Scientific Significance of Clinically Insignificant FcγRIIIa-V158F Polymorphism

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Running title: Significance of FcγRIIIa-V158F Polymorphism
Summary

Kenkre and colleagues report the absence of correlation between FcγRIIIa-V158F polymorphism and rituximab response in follicular lymphoma patients, a result which is in contrast with prior studies. This discrepancy recalls that many other factors (from the host and from the tumor) may influence rituximab’s efficacy in vivo.
In this issue of Clinical Cancer Research, the paper of Kenkre et al (1) investigated the influence of FcγRIIIa-V158F and FcγRIIa-H131R polymorphisms to predict response to rituximab.

FCGR3A polymorphism’s story began in 1997, when two different teams described for the first time a polymorphism located at amino acid residue 158 of FcγRIIIa leading to a substitution of a phenylalanine (F) with valine (V) that bound more efficiently to human IgG1 (2, 3). Concurrently, rituximab (MabThera®), a chimeric IgG1 directed against CD20, was approved in the treatment of indolent lymphoma and emerged as a paradigm changing therapy for CD20 expressing lymphomas and lymphoproliferative disorders. At this time, little was known on how rituximab works in vivo and it was speculated that rituximab induces both Fv- (apoptosis) and Fc-mediated effects (ADCC, CDC and ADPC; see Figure 1). Because of rituximab shares similar Fc portion than human IgG1 and, monocytes and NK cells, the main actors of ADCC, express FcγRIIIa, we hypothesised and demonstrated that FcγRIIIa V/V allotype was associated with better response and/or outcome to rituximab in patients with untreated/relapsed follicular lymphoma (4, 5). Similar results have been reproduced with rituximab in other clinical indications and also with other humanized IgG1 antibody such as trastuzumab (6) and cetuximab (7). All these works underlined the role of ADCC in the mechanism of action of these antibodies and also opened a new area for the optimization of therapeutic monoclonal antibodies via an increased affinity for FcγRIIIa either by mutation of amino-acid residues of Fc portion involved in Fc-FcγRIIIa interaction or by modification of the oligosaccharide located between the two Fc arms. Two of these glycoengineered mAbs are currently in clinical development (ublituximab, TG Therapeutics and obinutuzumab, Roche Genentech). Recently, a multicentric phase III trial, demonstrated that obinutuzumab significantly increased response rate, molecular response and progression-free survival compared to rituximab when associated with chlorambucil for unfit CLL patients (8). Those results would validate the clinical interest of mAbs with increased ADCC. However, the causal relationship between the optimized mechanism of action and clinical efficacy is not a straight line. Curves include that FcyRIIIa-V158F polymorphism has not been shown to influence response to rituximab in CLL patients, and secondly, obinutuzumab’s mechanism, as determined in vitro, is unique relative to rituximab with increased direct cytotoxic death and a lack of CDC. It is therefore...
difficult to discern the role of each mechanism (ADCC or direct cytotoxic death) in the observed clinical efficacy, which may also be questioned if the improved response rates translate to clinical benefit, as concluded in the recently reported, final results of the phase II GAUSS study (9).

In this context, Kenkre et al investigated the influence of FcerIIa-V158F and FcerIIa-H131R polymorphisms to predict response to rituximab. In our opinion, the response is simply none of clinical import. The predictive value of such tests is not sufficiently strong to avoid rituximab therapy for those patients exhibiting unfavourable genotype. For example, in the seminal paper, 67% of F-carriers patients experience response to rituximab (4). Building upon prior critical evaluation, we argue that rituximab remains a viable option for this patient subset as well (4).

None of studies cited by authors nor their own study have been designed to respond to the question of the interest of FCGR3A/FCGR2A testing. The majority are retrospective with the limitations of such. The fact that they did not observe correlation in their study does not signify that other studies where a correlation was found were false, regardless of the size of population. Authors demonstrated that in the context of their study no association was found. Thus, we have to understand why this could be possible.

The distribution of different genotypes has been reported to be different according to ethnicity. For example in the study of Kim et al. (10), demonstrating a correlation between FcerIIa-V158F polymorphism and response to R-CHOP, the frequency of VV patients was 47%, compared to 15% in Caucasian population. Such distribution could contribute to favour patient groups exhibiting a better response to rituximab leading to statistical difference in some studies which will be not seen with lower allotype frequency.
Affinity of Fc portion of IgG1 to FcγRIIIa is not the only factor influencing ADCC in vitro and thus probably in vivo. All in vitro ADCC tests were performed with a fixed effector/target ratio which does not reflect in vivo reality. In addition, analysis of concentration-effect relationship of rituximab dependent NK cell-mediated cytotoxicity showed that the EC50 obtained with NK cells from VV donors was 4.2 times lower than that obtained with NK cells from FF donors, whereas E_max and E_0 were not different (11). These data suggest that all conditions allowing to obtain lower rituximab concentration would favor VV allotype whereas saturating conditions reduced the potential advantage of F-carrier patients. We demonstrated that tumor burden (i.e E/T ratio) influenced response to rituximab mainly by influencing rituximab concentration (12). In addition, gender could potentially influence rituximab pharmacokinetics and then affect ADCC. KIR genotypes or different concentrations of KIR ligands could impart different thresholds of activation to the NK cell repertoire and thereby influence ADCC. Even chemotherapy is postulated to alter the effector cells involved in ADCC. Thus FcγRIIIa-V158F polymorphism, tumor burden, immune cells population, rituximab pharmacokinetics, KIR/KIR ligands status and the use of cytotoxic therapy could influence in vivo ADCC. Of course each of these factors could be different according to the patient but also inside each patient according to tumor microenvironment.

The role of FcγRIIa-H131R polymorphism in rituximab response has been suggested first in R/R follicular lymphoma [Weng et al]. However, a statistical analysis demonstrated evidence for a linkage disequilibrium in white patient between FcγRIIIa-V158F and FcγRIIa-H131R polymorphisms explaining contradictory clinical results (13).

In vitro studies clearly demonstrated that rituximab is also able to induce ADPC, CDC and direct apoptosis. All these mechanisms could be influenced by different factors depending on tumor cells, host- or antibody-related factors. For example, CD20 mutation/epitope can influence binding
or translocation to lipid raft which could be potentially affect lipid-raft-dependant activity of rituximab. Apoptosis can be modulated resulting in \textit{in vitro} resistance to rituximab.

Finally, clinical activity of rituximab is related to different and complex mechanisms of action. ADCC remains accepted as one of the mechanisms of action occurring certainly in human, and is influenced by inter-individual characteristics which vary according to a patient’s tumor and the surrounding microenvironment. This is not of trivial significance, since from these results different companies decided to develop new generations of anti-CD20 antibodies. The clinical interest of these new mAbs, with the limitation already exposed, should confirm or debunk our hypotheses. Pending such results, patients eligible for rituximab therapy should receive this antibody regardless of FcγRIIIa-V158F genotype.

References


Figure 1. Mechanisms of rituximab’s anti-lymphoma activity.

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity.
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