Bruton's Tyrosine Kinase Inhibitor (BTKi) treatment interruption elevates humoral and SARS-CoV-2 specific B cell responses, but not SARS-CoV-2 specific T cell responses in people with Waldenstrom Macroglobulinemia

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Introduction: People with Waldenström Macroglobulinaemia (WM) are at risk of severe COVID-19. Our group previously reported Bruton's Tyrosine Kinase inhibitors (BTKi) in WM profoundly reduced response to COVID-19 vaccination-induced anti-Spike IgG (ASAb) and viral neutralization. Here we determine the effects of BTKi treatment interruption on antigen-specific B and T cells. We also investigate off-target effects of BTKi on the T cells, which are incompletely understood.

Methods: Our cohort (N=12) included 3 participants each belonging to 4 treatment groups; (i) self-initiated 2-3 week BTKi pause (ii) continuous BTKi (iii) treatment naïve (iv) chemotherapy. AsAb were measured using a cell-based assay, and live virus neutralisation against variants. We measured antigen-specific B and T cells using a flow cytometric tetramer and OX40 assay, respectively. We performed single-cell protein (Abseq) + transcriptomic profiling of $CD45^+$ cells (BD Rhapsody).

Results: 100% of people on BTKi interruption had a strong ASAb response compared to 44.4% on continuous BTKi. Most people on BTKi interruption neutralized early clade and delta variants. Compared to continuous therapy, BTKi interruption resulted in significant elevation of AsAb and RBD-specific memory B cells but no change in antigen-specific $CD8^+$ T cells. Transcriptomic analysis revealed any BTKi treatment was associated with an expansion of NK-like memory $CD8^+$ T cells.

Conclusion: B cell depletion disables response to vaccination. The oral administration of BTKi and current pandemic provided an opportunity to study the effect of treatment interruption on SARS-CoV-2 booster response. BTKi interruption resulted in the elevation of ASAb and RBD-specific memory B cells, but not T cells. Our exploratory findings cannot be used to advocate for widespread BTKi interruptions around COVID-19 vaccination, and such strategies need to be weighed against clinical risks. However, given the widespread use of B cell depletion therapies, further investigation into vaccine strategies for treated patients against existing and new pathogens is warranted.