

Steven P. Treon MD, MA, PhD  
 Dana Farber Cancer Institute  
 Harvard Medical School, Boston MA

*Clinical Lymphoma, Myeloma & Leukemia*,  
 Vol. 10, No. 5, ???-???, 2010  
 DOI: 10.3816/CLML.2010.n.???

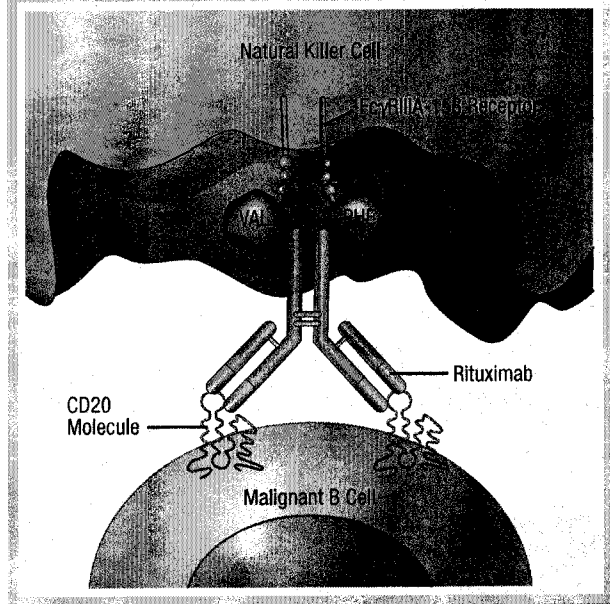
## *Fcγ Receptor Predictive Genomic Testing and the Treatment of Indolent Non-Hodgkin Lymphoma*

In this month's edition of *Clinical Lymphoma, Myeloma & Leukemia*, Zhuang et al provide an insightful review on the affect that polymorphic variants in Fcγ receptors (FcγRs) play in predicting response outcome in patients with non-Hodgkin lymphoma (NHL) who receive rituximab therapy.<sup>1</sup> The paper nicely outlines the potential role and limitations of predictive genomics involving FcγR polymorphisms (Figure 1). Since the report by Cartron et al in 2002 showing that polymorphisms in FcγRIIIA-158 were associated with response to rituximab in patients with follicular NHL, a number of interesting queries have arisen on just how polymorphic FcγR testing could be used in the real-world practice of hematologists and oncologists.<sup>2</sup> These queries have included:

- 1) In what B-cell malignancies do FcγRs polymorphisms influence rituximab response and progression-free survival (PFS)?
- 2) Which FcγR polymorphisms are important?
- 3) Which FcγR polymorphic variants predict response?
- 4) What role can FcγR predictive testing play in determining rituximab-based therapy?

Among the B-cell malignancies, supportive data demonstrating a role for FcγR polymorphic test in predicting rituximab response has so far been established only for the indolent NHL diseases, including follicular NHL and Waldenström macroglobulinemia (WM).<sup>2-5</sup> Why this is not the case for chronic lymphocytic leukemia (CLL) or aggressive NHLs is unclear, but other factors influencing rituximab response could be contributory. As pointed out by Zhuang et al, among indolent NHL patients, FcγR polymorphisms predict for rituximab monotherapy response and/or PFS, but their affect in predicting outcome with combination rituximab therapy has been variable.<sup>1</sup> Adding to the debate, a large Southwest Oncology Group (SWOG) study that randomized patients to either CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) or CHOP plus rituximab (CHOP-R) showed that polymorphisms in FcγRIIIA were highly predictive of PFS among patients receiving CHOP-R but not CHOP.<sup>6</sup> Hunter et al similarly showed that depth of response and long-term disease control were dependent on FcγRIIIA polymorphisms in patients with WM who received chemoimmunotherapy with rituximab.<sup>7</sup> The potential affect for polymorphisms in FcγR in determining the outcome of maintenance rituximab therapy was recently shown by Pierz et al,

Figure 1 ??????



The FcγRIIIA receptor displays a polymorphism at amino acid position 158 (FcγRIIIA-158) that can result in expression of valine (VAL) or phenylalanine (PHE) and differentially affect binding of rituximab through interaction with its Fc domain.

who examined the outcome of patients with follicular NHL who received induction therapy with rituximab and then were randomized to either observation or maintenance rituximab.<sup>8</sup> These studies showed that patients who expressed FcγRIIIA-158-V/V (valine/valine) and FcγRIIIA-V/F (valine/phenylalanine) responded better to rituximab induction and maintenance therapy than patients with FcγRIIIA-158-F/F genotype. The affect of polymorphisms in FcγRIIIA-158 has also been investigated in the PRIMA study, wherein patients with indolent NHL receiving chemoimmunotherapy were randomized to observation or maintenance rituximab. Superior PFS was observed for patients receiving maintenance rituximab, and the affect of FcγRIIIA-158 in predicting maintenance response outcome is awaited.<sup>9</sup>

A number of polymorphisms, both in activating and inhibitory FcγR receptors have been investigated for their predictive role in rituximab response. Only polymorphisms at FcγRIIA-131,



This summary may include the discussion of investigational and/or unlabeled uses of drugs and/or devices that may not be approved by the FDA. Electronic forwarding or copying is a violation of US and International Copyright Laws. Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by CIG Media Group, LP, ISSN #1526-8209, provided the appropriate fee is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923 USA. www.copyright.com 978-750-8400.

FcγRIIIA-48, and FcγRIIIA-158 have been reported to be associated with rituximab response in indolent NHL.<sup>2-5</sup> The affect of FcγRIIA-131, while validated in some but not other studies, has been questioned as a predictive marker since rituximab is an IgG<sub>1</sub> class immunoglobulin, and FcγRIIA-131 is believed to be a determinant of IgG<sub>2</sub> but not IgG<sub>1</sub> antibody binding.<sup>10</sup> One potential explanation unifying these observations is the tight genetic linkage between FcγRIIA and FcγRIIIA polymorphisms. In a previous edition of *Clinical Lymphoma, Myeloma & Leukemia*, Hatjiharissi et al demonstrated that polymorphisms in FcγRIIA-131 showed linkage disequilibrium with polymorphisms in both FcγRIIA-48 and FcγRIIA-158.<sup>11</sup> Others have reported similar results, and have suggested a primacy for FcγRIIIA-158 in determining rituximab response outcome in patients with indolent NHL.<sup>4,12</sup>

A challenging aspect on the use of FcγRIIIA-158 receptor polymorphisms is clarifying what exactly is the predictive role for those patients who are heterozygous. Approximately 40%-50% of the North American population is heterozygous for V/F at FcγRIIIA-158, while 10%-15%, and 35%-40% of the population are homozygous for V/V and F/F, respectively.<sup>11</sup> In some studies, patients who were FcγRIIIA-158-V/F showed outcomes analogous to those patients who were heterozygous for phenylalanine (ie, FcγRIIIA-158-F/F), whereas in other studies these patients demonstrated more robust clinical outcomes in line with patients who were homozygous for valine (ie, FcγRIIIA-158-V/V). By in vitro studies, human IgG<sub>1</sub> binding by FcγRIIIA-158-V/F receptors is intermediate to those of FcγRIIIA-158-F/F and FcγRIIIA-V/V, though an additional influence by polymorphisms at FcγRIIIA-48 may also contribute to binding affinity.<sup>13</sup>

Perhaps the most challenging of all queries is the precise positioning of FcγR polymorphism testing in the care of patients with indolent NHL. At present, only testing for FcγRIIIA-158 is cleared by the US Food and Drug Administration. While the obvious use for FcγRIIIA-158 polymorphic testing is for identifying indolent NHL patients who are more likely to respond to rituximab, there are a few points considering. Not all patients who exhibit FcγRIIIA-158-F/F fail to respond, nor do all patients who express valine at FcγRIIIA-158 demonstrate a response to rituximab. In addition, rituximab may also promote anti-tumor activity by other mechanisms including chemosensitization, and possibly induction of secondary immunity. Despite these considerations, there are several important decision trees where FcγRIIIA-158 polymorphic testing might be useful in the care of patients with indolent NHL, and deserve greater research efforts: (1) identification of candidates for whom rituximab treatment alone may produce results as good as those in combination with chemotherapy; (2) identification of candidates who are more likely to benefit with maintenance rituximab therapy; (3) identification of candidates who are more likely to respond to non-rituximab-based therapy; (4) identification of candidates who may benefit with alternative antibody-based therapy that is independent of FcγRIIIA-158 polymorphisms such as radioimmunotherapy with tositumomab or ibritumomab tiuxetan, or with newer unconjugated antibodies such as GA101.<sup>14,15</sup> GA101, a novel glycoengineered anti-CD20

humanized antibody, possesses an Fc domain that exhibits greater indifference to FcγRIIIA-158 polymorphisms and also induces direct tumor cell apoptosis versus rituximab; and (5) use in predicting response to other IgG<sub>1</sub> class antibodies in patients with indolent NHL such as alemtuzumab and ofatumumab.

In this era of expanding treatment options for patients with NHL and imposing pharmacoeconomics, predictive genomic testing can play an integral role in its care. The use of FcγRIIIA-158 polymorphism testing to predict outcomes with agents such as rituximab has the capacity to contribute to the individualized care of patients with indolent NHL, and provide more directed, effective, and possibly cost-effective therapy. Such considerations clearly warrant further exploration of FcγRIIIA-158 polymorphism testing in the care of patients with indolent NHL.

Steven P. Treon, MD, MA, PhD

## References

- Zhuang Y, Xu W, Shen Y, et al. FcγR polymorphisms and clinical efficacy of rituximab in non-Hodgkin's lymphoma and chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk* 2010; 10:??????????.
- Carrton G, Dacheux L, Salles G, et al. Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcγRIIIA gene. *Blood* 2002; 99:754-8.
- Weng WK, Levy R. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol* 2003; 21:3940-7.
- Treon SP, Hansen M, Branagan AR, et al. Polymorphisms in FcγRIIIA (CD16) receptor expression are associated with clinical response to rituximab in Waldenström's macroglobulinemia. *J Clin Oncol* 2005; 23:474-81.
- Paiva M, Marques PM, Martins A, et al. FcγRIIIa polymorphism and clinical response to rituximab in non-Hodgkin lymphoma patients. *Cancer Genet Cytogenet* 2008; 183:35-40.
- Persky DO, Dornan D, Goldman BH, et al. Fc gamma receptor 3A genotype predicts overall survival for follicular lymphoma patients treated on Southwest Oncology Group Trials with combined monoclonal antibody plus chemotherapy but not chemotherapy alone. Presented at: 51st American Society of Hematology Annual Meeting and Exposition; December 5-8, 2009; New Orleans, LA. Abstract 111.
- Hunter ZR, Yang G, Ioakimidis LI, et al. Association of CR/VGPR with progression-free survival in rituximab-naive WM patients undergoing rituximab-based therapy, as predicted by polymorphisms in FcγRIIIA-158. *J Clin Oncol* 2010; 28(15 suppl):600s (abstract 8108).
- Pierz K, Gu S, Lewis M, et al. Predictive value of FCGR3A genotype on response to rituximab induction and maintenance therapy in follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2010; 28(15 suppl): 589s (abstract 8065).
- Salles GA, Seymour JF, Feugier P, et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy. *J Clin Oncol* 2010; 28(15 suppl):574s (abstract 8004).
- Warmerdam PA, van de Winkel JG, Vlug A, et al. A single amino acid in the second Ig-like domain of the human Fc gamma receptor II is critical for human IgG2 binding. *J Immunol* 1991; 147:1338-43.
- Hatjiharissi E, Hansen M, Santos DD, et al. Genetic linkage of Fc gamma RIIa and Fc gamma RIIIa and implications for their use in predicting clinical responses to CD20-directed monoclonal antibody therapy. *Clin Lymphoma Myeloma* 2007; 7:286-90.
- Lejeune J, Thibeault G, Ternant D, et al. Evidence for linkage disequilibrium between FcγRIIIa-V158F and FcγRIIa-H131R polymorphisms in white patients, and for an FcγRIIIa-restricted influence on the response to therapeutic antibodies. *J Clin Oncol* 2008; 26:5489-91.
- de Haas M, Koene HR, Kleijer M, et al. A triallelic Fc gamma receptor type IIIA polymorphism influences the binding of human IgG by NK cell Fc gamma RIIIa. *J Immunol* 1996; 156:3948-55.
- Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 2010; 115:4393-402.
- Yang G, Gong P, Xu L, et al. Activity of the CD20-directed monoclonal antibody GA101 relative to rituximab in Waldenström's macroglobulinemia (WM), and applicability to patients expressing FcγRIIIA-158 F/F. *J Clin Oncol* 2010; 28(15 suppl):601s (abstract 8112).