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PLASMA CELL DEPLETION FOR SEVERE GRAVES' DISEASE: PRIMARY OUTCOME AND MECHANISTIC ANALYSIS OF A RANDOMISED CLINICAL TRIAL

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Objectives: Patients with severe Graves' disease are rarely cured by antithyroid drugs (ATD), even following prolonged administration. The directly aetiological TSH receptor stimulating antibodies (TRAbs) are secreted from terminally differentiated B-lymphocytes, known as plasma cells and plasmablasts that express cell-surface CD38. We aimed to investigate whether daratumumab, an anti-CD38 plasma cell depleting monoclonal antibody, could modify the natural history of severe Graves' hyperthyroidism.

Methods: We conducted a randomised trial of patients with severe Graves' hyperthyroidism. The first 15 patients were randomised to 4 different daratumumab doses (0.5mg/Kg, 1mg/Kg, 3mg/Kg and 9mg/Kg) or placebo administered by 2 intravenous infusions, 2 weeks apart. Following an interim dose-response analysis, a further 15 patients were randomised to higher doses of daratumumab (9mg/Kg and 16mg/Kg) or placebo. ATDs were continued throughout. The primary outcome was change in the TRAb concentration from baseline at 12 weeks, as a measure of disease modifying potential.

Results: 22 women and 8 men were recruited. Mean FT4 at diagnosis was 79pmol/L [range 32.3->100] and baseline mean TRAb was 73.3U/L [range 11-694]. Overall, there was no evidence of a significant dose-response (p=0.15) although there was an indication that TRAb at 12 weeks reduced more rapidly in participants allocated to higher doses of daratumumab (9mg/Kg and 16mg/Kg) than placebo (ATD only). Mean TRAb reduction was 48%, 75% and 60% in placebo, 9mg/Kg and 16mg/kg, respectively.
Combining the 9mg/kg and 16mg/kg doses, there was a significant drop in mean serum IgA (73%), IgM (56%) and IgG (44%), baseline to 12 weeks. There was a significantly lower reduction in IgG compared to TRAb. Flow cytometry of PBMC showed an initial fall in plasma cells (CD38+/IgD-) at 6 weeks with levels rising again from 12 weeks onwards. Whole blood plasma cell transcriptomic markers (BCMA and IgJ) demonstrated a similar pattern with a later 1.5-fold rebound increase between 6 and 12 weeks. Serum BAFF rose from baseline to 6 weeks, likely in response to plasma cell depletion and this may explain the rebound in BCMA and IgJ.
Adverse events included transient infusion-related reactions (n=21 patients) and one late episode of bacterial pneumonia.

Conclusions: We show for the first time that anti-CD38 therapy with daratumumab shows promise by reducing serum TRAb and therefore has potential to modify the natural history of severe Graves' hyperthyroidism. This study also demonstrates that anti-plasma cell therapies may preferentially target the antibody-secreting cells actively involved in the humoral autoimmune response.