Clinical Cancer Research

Fc Gamma Receptor 3A and 2A Polymorphisms Do Not Predict Response to Rituximab in Follicular Lymphoma

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Abstract

Purpose: Preclinical studies suggest that SNPs in the Fc gamma receptor (*FCGR*) genes influence response to rituximab, but the clinical relevance of this is uncertain.

Experimental Design: We prospectively obtained specimens for genotyping in the rituximab extended schedule or re-treatment trial (RESORT) study, in which 408 previously untreated, low tumor burden follicular lymphoma (FL) patients were treated with single agent rituximab. Patients received rituximab in 4 weekly doses and responders were randomized to rituximab re-treatment (RR) upon progression versus maintenance rituximab (MR). SNP genotyping was performed in 321 consenting patients.

Results: Response rates to initial therapy and response duration were correlated with the *FCGR3A* SNP at position 158 (rs396991) and the *FCGR2A* SNP at position 131 (rs1801274). The response rate to initial rituximab was 71%. No *FCGR* genotypes or grouping of genotypes were predictive of initial response. A total of 289 patients were randomized to RR ($n = 143$) or to MR ($n = 146$). With a median follow-up of 5.5 years, the 3-year response duration in the RR arm and the MR arm was 50% and 78%, respectively. Genotyping was available in 235 of 289 randomized patients. In patients receiving RR ($n = 115$) or MR ($n = 120$), response duration was not associated with any *FCGR* genotypes or genotype combinations.

Conclusions: Based on this analysis of treatment-naïve, low tumor burden FL, we conclude that the *FCGR3A* and *FCGR2A* SNPs do not confer differential responsiveness to rituximab. *Clin Cancer Res; 22(4); 821–6. ©2015 AACR.*

See related commentary by Cartron et al., p. 787

Introduction

Follicular lymphoma (FL) patients who are asymptomatic and with low tumor burden are candidates for a watch and wait strategy, as early treatment has not been shown to improve survival (1, 2). However, single agent rituximab is often administered to these patients, with a goal of delaying the need for chemotherapy (3–7). Rituximab, an IgG1 subclass monoclonal antibody to CD20, has revolutionized therapy of FL by improving response rates, duration of responses (DORs), and overall survival (5, 8–13). One postulated mechanism of action is antibody-dependent cell-mediated cytotoxicity (ADCC). In this process, binding of the Fc gamma receptor (FCGR) on macrophages and NK cells to the Fc portion of the rituximab antibody induces phagocytosis of the target cell, to which the antibody is bound (14).

In vitro and animal studies have suggested that variation in specific SNPs in the *FCGR* sequence might confer variable responses to rituximab, due to the efficacy of Fc binding and triggering of ADCC (15, 16). The FCγRIIIA receptor (CD16a) is present on NK cells, monocytes, and macrophages (17). A valine/phenylalanine (V/F) polymorphism at amino acid position 158 of *FCGR3A* (rs396991) has been identified in humans, with the valine allele demonstrating higher affinity to human IgG1 than phenylalanine, resulting in enhanced ADCC (18). The FCγRIIA receptor is present on monocytes and macrophages, but not NK cells (17). A histidine/arginine (H/R) polymorphism at position 131 of *FCGR2A* (rs1801274) affects binding affinity of IgG2, with the histidine allele binding more strongly.

The first clinical study in FL examining the influence of these SNPs in FL suggested the *FCGR3A* valine/valine (VV) genotype, (but not the *FCGR2A* HH genotype) was associated with improved response rates to single agent rituximab (3). A retrospective analysis from Stanford University then reported improved response rates and time to progression in patients with a *FCGR3A* VV genotype, and in patients with a *FCGR2A* histidine/histidine (HH) genotype (19). A prospective multicenter trial of single agent rituximab for FL found the *FCGR3A* VV genotype was associated with event-free survival but not response rate (4). These three studies support the hypothesis that ADCC plays an important role in cell killing and that certain polymorphisms in *FCGR3A* and *FCGR2A* may influence ADCC. However, each study had different findings on the relative importance of *FCGR3A* versus *FCGR2A* and different findings about the influence on response

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Translational Relevance

Presented here are results of a correlative science study from the E4402 [rituximab extended schedule or re-treatment trial (RESORT)] study, which indicate a lack of predictive value of Fc gamma receptor (*FCGR*) polymorphisms in determining rituximab response in patients with previously untreated, low tumor burden follicular lymphoma. Prior studies have indicated differential responses to rituximab based on these polymorphisms. However, the prior studies tended to be small, retrospective analyses with heterogeneous patient populations. The submitted study was a prospectively planned evaluation of a large, homogeneous follicular lymphoma population, all treated with single agent rituximab. We were unable to find a differential response based on FCGR genotype or any combination of genotype. This manuscript presents definitive results, concluding that FCGR3A and 2A should not be used to select patients for single agent rituximab therapy.

rate and/or response duration. Using patient derived samples from E4402, the rituximab extended schedule or re-treatment trial (RESORT), we conducted a correlative analysis, evaluating the impact of these candidate SNPs in the *FCGR3A* and *FCGR2A* genes. The goal was to definitively determine the clinical significance of these two polymorphisms.

Methods

Patients

RESORT was a multicenter randomized trial that enrolled 408 FL patients between November 2003 and September 2008 (20). Patients received single agent rituximab (375 mg/m2) in 4 weekly doses, followed by randomization for responders to re-treatment with rituximab upon progression (375 mg/m^2 $\times$ 4 weekly doses) versus maintenance rituximab (MR) (375 mg/m^2 once every 12 weeks) (Fig. 1).

DNA extraction and genotyping

SNP genotyping was performed to assess the *FCGR3A* SNP genotype for rs396991 [valine (V) or phenylalanine (F)] and the *FCGR2A* SNP genotype at rs1801274 [histidine (H) or arginine (R)]. Using banked PBMCs ($N = 212$) or formalin-fixed paraffin-embedded tumor tissue (FFPE) ($N = 109$), DNA was extracted using an automated platform (AutoGen FlexStar Qiagen chemistries), followed by quantification by UV absorbance and quality control by 260/280 OD ratio and PicoGreen, and then storage in TE buffer. For SNP genotyping, samples were plated into 96 well plates and genotyped on the Taqman (TM) platform (Applied Biosystems 7900HT Fast RealTime PCR System). Sequence data and assay conditions for rs396991 (*FCGR3A*) and rs1801274 (*FCGR2A*) are provided at SNP500 (http://snp500cancer.nci.nih.gov). Genotype data were analyzed using Applied Biosystems SDS 2.3 analysis software. Quality control samples included study replicates (5%); *FCGR2A* and *FCGR3A* known wild-type homozygotes, heterozygotes, homozygote variants; and a DNA negative control. We summarized the call rates per SNP as well as per sample, examining samples that failed in 5% or more of SNPs. SNPs that failed in 5% or more of individuals were evaluated by Sanger sequencing. Likewise, if the error rate in the subjects for whom repeated genotypes was judged to be unacceptably high (>2%), genotyping was repeated until consistent results were achieved.

The *FCGR3A* rs396991 SNP has been reported to be difficult to accurately genotype, due to high copy number variation and high homology (97%) between *FCGR3A* and *FCGR3B* genes. *FCGR3B* carries an invariant G at the position that corresponds to *FCGR3A* 4985T > G and co-amplification of *FCGR3A* and *FCGR3B* can lead to SNP miscalls. Transgenomics, Inc., Omaha, NE developed primers and probes specific for genotyping the *FCGR3A* that does

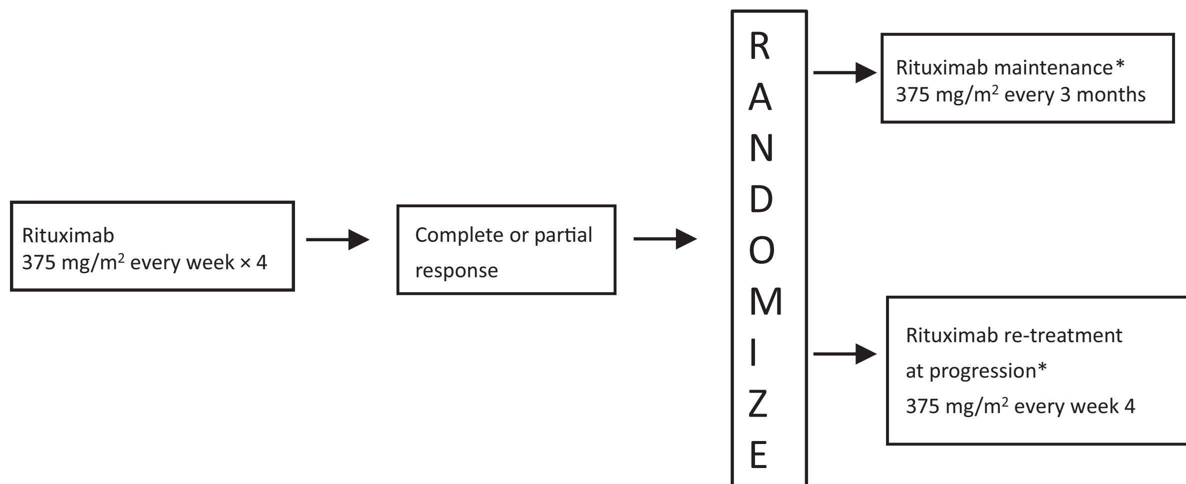

Figure 1.
Treatment schema for E4402 (RESORT) trial.

Table 1. Patient characteristics for patients from RESORT trial as well as subset who had SNP sequencing

Patient characteristics	All FL patients on RESORT study ($n = 408$) %	FL patients on study with SNP sequencing ($n = 321$) %
Age (median, range)	58 (25–86)	60 (25–86)
Gender (M/F)	48/52	46/54
PS (0/1)	85/15	86/14
Stage		
III	50	49
IV	49	50
FLIPI		
0—1	18	17
2	46	48
3—5	36	35
B2M elevated	41	42

not co-amplify the *FCGR3B*. To test the transgenomics (TG) proprietary technology, cases with available PBMC DNA ($N = 212$) were run in duplicate using both the commercial TM platform and the TG platform. All PBMC cases were also subjected to Sanger sequencing, with the sequencing result used as the reference gold standard to determine assay accuracy.

Statistical analysis

Fisher's exact test was used to compare response rates among the different genotypes. A logistic regression model was employed to evaluate the polymorphism effect on response rate accounting for other patient characteristics. DOR was defined as the time from documented response to documented progression and estimated using the Kaplan and Meier method. Logrank test (one-sided significance level of 0.05) was used to compare DOR. A Cox proportional hazards regression model was used to evaluate the significance of polymorphism effect on DOR after adjusting for other patient characteristics.

Results

A total of 408 FL patients were enrolled in RESORT. Of these, 321 underwent SNP genotyping, whereas unavailable clinical material precluded genotyping in 87 patients. There were no major differences in the baseline characteristics when comparing the genotyped population to the entire population (Table 1). PBMCs were the DNA source in 212 cases and FFPE tissue was the DNA source in 109 cases. PBMC DNA was subjected to genotyping by both commercially available TM technology and TG proprietary pyrosequencing technology. Using TM for genotyping the *FCGR3A* SNP, three cases could not be genotyped and 18 cases were miscalled (using sequencing as the gold standard) for an accuracy rate of 90% (191/212). Using TG genotyping for the *FCGR3A* SNP, there were nine cases that could not be genotyped and one case miscalled for an accuracy rate of 95% (202/212). Using TM for genotyping the *FCGR2A* SNP, five cases could not be genotyped and three cases were miscalled for an accuracy rate of 96% (204/212). Using TG for genotyping the *FCGR2A* SNP, there were no failures to genotype and there was one miscall for an accuracy rate of 99% (211/212). Including the 109 FFPE cases and the 212 PBMC cases, and after adjudicating discrepant PBMC cases by sequencing, the final *FCGR3A* and *FCGR2A* genotype frequencies were VV 14%, VF 45%, FF 40% and HH 28%, HR 47%, rituximab re-treatment (RR) 22%, respectively.

The overall response rate (ORR) to initial rituximab was 71%. The likelihood of obtaining a complete response or any response was not correlated with *FCGR3A* genotype (VV vs. VF vs. FF, or VV vs. F carrier; Table 2). Similarly, the likelihood of obtaining a complete response or any response was not correlated with *FCGR2A* genotype (HH vs. HR vs. RR, or HH vs. R carrier; Table 3). Additionally, no combination of genotypes (e.g., VV/HH vs. FF/RR) was associated with complete response or ORRs (data not shown).

Genotyping was performed in 235 of 289 randomized patients, RR ($n = 115$) or to MR ($N = 120$). With a median follow-up of 5.5 years, the 3-year response duration in the RR arm and the MR arm was 50% and 78%, respectively. The *FCGR3A* genotype was not associated with response duration in the RR ($P = 0.92$) or the MR ($P = 0.58$) treatment arms (Fig. 2A). Similarly, the *FCGR2A* genotype was not associated with response duration in the RR ($P = 0.19$) or the MR ($P = 0.61$) treatment arms (Fig. 2B). Additionally, no combination of genotypes (e.g., VV/HH vs. FF/RR) influenced DOR or survival (data not shown).

Discussion

Based on this analysis of a treatment-naïve population of low tumor burden FL, we conclude that the two candidate missense SNPs in *FCGR3A* (rs396991) and *FCGR2A* (rs1801274), alone or in combination, does not predict the likelihood or the durability of response to single agent rituximab. These data are in contrast to three early reports examining this question and suggesting these polymorphisms impact the efficacy of rituximab.

In a study with a patient population similar to ours, Cartron and colleagues, determined the *FCGR3A* and *FCGR2A* genotypes in 49 patients receiving rituximab (3). The objective response rates at 12 months were 90% for VV patients and 51% for F carriers ($P = 0.03$). Progression-free survival (PFS) at 3 years was 56% for VV patients and 35% for F carriers ($P =$ NS). There was no impact of the *FCGR2A* polymorphism on outcome. A retrospective analysis of 87 FL patients receiving single agent rituximab at Stanford University demonstrated that *FCGR3A* V/V patients ($n = 13$) and *FCGR2A* H/H patients ($n = 20$) experienced higher response rates and more durable remissions compared with *FCGR3A* F carriers and *FCGR2A* H carriers, respectively (19). Finally, a retrospective analysis from the SAKK (Swiss group for Clinical Cancer Research), in which patients with follicular and mantle cell lymphoma were treated with single agent rituximab, followed by no further treatment or MR, the *FCGR3A* V/V genotype was associated with superior event-free survival (4). Because these studies were retrospective, relatively small with a heterogeneous FL population, the true impact of these polymorphisms remained unclear. Analysis of the RESORT patients was an ideal opportunity to evaluate these findings in a large prospective study of homogeneous FL patients. The findings from the present work should be considered definitive and highlight the importance of prospective

Table 2. Induction response by FCGR3A genotype. Three out of 321 samples have no FCGR3A data

VV ($n = 43$)	VF ($n = 145$)	FF ($n = 130$)	*P* value
CR 4 (9%)	19 (13%)	15 (11%)	0.78
ORR 33 (76%)	106 (73%)	97 (74%)	0.88
SD 6 (14%)	33 (23%)	25 (19%)	
PD 2 (5%)	3 (2%)	3 (2%)	

Table 3. Induction response by FCGR2A genotype. Six out of 321 samples have no FCGR2A data

HH (n = 91)	HR (n = 153)	RR (n = 71)	P value
CR 9 (10%)	18 (12%)	11 (16%)	0.54
ORR 65 (72%)	113 (74%)	53 (76%)	0.86
SD 17 (19%)	33 (22%)	13 (19%)	
PD 5 (6%)	2 (1%)	1 (1%)	

studies in homogenous populations and with adequate power to identify predictive biomarkers.

Consistent with our findings, another large prospective study evaluating these polymorphisms in FL patients receiving single agent rituximab found no association with response rate or response duration (21). This United Kingdom sponsored intergroup trial randomized low tumor burden and asymptomatic FL to "watch and wait" versus rituximab induction alone versus rituximab induction followed by rituximab maintenance. No difference was seen in the 257 patients for whom *FCGR* genotyping was available with respect to CR rate, time to next treatment, or PFS.

Analyses of previously untreated high tumor burden FL patients treated with combination rituximab-chemotherapy, similarly found no impact of these SNPs on response rate, progression, or overall survival (22, 23). The PRIMA study (24), which showed an improvement in PFS after MR in patients who were treated with immunochemotherapy induction, was designed with prespecified objectives to clarify the role of *FCGR* polymorphisms in this context. The PRIMA investigators also found no impact of different *FCGR* genotypes on response rates to initial immunochemotherapy or MR, nor any difference in PFS at any timepoint (22).

Our results were somewhat unexpected given the strong preclinical data suggesting the *FCGR3A* 158V/F polymorphism positively influences both the binding of IgG as well as the expression of CD16 by NK cells (18, 19). It is possible that the models do not accurately recapitulate the human tumor environment or it is possible that ADCC is not the major mechanism of cell killing after rituximab therapy. Rituximab's precise mechanism of action remains ill-defined and could include components of ADCC, complement-mediated cytotoxicity, and direct killing (13, 15, 25, 26). Direct effects attributed to rituximab include

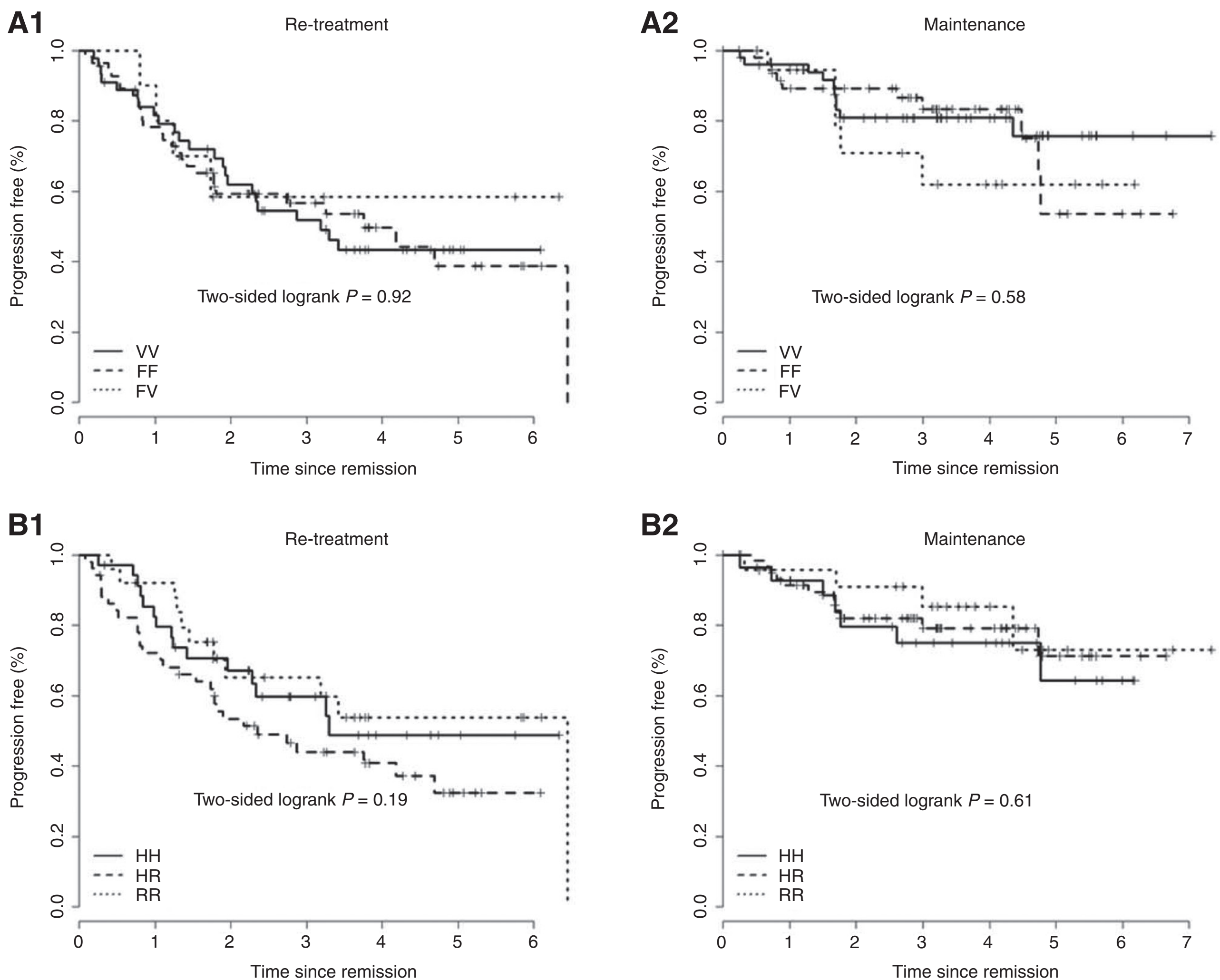

Figure 2.
Response duration by FCGR3A genotype on RR arm (A1) and MR arm (A2) and by FCGR2A genotype on RR arm (B1) and MR arm (B2).

inhibition of cell proliferation, induction of phosphatidylserine translocation, cell signaling via increased phosphorylation, and induction of apoptosis (27).

Many factors can influence FL response to rituximab, including biologic heterogeneity, clonal evolution, tumor bulk, prior treatments, and host factors. This analysis attempted to minimize many of these factors, by evaluating a relatively homogeneous FL population with low tumor burden, no prior therapy, and protocolized treatment and follow-up of patients. Despite this, we were unable to find a differential response based on *FCGR* genotype at the two candidate loci, as hypothesized by preclinical and small clinical studies. Although this does not preclude a role of other genetic variation in these genes in treatment response and outcomes, none has been identified to date. Given these definitive results, we conclude that the selection of patients for single agent rituximab therapy should not be based upon these *FCGR3A* or *FCGR2A* genotype status and these data raise additional questions regarding the mechanism of rituximab cytotoxicity.

Disclosure of Potential Conflicts of Interest

J.R. Cerhan is a consultant/advisory board member for Genentech. R.D. Gascoyne reports receiving speakers bureau honoraria from Seattle Genetics, and is a consultant/advisory board member for Celgene and Janssen. S.J. Horning has ownership interest (including patents) in Roche. B. Kahl is a consultant/advisory board member for Roche.

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