

The impact of *FcγRIIa* and *FcγRIIIa* gene polymorphisms on responses to RCHOP chemotherapy in diffuse large B-cell lymphoma patients

SAMO ROŽMAN¹, SRDJAN NOVAKOVIĆ², IZTOK GRABNAR³,
PETRA CERKOVNIK² and BARBARA JEZERŠEK NOVAKOVIČ⁴

Departments of ¹Pharmacy and ²Molecular Diagnostics, Institute of Oncology Ljubljana;

³Department of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, University of Ljubljana;

⁴Division of Medical Oncology, Institute of Oncology Ljubljana, Ljubljana 1000, Slovenia

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Abstract. Rituximab is a monoclonal antibody routinely used in the treatment of B-cell non-Hodgkin lymphomas. It mediates antibody-dependent cellular cytotoxicity of B lymphocytes by bridging them with Fcγ receptors (FcγR) on effector cells. Several polymorphisms in the *FcγR* genes have been identified to influence rituximab binding to FcγR, thus altering its antitumor effect in indolent lymphomas. In the present study, the impact of *FcγRIIa* and *FcγRIIIa* polymorphisms on the survival and response to immunochemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone was evaluated in diffuse large B-cell lymphoma (DLBCL) patients. A total of 29 Slovenian DLBCL patients were studied. Genotyping was conducted for *FcγRIIa*-27, *FcγRIIa*-131, *FcγRIIIa*-48 and *FcγRIIIa*-158 polymorphisms. The median follow-up time was 29.7 months (range, 9.7-45.4 months). No significant impact of the genotypes was observed on the treatment response, progression-free or overall survival of DLBCL patients. There was a non-significant trend of an improved response to chemotherapy without additional irradiation in patients homozygous for Val at *FcγRIIIa*-158 compared to Phe carriers. The findings of the present study indicate that *FcγR* polymorphisms have no influence on the survival of DLBCL patients.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) accounting for ~30% of all NHL cases (1). The addition of rituximab to

the chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) has significantly improved the clinical outcome of patients with various forms of indolent and aggressive CD20-positive NHL, including DLBCL (2). The mechanisms of rituximab action remain a matter for debate, but are considered to include the antibody-dependent cellular cytotoxicity (ADCC) utilizing Fcγ receptors (FcγR), complement-dependent cytotoxicity, and induction of apoptosis in B lymphocytes (3).

Rituximab is a monoclonal antibody directed against the CD20 antigen expressed on the surface of normal and malignant B lymphocytes (4). Upon binding, it bridges CD20-positive B lymphocytes with FcγR present on the effector cells, such as natural killer cells and macrophages (5). Several distinct FcγR classes have been described. FcγRI, FcγRIIa, FcγRIIc and FcγRIIIa function as activating receptors, while FcγRIIb and FcγRIIb function as inhibitory receptors (6).

It has been shown that polymorphisms in the *FcγRIIa* and *FcγRIIIa* genes can impair binding of rituximab to FcγR, thereby compromising its ADCC effects (5,7-9). Four polymorphisms in the *FcγRIIa* and *FcγRIIIa* genes (*FcγRIIa*-27, *FcγRIIa*-131, *FcγRIIIa*-48, *FcγRIIIa*-158) have garnered particular attention and have been described to have variant allele present with the frequency of >10% in Caucasians (10). Individuals homozygous for His at *FcγRIIa*-131 show much more effective phagocytosis of IgG-opsonized particles than those homozygous for Arg (7). Individuals homozygous for Val at *FcγRIIIa*-158 demonstrate tighter FcγR binding to IgG compared to those homozygous for Phe (8). The *FcγRIIa*-27 and *FcγRIIIa*-48 substitutions, on the other hand, do not affect the receptor affinity for IgG (8,11). Despite *FcγRIIa*-27 and *FcγRIIIa*-48 polymorphisms being nonfunctional, they are genetically linked to the *FcγRIIa*-131 and *FcγRIIIa*-158 polymorphisms (10). Available data on the association between polymorphisms in the *FcγR* gene and the clinical outcome in various lymphoma types are inconclusive (12-16). The objective of our prospective study was to investigate the distribution of *FcγRIIa* and *FcγRIIIa* polymorphisms in Slovene DLBCL patients. The present study aimed to evaluate the impact of the 4 most common polymorphisms in

Correspondence to: Professor Barbara Jezeršek Novaković, Division of Medical Oncology, Institute of Oncology Ljubljana, Zaloška 2, Ljubljana 1000, Slovenia
E-mail: bjezersek@onko-i.si

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the *FcyRIIa* and *FcyRIIIa* genes on the response to RCHOP therapy in previously untreated Slovenian DLBCL patients. Furthermore, the association between *FcyRIIa* and *FcyRIIIa* polymorphisms and survival outcomes, including overall survival (OS) and progression free survival (PFS) were analyzed.

Materials and methods

Patient population. A total of 29 patients with newly diagnosed CD20-positive DLBCL, who were treated at the Institute of Oncology Ljubljana (Ljubljana, Slovenia) were enrolled in the study. All patients received 8 cycles of RCHOP regimen every three weeks according to the National guidelines for the treatment of NHL (17). To minimize adverse drug reactions associated with the treatment regimen, patients were pre-medicated with clemastine, acetaminophen, and granisetron, followed by rituximab at a dose of 375 mg/m². Subsequently, patients received chemotherapy regimen consisting of cyclophosphamide, doxorubicin, vincristine and prednisone. Patient exclusion criteria were as follows: History of central nervous system lymphomatous disease, other malignancies, infections, or any other medical condition that would preclude treatment according to the protocol.

Clinical response was evaluated according to the revised response criteria for malignant lymphoma proposed by International Harmonization Project (18). Complete response (CR) was defined as a complete absence of all detectable evidence of disease. Partial response (PR) was defined as $\geq 50\%$ decrease in the sum of the products of the greatest diameters (SPD) of the six largest nodal masses. Progressive disease (PD) was defined as $\geq 50\%$ increase from nadir in the SPD of any previously identified abnormal node or appearance of new lesion. Stable disease (SD) was defined as less than PR, but not PD. Overall response rate (ORR) was defined as the proportion of patients with reduction in tumor burden (CR+PR).

The study was approved by the Institutional Review Board at the Institute of Oncology Ljubljana (no. 03-Z/KSOPKR-22) and National Medical Ethics Committee of Republic of Slovenia (no. 38/10/09). Written informed consent was obtained from all patients prior to inclusion in the study.

***FcyRIIa* and *FcyRIIIa* genotyping.** Genomic DNA was extracted using an innuPREP DNA blood kit (Analytik Jena AG, Jena, Germany) according to the manufacturer's instructions. The Gln to Trp substitution at position 27 and the Arg to His substitution at position 131 of the *FcyRIIa* gene were amplified using the following primers: Gln>Trp 27, F 5'-TGT AAAACGACGGCCAGTCCGCTGCAAGTACAGATCTT-3' and R 5'-CAGGAAACAGCTATGACCTCCTCCACTGAC CGGAAAGC-3'; Arg>His 131, F 5'-TGTAACGACG GCCAGTACGTACCTCTGAGACTGAAAA-3' and 5'-CAG GAAACAGCTATGACCATCTTGGCAGACTCCCCA TA-3' (10). EXPRESS SYBR® GreenER™ qPCR SuperMix Universal was used for amplification of DNA sequences with the following components: Master Mix, water, forward and reverse primers and genomic DNA (ThermoFisher Scientific, Waltham, Massachusetts, US). PCR conditions were as follows: 10 min of initial denaturation at 95°C, followed by 45 cycles at 95°C for 45 sec, 65°C for 45 sec and 72°C for 55 sec.

Table I. Patients' characteristics.

Patients' characteristics	Number of patients (n=29)	%
Gender		
Male	16	55.2
Female	13	44.8
Age		
>60 years	17	58.6
≤60 years	12	41.4
Ann Arbour clinical stage		
I-II	11	37.9
III-IV	18	62.1
IPI		
0-2	19	65.5
3-5	10	34.5
Bulky disease		
Yes	10	65.5
No	19	34.5
Irradiation first line		
Yes	16	55.2
No	13	44.8
Response		
CR	25	86.2
PR	2	6.9
PD/SD	2	6.9
ORR (CR+PR)	27	93.1

IPI, International prognostic index; CR, complete response; PR, partial response; PD/SD, progressive disease/stable disease; ORR, overall response rate.

PCR purification was performed using ExoSap IT (Affymetrix, Santa Clara, CA, USA). Sequencing was performed using BigDye Terminator v3.1 Cycle Sequencing Kit (ThermoFisher Scientific) with the following conditions: Denaturation at 96°C for 1 min, followed by 30 cycles at 96°C for 10 sec, 50°C for 5 sec and 60°C for 4 min. Sequence clean-up was conducted using ethanol and EDTA, and sequences were detected on an Analyzer 3500 (ThermoFisher Scientific).

The Leu to His or Arg substitution at position 48 of the *FcyRIIIa* was amplified using the following primers: F 5'-TGTAACGACGACGCCAGTCACCAAGCATGGGTT TGCAAT-3' and R 5'-CAGGAAACAGCTATGACCGCAC CTGTACTCTCCACTGTCTGTC-3' (10). The PCR reaction, purification, sequencing and detection were performed with the same reagents under the same conditions as described above.

The Val to Phe substitution at position 158 of the *FcyRIIIa* was amplified using the following primers: F 5'-ATATTTACA GAATGGCACAGG-3' and R 5'-CAGGAAACAGCTATGA CCCCACTCAACTTCCCAGTGTGATT-3' primers (10,19). The LightCycler® 480 High Resolution Melting Master (Roche Applied Science, Mannheim, Germany) was used for amplification of specific DNA sequences with the following

Table II. Genotype frequency.

		Number of patients (%)							
		<i>FcγRIIa</i> -27		<i>FcγRIIa</i> -131		<i>FcγRIIIa</i> -48		<i>FcγRIIIa</i> -158	
Genotype	Gln	23 (79.3%)		Arg	5 (17.2%)	Leu	24 (82.8%)	Val	3 (10.3%)
	Gln/Trp	6 (20.7%)		Arg/His	16 (55.2%)	Leu/His	4 (13.8%)	Phe/Val	16 (55.2%)
	Trp	0 (0.0%)		His	8 (27.6%)	Leu/Arg	1 (3.4%)	Phe	10 (34.5%)

components: Master Mix, MgCl₂, water, forward and reverse primers and genomic DNA. PCR conditions were as follows: 10 min of initial denaturation at 95°C followed by 45 cycles at 95°C for 35 sec, 65°C for 55 sec (decreased 0.5°C per cycle), and 72°C for 45 sec. PCR purification, sequencing and detection was conducted in a similar manner as described above.

Statistical analysis. Summary statistics were used to describe patients' characteristics. Observed genotype frequencies were tested for deviation from Hardy-Weinberg equilibrium with the Chi-square test. Categorical variables were compared using the Chi-square test. Survival rates according to *FcγR* polymorphisms were analyzed using the Kaplan-Meier method and log-rank test was used to compare survival between the groups. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using the SPSS Statistics 22.0 software package (IBM SPSS, Armonk, New York, USA).

Results

Patient characteristics. The study population consisted of 13 women and 16 men of Caucasian ethnic origin with DLBCL. Baseline characteristic of participants, including Ann Arbor clinical stage, International prognostic Index (IPI), presence of bulky disease and irradiation in first line therapy are presented in Table I. The median age at the start of treatment was 62 years. A total of 19 patients were low to low-intermediate risk group according to IPI, whereas 10 patients had bulky disease. All patients were treated with RCHOP chemotherapy. A total of 16 patients with residual disease were additionally irradiated as a part of the first line treatment.

***FcγRIIa* and *FcγRIIIa* genotype frequencies.** The genotype distribution of *FcγRIIa* and *FcγRIIIa* alleles is presented in Table II. There were no significant differences between genotype groups in terms of gender, age, clinical stage, IPI and presence of bulky disease. The observed genotype frequencies did not deviate from those expected under the Hardy-Weinberg equilibrium ($P > 0.05$).

Linkage disequilibrium between *FcγRIIa*-27 and *FcγRIIIa*-48 alleles was observed. Patients homozygous for Gln at *FcγRIIa*-27 were more likely to be homozygous for Leu at *FcγRIIIa*-48 ($P = 0.03$).

Response to frontline RCHOP therapy. Response to frontline therapy was as follows: 25 patients achieved CR, 2 patients PR, while 2 patients had PD (Table I). The ORR was 93%.

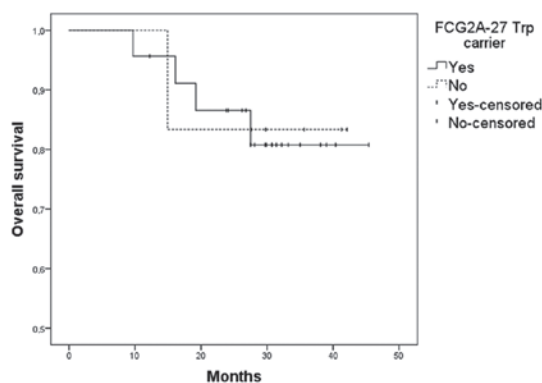
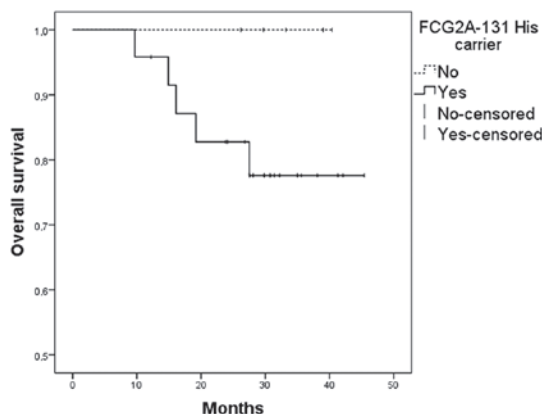
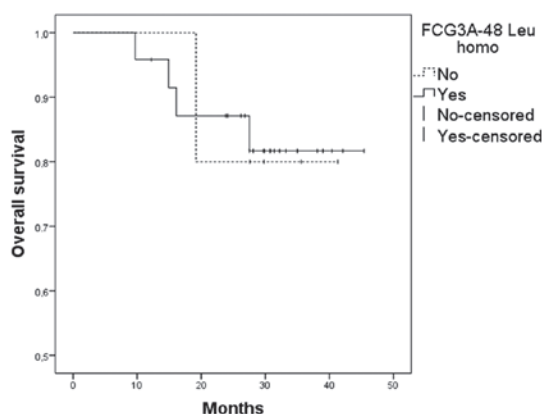
No significant differences were observed between different genotypes and ORR. With the median follow-up time of 29.7 months (range 9.7-45.4), the OS and PFS were 83%. No significant differences were observed among various genotypes and OS (Figs. 1-4) or PFS (data not shown). At the end of follow-up, 5 patients have died. Four of the patients had IPI 4 and one had bulky disease. Patients with IPI equal or < 3 were more likely to be alive at the end of follow-up ($P = 0.001$).

All patients (3/3) homozygous for Val at *FcγRIIIa*-158 achieved CR without additional irradiation, whereas only 41% (9/22) Phe carriers did so (Table III). The P-value for this comparison was approaching statistical significance ($P = 0.096$).

Discussion

Rituximab has been integrated into routine clinical practice in the treatment of different B-cell lymphomas (2). However, the response among lymphoma types and among different patients within each type is highly variable (15). Therefore, there is an urgent need to identify patients who are likely to respond to rituximab prior to the start of the treatment.

One of the potential mechanisms of rituximab activity is ADCC via *FcγR* on effector cells. Accordingly, it has been assumed that functional polymorphisms in the *FcγRIIa* and *FcγRIIIa* genes may alter rituximab binding to effector cells and thereby modify its antitumor effect in the DLBCL patients (12,16). However, the clinical data supporting this hypothesis are inconclusive. In a study of 113 patients of Asian ethnic origin, patients homozygous for Val at *FcγRIIIa*-158 had an improved outcome after RCHOP therapy (16). Conversely, Ahlgrim and colleagues detected no statistically significant association between the response to RCHOP therapy and *FcγR* alleles in 512 DLBCL Caucasian patients (12). However, the authors did notice a trend toward superior CR rates for carriers of Val at *FcγRIIIa*-158 (12). Three smaller European studies also failed to detect a link between the RCHOP therapy and *FcγR* alleles in DLBCL (20-22). In line with these findings, the present study likewise reports no significant association between response to RCHOP therapy and *FcγR* alleles. If any, there was a trend for better response to chemotherapy without the need for additional irradiation in patients homozygous for Val at *FcγRIIIa*-158. The difference between the present study in Caucasian patients and the study with Asian participants may be partly explained by unidentified genetic differences between races and a higher number of included patients by Kim and colleagues (16).

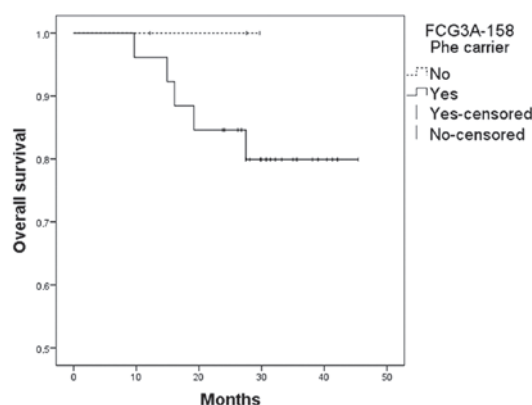
Figure 1. *FcγRIIa*-27 polymorphisms and overall survival.Figure 2. *FcγRIIa*-131 polymorphisms and overall survival.Figure 3. *FcγRIIIa*-48 polymorphisms and overall survival.

Contrary to aggressive types of lymphoma, studies on indolent lymphomas treated with rituximab monotherapy have shown that patients homozygous for Val at *FcγRIIIa*-158 have better responses than Phe carriers (13-15). Treon and colleagues have also shown better responses in patients carrying Leu and His at *FcγRIIIa*-48, whereas Weng and colleagues observed better responses in patients homozygous for His at *FcγRIIa*-131. The available evidence suggests that polymorphisms in *FcγR* may affect response only when rituximab is used as monotherapy, as in trials with indolent lymphomas.

Table III. Irradiation and genotype frequency in patients with complete response (n=25).

	CR without irradiation	CR with irradiation	P-value
<i>FcγRIIa</i> -27			
Gln	10	10	0.541
Gln/Trp+Trp	2	3	
<i>FcγRIIa</i> -131			
Arg	2	2	0.672
Arg/His + His	10	11	
<i>FcγRIIIa</i> -48			
Leu	11	10	0.328
Leu/His+Leu/Arg	1	3	
<i>FcγRIIIa</i> -158			
Val	3	0	0.096
Phe/Val+Phe	9	13	

CR, Complete response.

Figure 4. *FcγRIIIa*-158 polymorphisms and overall survival.

FcγRIIa and *FcγRIIIa* polymorphisms had no impact on OS or PFS in the present study. A number of other previous studies also failed to show significant difference in survival in regard to *FcγR* genotypes, in both aggressive and indolent lymphomas (12-14,16,20-22). There is only one study in follicular lymphoma that reported improved PFS in patients homozygous for Val at *FcγRIIIa*-158 and homozygous for His at *FcγRIIa*-131 (15).

Finally, no differences in patients' characteristics or frequency of genotypes were observed in the present patient population compared to other published data from Europe, United States and Asia (10,16,23,24). Genetic linkage between *FcγRIIa*-27 and *FcγRIIIa*-48 polymorphisms was noted. Genetic linkage among polymorphisms within and between *FcγRIIa* and *FcγRIIIa* has also been confirmed by Hatjiharissi and colleagues (10). In the present study, only a single genetic linkage was observed, most likely due to the small number of patients included, whereas Hatjiharissi *et al* (10) found extensive genetic linkage between all four major polymorphisms of *FcγRIIa* and *FcγRIIIa*. This may also provide an explanation

for why some polymorphisms at *FcγRIIIa*-48 are associated with a better clinical response to rituximab despite the lack of impact on IgG1 binding, as seen in the study of Treon and colleagues (14).

The present study has several limitations that merit consideration. The sample size was quite modest and the follow-up relatively short. In addition, ADCC may not be the predominant mechanism of rituximab activity in DLBCL, so investigating polymorphisms in genes implicated in other pathways of rituximab activity may be necessary for reliable interpretation of results.

In summary, the results of the present study indicate that *FcγRIIa* and *FcγRIIIa* polymorphisms do not impact the survival of DLBCL patients on RCHOP therapy. Due to a trend for better response to RCHOP therapy in patients homozygous for Val at *FcγRIIIa*-158, larger studies are needed to reach a clear conclusion about the potential predictive and prognostic value of *FcγRIIa* and *FcγRIIIa* polymorphisms.

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