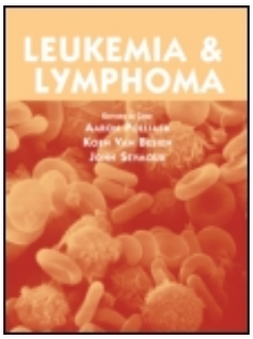

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COMMENTARY

New anti-CD20 monoclonal antibodies: which is the best?

Anne-Laure Gagez & Guillaume Cartron

Hematology Department, CHRU Montpellier, UMR CNRS 5235, Montpellier, France and LabEx MAbImprove, Tours, France

Rituximab (MabThera®, Rituxan®), a chimeric immunoglobulin G1 (IgG1) monoclonal antibody (Mab) targeting CD20, has dramatically improved the outcome of most B-cell lymphoproliferative disorders. Regarding the clinical efficacy of this Mab, little is known however on how rituximab works *in vivo*, and it is speculated that rituximab induces both Fv-mediated (apoptosis) and Fc-mediated effects (antibody-dependent cell-mediated cytotoxicity [ADCC], complement-dependent cytotoxicity [CDC] and phagocytosis). A pioneering study [1] demonstrated that FcγRIIIa-158V/F polymorphism correlated with clinical response, patients with homozygous FcγRIIIa-158V showing a better response to rituximab in those with untreated follicular lymphoma. Similar results have been obtained with rituximab in other clinical indications [2,3], but also with other humanized IgG1 antibodies such as trastuzumab [4] and cetuximab [5]. These studies underline the role of ADCC in the mechanism of action of these antibodies, but have also opened up a new area of development of therapeutic Mabs having increased affinity for FcγRIIIa. This can be obtained either by mutation of amino acid residues of the Fc portion involved in Fc–FcγRIIIa interaction [6] (Fc-mutated Mab) or by modification of the oligosaccharide located between the two Fc arms [7,8]. Thus, it has been demonstrated that a Mab with oligosaccharide containing a low fucose content (low-fucose Mab) or Fc-mutated Mab has an increased affinity for FcγRIIIa, translating to higher ADCC in lymphoma cell lines. Very recently, a multicenter phase III trial demonstrated clearly that the first low-fucose anti-CD20 Mab, obinutuzumab, significantly increased the response rate (RR), molecular response and progression-free survival compared to rituximab when associated with chlorambucil for unfit patients with chronic lymphocytic leukemia [9]. These results validate the clinical interest in Mabs with increased ADCC. However, obinutuzumab is also characterized by increased direct cytotoxic death and a lack of CDC compared to rituximab, *in vitro*. It is therefore difficult to discern the role of each mechanism (ADCC or direct cytotoxic death) in the clinical advantage observed in clinical trials.

Ganjoo *et al*. report [10] a phase I/II study of ocaratuzumab (AME-133v) in patients with low affinity FcγRIIIa with previously treated follicular lymphoma. Ocaratuzumab is the first Fc-mutant Mab to be tested in a clinical trial. It is characterized by two amino acid changes introduced into its Fc portion [11]. These amino acid changes led to increased ADCC *in vitro* (six-fold more potent that rituximab). They also selected an anti-CD20 Mab clone that had increased CD20 binding affinity (13–20-fold increase in binding affinity) compared to rituximab. No data are available on the consequences of this increased affinity, especially in terms of CDC. In the clinical trial reported by Ganjoo *et al*. [10], a RR of 32% was observed, which included a 10% complete remission (CR) rate. Comparison of such results with rituximab data is difficult, but rituximab in FcγRIIIa-158F carriers led to a 67% RR in first line for low tumor burden follicular lymphoma [1] and 59% RR in relapsed indolent lymphoma [12]. Most of the patients treated in this phase I/II study were previously treated with rituximab, and the RR observed with ocaratuzumab was reasonably similar to that observed following retreatment with rituximab, with 40% RR including 11% CR, whatever the FcγRIIIa genotype [13].

The choice of patient population included in this trial has raised some questions, because all patients with favorable FcγRIIIa genotype (i.e. homozygous FcγRIIIa-158V) did not obtain a CR after rituximab therapy [1], and the increased affinity for FcγRIIIa observed with mutated-Fc Mab and low-fucose Mab was observed with the two receptor allotypes (F and V) [8]. Thus, all patients, whatever their genotype, would benefit from this new Mab. These clinical results could, however, lead to clinical arguments in discerning the best strategy for Fc engineering (Fc-mutated versus low-fucose Mab) in agreement with *in vitro* studies demonstrating that whatever receptor allotype, low-fucose Mab showed better affinity for FcγRIIIa and ADCC than mutated Mab [8]. The clinical data appear to justify the *in vitro* data.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

Correspondence: Guillaume Cartron, Hematology Department, CHRU Montpellier, UMR CNRS 5235, Montpellier, France. E-mail: g-cartron@chu-montpellier.fr

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