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Comparative pharmacology of ofatumumab versus ocrelizumab in humanised-CD20 transgenic mice

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Introduction: Therapeutic strategies aiming at depleting CD20$^+$ B cells are effective in treating MS. Pilot work suggested improved lymph node (LN)-targeting for subcutaneous ofatumumab (OMB-sc) *vs* intravenous ocrelizumab (OCR-iv) and further differentiation is expected from a head-to-head comparison.
Objective: To benchmark the potency of OMB-sc and OCR-iv at depleting B cells expressing the human-CD20 molecule (*hu*CD20) in transgenic mice.
Design/Methods: *Hu*CD20 mice (C57BL/6-Ms4a1tm2(hCD20)Smoc) treated once with OMB-sc or OCR-iv at various doses were monitored for drug levels (IgG-binding ELISA assays) and B-cell counts (flow cytometry) in blood and lymphoid organs (spleen, inguinal LN, bone marrow).
Results: Both OMB-sc and OCR-iv achieved dose-proportional drug levels with B-cell depletion in all compartments. In blood, at 3 days post-treatment, serum levels needed for 50%/90% efficacy (EC50/EC90) were ~0.01/0.3 mg/mL for OMB-sc *vs* 0.2/5.0 mg/mL for OCR-iv, indicating a 20-fold higher potency for OMB-sc at depleting circulating B cells. At human-equivalent dose (*hu*D), OMB-sc (6 mg/mouse) reached its EC50 whereas OCR-iv (200 mg/mouse) was supramaximal (~40-fold above its EC90). In spleen and LN, drug level ratios *vs* serum were 5-20 and ≤1 for OMB-sc and OCR-iv, respectively, confirming improved lymphoid organ targeting for OMB-sc. With similar EC50s around 0.2 mg/mL, both OMB-sc and OCR-iv treatments appeared equipotent at depleting non-circulating B cells. Further analysis revealed that marginal zone (MZ) and follicular (FO) B cells in secondary lymphoid organs were markedly depleted by OCR-iv but spared by OMB-sc, both at *hu*D. In BM, at*hu*D, OMB-sc achieved drug levels 10-fold below EC50 whereas OCR-iv reached its EC90, suggesting a lower impact for OMB-sc on BM-resident CD20 expressing cells.
Conclusions: OMB-sc demonstrated better efficiency vs OCR-iv at targeting lymphoid organs and showed a 20-fold higher depleting potency on circulating B cells and equipotency on non-circulating B cells. Furthermore, a sparing effect on MZ and FO B cells, key for the development of germinal center reactions and for immune surveillance, as well as on bone marrow, important for B-cell repletion and preservation of immune responses, was observed with OMB-sc. If translating to humans, OMB-sc offers a convenient s.c. pharmacological-dose medication combining high efficacy and potential lower risks for long term safety *vs* supra-maximal in vivo dosing for OCR-iv.
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