Cross-reactivity of anti-drug antibodies against anti-CD20 therapeutic monoclonal antibodies with other anti-CD20 antibodies

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CD20 targeting therapeutic antibodies

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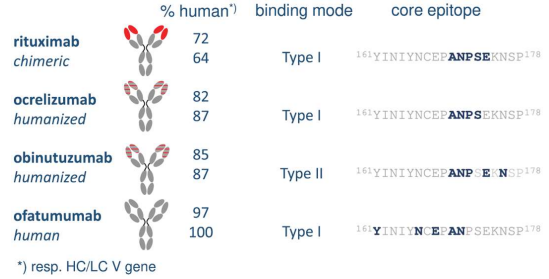
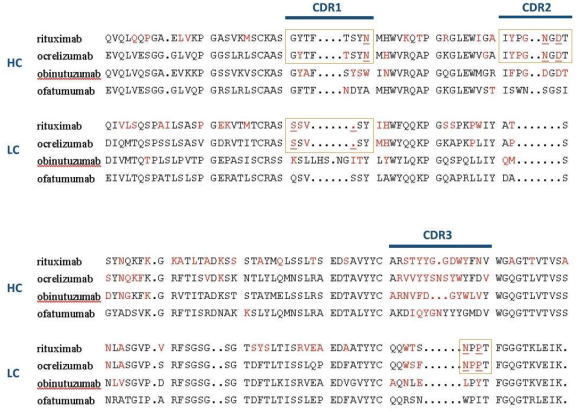
- B-cell depletion by ADCC and/or CDC
- Effective treatment for leukaemia and autoimmune diseases
- Anti-drug antibodies → lack of response and adverse events

- Rituximab, first in class since 1997(US)/1998(EU)
- Succeeded by ofatumumab, obinutuzumab and ocrelizumab
- Different epitope and binding mode and main B-cell depleting mechanism

- Anti-drug antibodies (ADAs) to target binding site might cross-react with alternative anti-CD20 treatments
- Cross-reactive ADAs could affect effectivity and safety of alternative drugs



Overview of anti-CD20 Abs used in this study.



Sequence alignment of H and L chain variable domain. Red residues are mismatches to closest matching germline V and J sequences. Boxes indicate sequence homology between rituximab and ocrelizumab within the CDRs.

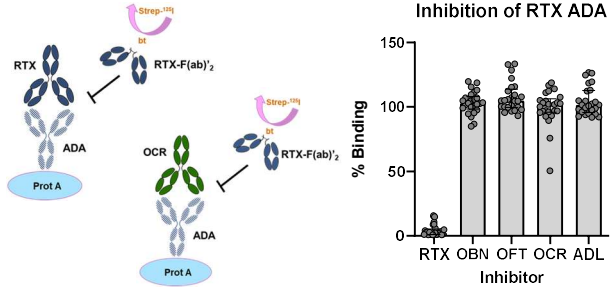


Figure 1: Cross-reactivity of ADAs with other drugs was tested in the depicted assay set-up.

Real-world samples from patients developing ADA to rituximab were tested in the rituximab ADA assay in the presence of different inhibitors (the three other anti-CD20 Abs and the anti-TNF drug adalimumab as negative control).

In 2/25 patient samples treated with rituximab ADA response could be blocked by addition of ocrelizumab. No cross-reactivity was seen for obinutuzumab ofatumumab or anti-TNF drug adalimumab (negative control).

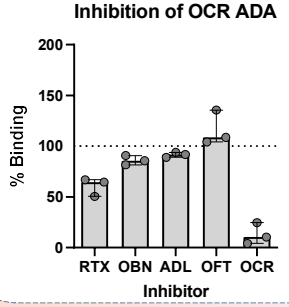


Figure 4: Detection of ocrelizumab ADA is inhibited by the addition of anti-CD20 rituximab and anti-CD20 ocrelizumab, but not with anti-CD20 Abs obinutuzumab and ofatumumab or negative control anti-TNF adalimumab.

Results

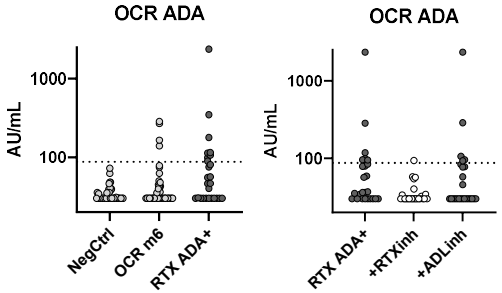


Figure 2: A portion of ocrelizumab and ADA+ rituximab treated patients is positive in the ocrelizumab ADA assay (left). Specificity is shown by block of signal after addition of rituximab and not with anti-TNF adalimumab (right).

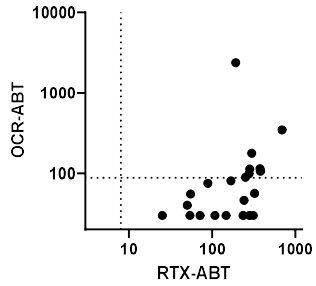


Figure 3: Correlation between rituximab ADA level and signal intensity in the ocrelizumab ADA assay for samples from rituximab treated patients.

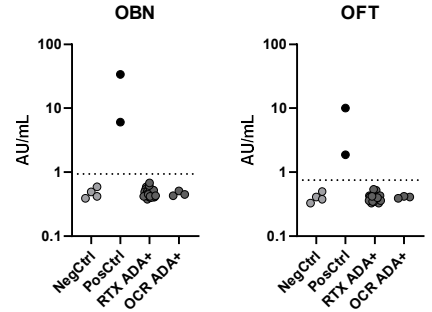


Figure 8: ADA in patient samples raised against either rituximab or ocrelizumab do not give a signal in anti-obinutuzumab or anti-ofatumumab assay. Positive control is anti-κ antibody. No patient samples containing ADA against Obinutuzumab or ofatumumab were available.

RTX: rituximab (anti-CD20) OBN: obinutuzumab (anti-CD20) ADL: adalimumab (anti-TNF)
OCR: ocrelizumab (anti-CD20) OFT: ofatumumab (anti-CD20)

Conclusions

✓ADAs raised against rituximab are cross-reactive with ocrelizumab and vice versa
✓There is no cross-reactivity observed for the other two CD20 targeting therapeutic Abs
✓Sequence alignment shows high homology of rituximab and ocrelizumab in CDRs
✓Careful monitoring may be useful when switching between rituximab and ocrelizumab