Genetic variants contribute to differences in response and toxicity to drugs used in autoimmune diseases: Rheumatoid arthritis and systemic lupus erythematosus

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Chapter 5

FcGR genetic polymorphisms and the response to adalimumab in patients with rheumatoid arthritis

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Abstract

Aims

The aim of our study was to explore the potential of *FcGR* genetic polymorphisms as a predictor of adalimumab efficacy in rheumatoid arthritis patients.

Materials and methods

The study population was composed of 302 Dutch RA patients receiving adalimumab therapy. The *FcGR2A* (R131>H) (rs1801274) and *FcGR3A* (F158>V) (rs396991) genetic variants were genotyped using the TaqMan® allelic discrimination technology. Treatment outcome was evaluated with the use of the 28-joint disease activity score criteria (DAS28) and good response and remission were classified according to EULAR criteria.

Results

Comparing allelic frequencies between responders and non-responders, the presence of the *FcGR*2A*R allele was associated with EULAR good response at 14 weeks ($p = 0.017$, OR = 1.53, 95% CI 1.08–2.17). No significant association was found for *FcGR3A*, with good response or remission. The combined effect of both *FcGR2A* and *FcGR3A* SNPs showed a trend for association with EULAR good response ($p = 0.041$, OR = 1.38, 95% CI 1.01–1.89).

Conclusions

Our results indicate that *FcGR* polymorphisms could be a determinant of adalimumab efficacy in RA patients.

INTRODUCTION

The treatment with anti-TNF biological therapy has revolutionized the management of rheumatoid arthritis (RA). Anti-TNF treatment has demonstrated to be effective in suppressing inflammation and reducing the amount of long-term joint and tissue damage (1). However, despite the proven therapeutic value of TNFα antagonists, about 25% of patients show insufficient or no response (1-3).

At present, five TNF inhibitors are available for the treatment of RA, three of which are full-length monoclonal antibodies: infliximab, adalimumab and golimumab. The fourth agent, etanercept, is a fusion protein of two TNFR2 receptor extracellular domains and the Fc fragment of human immunoglobulin 1 (IgG1). Certolizumab is a humanized Fab fragment conjugated to polyethylene glycol (PEG) without IgG1 region (4).

Biological agents exert their pharmacological effects through their variable portion (designed to block the target molecule) and their constant portion (the Fc fragment of IgG1), which specifically binds the human FcG receptors (FcGRs) (5-8). FcGRs are expressed on the surface of most immune cells. Engagement of FcGRs by TNF antagonists could affect a number of cellular functions, including phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis, cytokine release and macrophage-mediated clearance of immune-complexes (8, 9).

Six types of human FcGR have been described: FcGR1A, FcGR2A, FcGR2B, FcGR2C, FcGR3A and FcGR3B (10).

Several candidate gene studies have suggested that the response to anti-TNF treatment is dependent on heterogeneity of the FcGR (11-16). Indeed, two FcGR subclasses, *FcGR*2A and *FcGR*3A, are known to be subject to genetic polymorphisms resulting in differential ligand binding. Each of these polymorphisms is located in the extracellular Fc-binding portion of the FcGR and hence affects the affinity with which the FcGR interacts with the various IgG subclasses (17) and thus may affect the clearance of immune complexes (18).

The *FcGR2A* polymorphism displays a single nucleotide polymorphism (A>G, Arg131His rs1801274) in the region specifying its ligand binding domain, causing an Arginine (R) to Histidine (H) amino acid substitution at position 131 (19). FcGR2A-H131 has higher affinity for human IgG1 and is the only FcGR that interacts with IgG2 (5). The functional consequence of this polymorphism was shown using IgG2-opsonized particles which were poorly internalized by phagocytes from FcGR2A-R131 homozygous donors, however, IgG2-opsonized particles were efficiently phagocytosed by FcGR*2A*-H131 expressing cells (20, 21). It has been suggested that FcGR*2A*-RR patients may clear anti-TNF drugs less efficiently

compared to patients carrying high affinity variants (HH or RH) and thus experience an increased beneficial clinical effect of anti-TNF drugs (11).

The *FcGR3A* (Phe158Val rs396991) displays an A>C substitution resulting in a Phenylalanine (F) to Valine (V) substitution at amino acid position 158. The FcGR*3A*-V158 allelic variant of FcGR3A protein has higher affinity for IgG1, IgG2 and IgG3 compared to the F158 allelic variant, and is also able to interact with IgG4 (17). It has been suggested that patients with FcGR*3A*-FF clear anti-TNF drug less efficiently from the circulation, thus increasing its beneficial clinical effect (11).

Several studies (Table 5.1) have evaluated the hypothesis of a decreased clearance due to *FcGR2A* and *FcGR3A* genetic polymorphisms by analyzing the effect of these SNPs on the response to different TNFα antagonists including infliximab, etanercept, and adalimumab in RA albeit with conflicting results (11-16). These disconcordant results may be explained by the small sample size, heterogeneity in the design (different anti-TNF agents), the use of different definitions of response and importantly also the use of different methods for genotyping. Indeed, genotyping of *FCGR3A* polymorphisms has shown to be difficult with some methods due to co-amplification of the homologous gene *FcGR3B*. As a result of the latter, reported allele frequencies of *FcGR3A* differ between studies and several studies report deviations from Hardy Weinberg equilibrium (HWE) (22). The aim of the current study was to explore *FcGR2A* and *FcGR3A* genetic polymorphisms for association with adalimumab efficacy in RA patients.

MATERIAL AND METHODS

Patients and treatment

Clinical data of 325 adalimumab treated patients were obtained from a database of AptheekZorg which facilitated the Dutch distribution of adalimumab. All patients were diagnosed with RA according to the 1987 revised American College of Rheumatology (ACR) criteria (26, 27). At that time of the study, adalimumab was reimbursed in the Netherlands only if prescribed according to the following protocol: 1) patients have used 2 DMARDs including MTX and 2) patients have a Disease Activity Score based on a 28-joint count (DAS28) of at least 3.2. Aditional inclusion criteria to the use of adalimumab for RA treatment were 18 years of age or older, an erythrocyte sedimentation rate (ESR) of at least 28 mm/hour, patient´s global assessment of their general well-being measured on a 100 mm horizontal visual analogue scale (VAS), the left end representing as good as can be and the right end representing as worse as possible, of at least 20 mm. Adalimumab

Table 5.1: Overview of pharmacogenetic studies involving *FcGR* polymorphisms and anti-TNF treatment in RA

Ref	Anti-TNF	n	Genotype	Endpoints	OR (95% CI), p-value (Low affinitiy genotype vs No-low affinity genotypes) (RR vs no RR for 2A, FF vs no FF for 3A)**	Genotyping methods
Cañete 2009 (11)	Infliximab	91	*FcGR2A*	ACR 20 at 30 weeks	2.89 (1.04–8.01), p = 0.035	PCT-SBT method
			FcGR3A	ACR 50 at 6 weeks	7.83 (1.26–48.54), p = 0.003	
				EULAR at 6 weeks	2.61 (0.98–6.92), p = 0.044	
Montes 2014 (16)	Infliximab	246	*FcGR2A*	EULAR at 3 months*	0.51 (0.32–0.81), p = 0.005	SNaPshot
	Adalimumab/ etanercept	164	*FcGR2A*	EULAR at 3 months*	Frequencies are not showed, p > 0.05	Multiplex Kit
Tutuncu 2005 (12)	Etanercept/ adalimumab/ infliximab	30	*FcGR3A*	No EULAR no ACR criteria 3 months	12.0 (0.63–226.5), p < 0.01	PCR-based specific method
Morales-Lara 2010 (13)	Infliximab	41	*FcGR3A*	ACR ≥ 20 at 12 months	4.27 (0.82–22.07), p = 0.0392	PCR and RFLP
				EULAR at 3 months*	2.84 (0.43–18.73), p = 0.130	
				ACR at 3 months	0.48 (0.12–1.89), p = 0.239	
Kastbom 2006 (14)	Infliximab/etanercept	282	*FcGR3A*	ACR 20 at 3 months ACR50 at 3 months ACR70 at 3 months EULAR at 3 months	Frequencies are not showed p = 0.8 p = 0.6 p = 0.9 data not showed	PCR and HPLC

Table 5.1 continues on next page.

Table 5.1: ***Continued***

Ref	Anti-TNF	n	Genotype	Endpoints	OR (95% CI), p-value (Low affinitiy genotype vs No-low affinity genotypes) (RR vs no RR for 2A, FF vs no FF for 3A)**	Genotyping methods
Criswell 2004 (15)	Etanercept	457	*HLA-DRB1* *TNF* *LTA* *TNFRSF1A* *TNFRSF1B* *FcGR2A* *FcGR3A* *FcGR3B*	ACR50 at 12 months	Frequencies are not showed	PCR and HPLC
Rooryck (23)	Infliximab	78	*FcGR3A* *TNFRSF1B* 	 ACR20 ACR50 ACR70	Frequencies are not showed p = 1 p = 0.924 p = 0.813	Primers designed and ABI-PRISM®
Sarsour (24)	Anti-TNF	390	*FcGR3A*	Changes in CDAI	Frequencies are not showed p > 0.05	Taqman®
Tsukahara (25)	Infliximab	33	*FcGR3A*	EULAR at 22 weeks	7.88 (0.34–183), p = 0.02	Taqman®

ACR, American College of rheumatology criteria; EULAR, European league against rheumatism.
* Response were considered good and moderate response.
** (RR vs no RR for 2A and FF vs no FF for 3A).

was subcutaneously administered at a dose of 40 mg every two weeks. The study protocol was approved by the ethics committee of the Leiden University Medical Center and all patients provided written informed consent.

Clinical evaluation

Clinical response was evaluated at 14 weeks and categorized in good response and remission according to EULAR criteria (26). Primary endpoint in our study was EULAR good response defined as a change of DAS28 > 1.2 and DAS28 at 14 weeks ≤ 3.2. EULAR remission was an exploratory endpoint defined as achieving DAS28 at 14 weeks ≤ 2.6.

FcGR2A and *FcGR3A* genotyping

After inclusion and with patients' written consent, 2 ml saliva samples were obtained for DNA extraction. Specifically, saliva samples were collected using OrageneTM DNA self-collection kit (DNA Genoteke Inc., Ottawa, Ontario, Canada) according to standard procedures. Isolation of DNA was performed according to manufacturer's prescription, quantified using nanodrop (Isogen, Maarsssen, The Netherlands) and diluted to 10 (ng/ul). *FcGR2A* rs1801274 and *FcGR3A* rs396991 were genotyped using pre-designed TaqMan® genotyping assays technology from Life Technologies and analyzed on a ViiA7® Real-time PCR system (Life Technologies, Bleiswijk, The Netherlands). Recently it was shown that standard genotyping methods are not always specific for *FcGR3A* but may co-amplify *FcGR3B* as well. Therefore, *FcGR3A* was also genotyped using a validated pyrosequencing method as described previously (22). Results for Taqman and pyrosequencing were in 100% concordance.

Statistical analysis

The statistical analysis was performed using SPSS v.20 (SPSS, Chicago, Illinois, USA). Initially SNPs were explored for associations under allelic and genotypic model using chi-square tests. The model that best described the data was selected and used for further analysis. Odds ratios (OR) and 95% confidence intervals (CI) were obtained according to Woolf's method (28). Hereafter, the potential influence of clinical and epidemiological factors including age, gender, concomitant MTX therapy and DAS28 at baseline on the clinical outcome was evaluated by logistic regression models. Since the study from which our data originate was not primarily designed to investigate the effect of *FcGR* genetic polymorphisms we performed a post-hoc power calculation.

Our study had a power of 97.4% (α = 0.025) to detect a 50% difference in response rate for carriers of the *FcGR2A*-RR compared to carriers of the *FcGR2A*-HR and *FcGR2A*-HH genotype.

Results were adjusted for age, gender, concomitant MTX and DAS28 at baseline. To correct for testing the effect of two independent genes (*FcGR2A* and *FcGR3A*) p-values lower than 0.025 were considered statistically significant.

RESULTS

Demographic and clinical features

For a total of 302 RA patients receiving adalimumab therapy a DNA sample was available. Clinical and demographic data and the distribution of *FcGR2A* and *FcGR3A* genotypes are shown in Table 5.2 and are similar to that reported for other Caucasian populations (14, 29, 30).

RA patients were aged (mean ± SD) 58.5 ± 11.5 years, 71.5% were female. The mean disease activity (DAS28) at baseline was 5.8 ± 0.97. The 82.1% of patients received concomitant MTX with an average dose of 22.36 ± 5.61 mg. In this cohort, 53 patients (17.9%) used adalimumab as monotherapy during evaluation period. Demographic, genetic and clinical characteristics are presented in Table 5.2.

EULAR response in RA patients

After 14 weeks of treatment with adalimumab 53.6% (162 out of 302 patients) and 31.1% (94 out of 302 patients) of the patients showed good response and remission response according to the EULAR criteria, respectively.

Genotype frequencies of *FcGR2A* and *FcGR3A*

Patients were genotyped for *FcGR2A*:p.Arg131His with a success rate of 94%. Genotype distribution was RR 29.8%, RH 47.4% and HH 22.80%. The call rate for *FcGR3A* p.Phe158Val was 94%, and genotype distribution was FF 38.54%, FV 45.18% and VV 16.28%. Genotype frequencies of both genes were in Hardy-Weinberg equilibrium (*FCGR2A* p = 0.38 and *FCGR3A* p = 0.32) and were similar to previously reported frequencies (6, 22).

Table 5.2: Epidemiological, clinical and genetic features of the study cohort (baseline and at 14 weeks)

Characteristics	Value
Number of RA patients	302
Age start-years (mean, SD)	58.5 (11.56)
Gender-female (%)	216 (71.5)
Concurrent MTX (%)	248 (82.1)
MTX dose/week in mg (mean, SD)	22.36 (5.61)
Previous biological agent (%)	12 (4.0)
SJC	
Baseline (mean, SD)	9.89 (4.93)
14 weeks (mean, SD)	2.56 (2.48)
TJC	
Baseline (mean, SD)	11.51 (7.63)
14 weeks (mean, SD)	2.35 (2.74)
ESR	
Baseline (mean, SD)	31 (23.5)
14 weeks (mean, SD)	16.38 (14.04)
VAS	
Baseline (mean, SD)	70.32 (17.17)
14 weeks (mean, SD)	25.83 (14.94)
DAS28	
Baseline (mean, SD)	5.80 (0.97)
14 weeks (mean, SD)	3.12 (1.10)
ΔDAS (mean, sd)	2.67 (1.02)
%change in DAS28 at 14 weeks (mean, SD)	47.71 (16.40)
Genotypes, n (%)	
*FcGR*2A	
GG (HH)	69 (22.8)
GA (HR)	143 (47.4)
AA (RR)	90 (29.8)
*FcGR*3A	
CC (VV)	49 (16.28)
CA (VF)	137 (45.51)
AA (FF)	115 (38.21)

SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate.

Association of *FcGR2A* and *FcGR3A* polymorphisms with response to anti-TNF-therapy

When comparing allelic frequencies between responders and non-responders, the presence of the *FcGR2A**R allele was associated with EULAR good response at 14 weeks (p = 0.017, OR = 1.53, 95% CI 1.08–2.17) (Table 5.3).

Table 5.3: Genotype distributions and allele frequencies of the *FcGR2A* (R>H) and *FcGR3A* (F>V) genetic variants in responder and non-responder RA patients treated with adalimumab at 14 weeks

		Genotype, N (%)			Allele test				
	Subgroup (N)	RR	RH	HH	R allele frequency (%)	p-value	OR (95% CI)	p-value*	OR (95% CI)*
FcGR2A	Good response (n = 162)	56 (35)	75 (46)	31 (19)	57.7	**0.026**	**1.43 (1.04–1.98)**	**0.017**	**1.53 (1.08–2.17)**
	No good response (n = 140)	34 (24)	68 (49)	38 (27)	48.6				
	Remission (n = 94)	33 (35.1)	38 (40.4)	23 (24.5)	55.3	0.54	1.11 (0.78–1.57)	0.56	1.18 (0.76–1.63)
	No remission (n = 208)	57 (27.4)	105 (50.5)	46 (22.1)	52.6				
	Subgroup (N)	FF	FV	VV	F allele frequency (%)	P-value	OR (95% CI)	P-value*	OR (95% CI)*
FcGR3A	Good response (n = 160)	61 (38.1)	70 (43.8)	29 (18.1)	60	0.61	0.92 (0.66–1.27)	0.87	1.03 (0.72–1.47)
	No good response (n = 141)	54 (38.3)	67 (47.5)	20 (14.2)	62.1				
	Remission (n = 93)	40 (43)	38 (40.9)	15 (16.1)	63.4	0.40	0.86 (0.61–1.23)	0.17	0.76 (0.51–1.13)
	No remission (n = 208)	75 (36.1)	99 (47.6)	34 (16.4)	36.6				

Odds ratio for the comparison between responder and non-responder patients.
* Adjusted by age, gender, concomitant MTX and DAS28 at baseline.

These differences were not observed for remission response. No significant associations were found for the *FcGR3A* polymorphism and good response or remission (Table 5.3).

To analyze the potential combined effect of the 2 SNPs, we also performed a combined analysis. The number of low-affinity alleles (FcGR*2A*-R and FcGR*3A*-F) per patient was calculated, ranging from 0 to 4, where 0 indicates the absence of low affinity alleles (HHVV genotype) and 4 indicates the presence of 4 low-affinity alleles (RRFF). The number of low-affinity alleles in a regression model showed a trend towards association with good response ($p = 0.041$, OR = 1.38, 95% CI 1.01–1.89, $R^2 = 0.19$) at 14 weeks (adjusted for age, gender, concomitant MTX and DAS28 baseline).

DISCUSSION

To the best of our knowledge this is the first study to investigate the influence of *FcGR2A* and *FcGR3A* genes on treatment response in a cohort of RA patients using adalimumab as the anti-TNF drug. Our results indicate that the *FcGR2A* genotype shows a trend towards association with clinical efficacy of adalimumab defined as EULAR good response at 14 weeks. Low-affinity *FcGR2A*-R* allele shows a better EULAR good response at 14 weeks. However, we did not find an association with good response or remission response for the *FcGR3A* genotype. Recently, Montes et al. (16) reported a significant association between the *FcGR2*A polymorphism and response to treatment with infliximab at three months, but they could not find such an association combining etanercept and adalimumab treated patients. Unfortunately, no analysis of patients treated with adalimumab or treated with etanercept could be performed separately because these two groups consisted of too small numbers of patients. In our study we were able to include 302 patients treated with adalimumab, the largest sample size for a pharmacogenetic study of adalimumab treated patients published to date.

Previously, three papers studying the association of *FcGR3A* polymorphisms and response to anti-TNF drugs have been published (12-14). In a small study consisting of 30 RA patients, Tutuncu et al. (12) found that patients with *FcGR3A*-FF genotype had a better response to several anti-TNF drugs after 12 weeks than those carrying at least one *FcGR3A*-V allele. However, the response to therapy was not evaluated according to accepted standards such as the EULAR criteria. In contrast, Morales-Lara et al. (13) found no significant association between the *FcGR3A*-FF and good response-EULAR or ACR20 criteria at 3 months in their small cohort of 41 RA patients treated with infliximab, but the genotype was associated with ACR20 response at 12 months using ACR criteria. Kastbom et al. (14) did not find

an association between *FcGR3*A genotype and efficacy in 282 RA patients treated with infliximab or etanercept using ACR criteria. We also analyzed the combined influence of low-affinity alleles (*FcGR2A*-R and *FcGR3A*-F) since anti-TNF drugs are affected by both of these FcGR. A linear regression model showed a trend towards association between the number of low-affinity alleles and EULAR good response but not for remission. Low-affinity alleles may additively result in decreased FcGR-mediated drug clearance of adalimumab. Indeed, in a pharmacokinetic study it was shown that RA patients with low-affinity *FcGR2A* and *3A* alleles showed a decreased clearance of infliximab (18). In our study we did not collect plasma for adalimumab drug level measurement and therefore we cannot associate our genetic findings with pharmacokinetic endpoints. The applied additive genetic model for *FcGR2*A and *FcGR3*A is one of the possible interactions between these two gene variants. However, a comprehensive test of all potential models is not feasible given the sample size of our study. In addition, other epistatic interactions and copy number variation of *FcGR* genes may also affect ADCC, but this is not taken into account in this study.

A recent meta-analysis (31) demonstrated that *FcGR*3A polymorphism is not associated with anti-TNF therapy but was associated with rituximab. Despite showing similar results to ours in terms of anti-TNF therapy, heterogeneity, confounding factors and different criteria used for evaluating the response, may affect the meta-analysis.

Interestingly, Morales-Lara et al. (13) studied the role of *FcGR3A* in the response to infliximab in patients with psoriatic arthritis and ankylosing spondylitis and unexpectedly found that the high-affinity-V158 allele was associated with a better response to infliximab in patients with ankylosing spondylitis. In addition, in a recent publication (6) the presence of high-affinity alleles of *FcGR2A* and *FcGR3A* was significantly associated with a better response in the intermediated point of treatment but not at the end of the treatment in 70 PsA patients treated with different anti-TNF drugs suggesting that ADCC-mediated apoptosis of TNF-bearing cells by natural killer cells and macrophages might induce a faster clearance of milder lesions than those with higher score disease. These results suggest that the role of *FcGR* polymorphisms in response to anti-TNF drugs may be dependent on the disease as well.

The limitations of our study include the lack of analysis of drug blood levels and the presence of anti-drugs antibodies. Also, the period studied could also have influence on the results. It was shown that adalimumab levels varied widely among ankylosing spondylitis patients, however, some of them improved based on clinical measurements despite low adalimumab levels (32). Recently it has been shown that genetic variants in other genes including *NLRP3* (rs4612666) and *INFG* (rs2430561) are also associated with

anti-TNF response (33). Further studies taking these factors into account are needed in an independent cohort to establish a robust pharmacogenetic marker. However, this is the largest study of RA patients treated with adalimumab published to date.

In conclusion, the presence of the low affinity *FcGR2A** R-allele is associated with EULAR good response at 14 weeks in adalimumab treated of RA patients. The combined effect of both *FcGR*2A and *FcGR3A* SNPs showed a trend for association with EULAR good response. These results indicate that *FcGR* polymorphisms could be a determinant of adalimumab efficacy in RA patients.

SUMMARY POINTS

- This is the largest study investigating the relation between *FcGR* polymorphisms and treatment response in a cohort of RA patients receiving adalimumab.
- By comparing allelic frequencies between responders and non-responders, the presence of the *FcGR2A**R allele was associated with EULAR good response at 14 weeks.
- No significant associations were found for the *FcGR3A* polymorphism and good response or remission.
- The combined number of low affinity *FcGR2A* and *FcGR3A* alleles tends to be associated with good response in adalimumab treatment of RA patients.
- Further studies taking these factors into account are needed to establish a robust pharmacogenetic marker.

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ERRATUM

The article "FcGR genetic polymorphisms and the response to adalimumab in patients with rheumatoid arthritis" by Cristina Lucía Dávila-Fajardo et al. (Pharmacogenomics (2015) 16(4), 373–381) contained an error.

For the SNP in *FcGR2A* (A131>G; rs1801274) the A (H) and G (R) alleles were incorrectly assigned. As a result, the conclusion of the article changes. The high affinity allele (*FcGR2A-H*) instead of the low affinity allele (*FcGR2A-R*) is associated with good response at 14 weeks (p = 0.017, OR: 1.53, 95% CI: 1.08–2.17, adjusted by age, gender, concomitant methotrexate and DAS28 at baseline). Similarly, the potential combined effect of the two SNPs changes. The number of high-affinity alleles (*FcGR2A*-H and *FcGR3A*-V) per patient was calculated, ranging from 0 to 4, where 0 indicates the absence of high-affinity alleles (RRFF genotype) and 4 indicates the presence of four high-affinity alleles (HHVV). After regression analysis with the correct allele assignments, the number of high-affinity alleles no longer shows a trend for association with good response at 14 weeks (p-value = 0.095, OR: 1.19, 95% CI: 0.97–1.48, R^2 = 0.19, instead of p-value = 0.041, OR: 1.38, 95% CI: 1.01–1.89, R^2 = 0.19, adjusted for age, gender, concomitant MTX and DAS28 baseline).

A potential explanation for the association of *FcGR2A-H* with good response is that the action of high affinity alleles of *FcGR2A-H131* might lead to enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) of pathogenetically relevant cells expressing TNF on their membranes, producing a more rapid clinical response. In fact, ADCC-mediated apoptosis of TNF-bearing cells by natural killer cells and macrophages has been pointed out as a relevant mechanism of action of TNF blockers in RA and psoriasis.

We would like to acknowledge dr. Gilles Thibault for bringing this erroneous allele assignment to our attention and for the fruitful and constructive discussion afterwards in preparing this erratum.

Table 5.2 (corrected): Epidemiological, clinical and genetic features of the study cohort (baseline and at 14 weeks)

Characteristics	Value
Number of RA patients	302
Age start-years (mean, SD)	58.5 (11.56)
Gender-female (%)	216 (71.5)
Concurrent MTX (%)	248 (82.1)
MTX dose/week in mg (mean, SD)	22.36 (5.61)
Previous biological agent (%)	12 (4.0)
SJC	
Baseline (mean, SD)	9.89 (4.93)
14 weeks (mean, SD)	2.56 (2.48)
TJC	
Baseline (mean, SD)	11.51 (7.63)
14 weeks (mean, SD)	2.35 (2.74)
ESR	
Baseline (mean, SD)	31 (23.5)
14 weeks (mean, SD)	16.38 (14.04)
VAS	
Baseline (mean, SD)	70.32 (17.17)
14 weeks (mean, SD)	25.83 (14.94)
DAS28	
Baseline (mean, SD)	5.80 (0.97)
14 weeks (mean, SD)	3.12 (1.10)
ΔDAS (mean, sd)	2.67 (1.02)
%change in DAS28 at 14 weeks (mean, SD)	47.71 (16.40)
Genotypes, n (%)	
*FcGR*2A	
GG (RR)	69 (22.8)
GA (HR)	143 (47.4)
AA (HH)	90 (29.8)
*FcGR*3A	
CC (VV)	49 (16.28)
CA (VF)	137 (45.51)
AA (FF)	115 (38.21)

SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate.

Table 5.3 (corrected): Genotype distributions and allele frequencies of the *FcGR2A* (R>H) and *FcGR3A* (F>V) genetic variants in responder and non-responder RA patients treated with adalimumab at 14 weeks

		Genotype, N (%)			Allele test				
	Subgroup (N)	HH	RH	RR	H allele frequency (%)	p-value	OR (95% CI)	p-value*	OR (95% CI)*
FcGR2A	Good response (n = 162)	56 (35)	75 (46)	31 (19)	57.7	**0.026**	**1.43 (1.04–1.98)**	**0.017**	**1.53 (1.08–2.17)**
	No good response (n = 140)	34 (24)	68 (49)	38 (27)	42.3				
	Remission (n = 94)	33 (35.1)	38 (40.4)	23 (24.5)	55.3	0.54	1.11 (0.78–1.57)	0.56	1.18 (0.76–1.63)
	No remission (n = 208)	57 (27.4)	105 (50.5)	46 (22.1)	52.6				
	Subgroup (N)	VV	FV	FF	V allele frequency (%)	P-value	OR (95% CI)	P-value*	OR (95% CI)*
FcGR3A	Good response (n = 160)	29 (18.1)	70 (43.8)	61 (38.1)	40	0.61	1.09 (0.78–1.52)	0.86	1.04 (0.71–1.50)
	No good response (n = 141)	20 (14.2)	67 (47.5)	54 (38.3)	60				
	Remission (n = 93)	15 (16.1)	38 (40.9)	40 (43)	36.6	0.40	0.86 (0.61–1.23)	0.17	0.76 (0.52–1.13)
	No remission (n = 208)	34 (16.4)	99 (47.6)	75 (36.1)	63.4				

Odds ratio for the comparison between responder and non-responder patients.
* Adjusted by age, gender, concomitant MTX and DAS28 at baseline.