) to a cohort of patients with severe RA between 1991-94[1]. We previously reported significant delays in immune reconstitution detectable 12 years after administration[2].

Objectives: To perform the 20 year follow-up of our unique cohort with regards to morbidity, mortality, lymphocyte reconstitution, circulating cytokines and response to vaccination.

Methods: Mortality and morbidity data (Mar 2006–Jan 2015) were collected from death certificates, case notes or interview. Alemtuzumab patients were age, sex and disease duration matched with RA controls. For both groups circulating lymphocyte subsets ($CD4^+$ and $CD8^+$ naïve, central memory and effector memory T cells; naïve, memory and $CD5^+$ B cells and $CD19^+CD24^{hi}CD38^{hi}$ Bregs; NK Cells and NK T Cells) were quantified by multicolour flow cytometry. Serum IL-15 and IFN-γ were measured by ELISA (MSD) and antigenic responses by generation of protective titres (as conventionally defined) following vaccination with influenza, Pneumovax II and combined diphtheria/tetanus/poliovirus vaccines

Results: 16 patients were alive at the time of this study, 9 agreed to interview, vaccines and peripheral blood analysis, a further 4 had case note review only and 3 were uncontactable. 8 matched RA controls were also recruited. Since our last review 10 patients had died with causes of death consistent with a population with long-standing RA. There was no suggestion of compromised immune function with no increase in new autoimmune conditions or severe infections in living patients. Alemtuzumab patients continued to demonstrate abnormalities in their lymphocyte compartment with persistent significant reductions in $CD4^+$ and $CD8^+$ central memory cells, $CD5^+$ B Cells and a new finding of significantly reduced naïve B cells when compared with previous analysis[2]. For the first time we examined $CD19^+CD24^{hi}CD38^{hi}$ Bregs which were also significantly reduced. Nonetheless vaccine responses were comparable between alemtuzumab recipients and controls. In addition, there were significantly higher IL-15 and IFN-γ levels in the serum of the alemtuzumab cohort. IL-15 levels inversely associated with $CD4^+$ total memory and central memory T cells.

Conclusions: In this unique patient cohort, after 20 years the effects of alemtuzumab treatment persist. Despite lymphocyte abnormalities, satisfactory vaccine responses are mounted and opportunistic infections remain absent. We hypothesise the reduced T-cell compartments trigger IL-15 via homeostatic mechanisms which, as a bystander effect, may activate NK cells causing IFN-γ release. An activated NK compartment could explain the lack of opportunistic infections in patients with lymphocyte abnormalities for 20+ years.

As lymphodepleting therapies, including alemtuzumab, continue to be administered this work is important with regard to long term drug safety and stages of immune recovery.

References: [1] Isaacs JD et al. *Arthritis Rheum.*2001;44(9):1998-2008

[2]Anderson AE et al. *Rheumatology (Oxford).*2012;51(8):1397-406

Disclosure of Interest: None declared