BIOLOGICAL FEATURES of B-CLL AND RESIDUAL IMMUNITY AT TREATMENT INITIATION, DETERMINE IMMUNITY ON BTKI THERAPY

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INTRODUCTION

- Impaired immunity on continuous BTKi therapy is associated with substantial infection related morbidity/mortality and poor response to vaccination.
- Results from the UK IMPROVE RCT (ISRCTN14197181)[1] found a 3 week pause in BTKi at the time of vaccination did not improve humoral responses to vaccination.
- Instead, heterogeneity in participant humoral immunity was observed.
- An appreciation of the biological determinants of poor immunity during covalent BTKi therapy and an improved understanding of why such variability exists amongst patients is now needed

AIMS

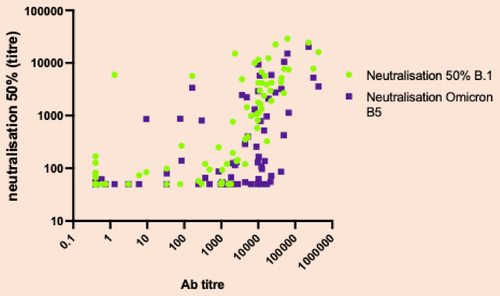
- To determine the biological features of CLL and humoral immunity that influence vaccine responsiveness during covalent BTKi therapy.

METHODS

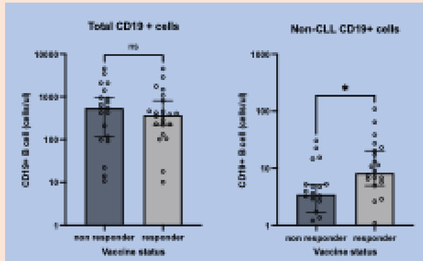
- B cell phenotype of non-CLL cells from vaccine responders and non-responders taken during the IMPROVE trial were analysed and compared using 10 colour flow cytometry panel.
- Calcium flux was assessed by ratio-metric dye and % calcium mobilisation during BTKi therapy in vaccine responders vs non-responders, following IgM stimulation.
- mRNA sequencing of magnetically sorted B cells from vaccine responders and non-responders were compared.
- Antigen specific B cells were identified by flow cytometry and phenotypical analysis undertaken in vaccine responders.
- Neutralisation of SARS-COV-2 virus was assessed for high affinity responses.
- Immunophenotyping of normal B cells was assessed using sequential samples (pre-treatment through to >1 year during therapy)
- Immunohistochemistry of pre-treatment bone marrow specimens were compared amongst vaccine responders vs. non-responders.

RESULTS

- Vaccine responsiveness was assessed in 99 patients with controlled CLL, after >1 year of BTKi therapy (mean age 70.5, SD 8.8)
- 32 participants (32%) demonstrated no SARS-CoV-2 Ab response despite a median of 5 (IQR 5-6) SARS-COV-2 vaccine doses.
- No difference in vaccine responsiveness was observed:
  - in first or subsequent therapy line,
  - Acalabrutinib or Ibrutinib therapy,
  - pausing or continuing BTKi for 3 weeks at the time of vaccination

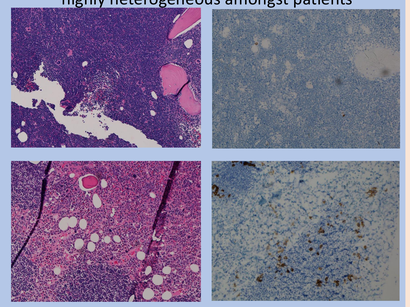


- Amongst antibody responders, neutralisation of live SARS-CoV-2 pseudovirus was observed[1,2].



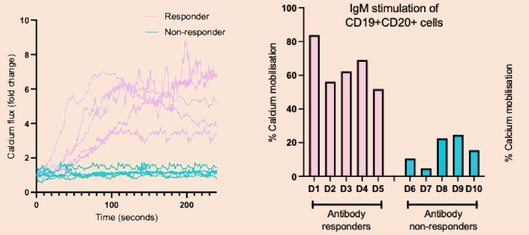
- The number of non-CLL B cells was significantly higher amongst those on BTKi who could generate an antibody response to vaccination compared to those who couldn't.

Pre-treatment residual normal B cell immunity is highly heterogeneous amongst patients

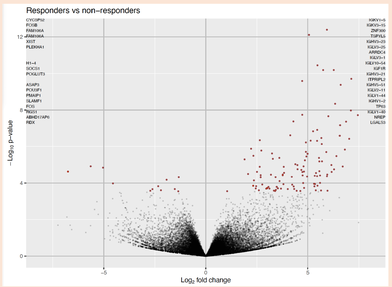


- Serial sample analysis by flow cytometry showed a lack of non-CLL B cells pre-treatment persists > 1 year after BTKi is commenced.

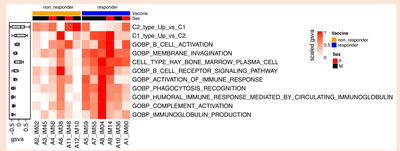
- Calcium flux was observed following IgM stimulation of CD19+/CD20+ B cells during continuous BTKi therapy



mRNA sequencing of enriched B cells from vaccine responders Vs non-responders



GSEA analysis identifies C2 transcription pathway in non-responders vs responders (p adj: 3.3e-35)[3]



Additionally, gene pathways important for healthy immune responses were evident amongst vaccine responders compared to non-responders taking continuous BTKi.

CONCLUSION

- Current IWCLL criteria for treatment initiation leads to heterogeneity in patient immunity at the time of treatment initiation.
- Heavy marrow infiltration is associated with depletion of normal B cells and this depletion persists once taking continuous BTKi.
- The poor prognostic C2 transcriptional profile of CLL is associated with poor immunity whilst taking BTKi.
- Amongst participants taking a BTKi who respond to vaccine, normal B cells are evident and calcium flux in response to IgM stimulation is evident.
- In vaccine responders taking BTKi, antibody responses are highly functional.

REFERENCES

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3. Ferreira P G et al. **Genome Research**. 2014; 24(2):212-226

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