# *FCGR2A/CD32A* and *FCGR3A/CD16A* Variants and EULAR Response to Tumor Necrosis Factor-α Blockers in Psoriatic Arthritis: A Longitudinal Study with 6 Months of Followup

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***ABSTRACT.*** ***Objective.*** The efficacy of antibody-based biological therapies currently used in psoriatic arthritis (PsA) depends not only on their blocking effect on the targeted molecule but also on their binding affinity to genetically defined variants of cell-surface Fc-γ receptors. Our objective was to assess the potential influence of functionally relevant *FCGR2A/CD32A* (H131R) and *FCGR3A/CD16A* (V158F) genetic polymorphisms on the EULAR response to tumor necrosis factor-α (TNF-α) blocker therapy in PsA.

***Methods.*** In total 103 patients with PsA starting anti-TNF-α therapy were included. The efficacy of therapy was evaluated according to EULAR response criteria at 3 and 6 months. *FCGR2A*-R131H and *FCGR3A*-F158V polymorphisms were genotyped. Potential correlations between clinical response and the *FCGR2A*-R131H and *FCGR3A*-F158V polymorphisms were evaluated.

***Results.*** EULAR response (moderate plus good) was 85.4% at 3 months and 87.4% at 6 months, while good EULAR response was 61.2% and 62.1%, respectively. More patients with high-affinity *FCGR2A* genotypes (homozygous or heterozygous combinations) achieved a EULAR response at 6 months compared to patients with the low-affinity genotype (RR; p = 0.034, adjusted comparison error rate < 0.025). This association was due mainly to the group of patients treated with etanercept. No correlation was found for the *FCGR3A* polymorphism. Similarly, no effect of C-reactive protein levels was observed.

***Conclusion.*** Our data indicate that *FCGR2A* polymorphism may influence the response to TNF-α blockers (namely etanercept) in PsA in a direction opposite to that previously found in patients with rheumatoid arthritis. (First Release April 1 2012; J Rheumatol 2012;39:1035–41; doi:10.3899/jrheum.110980)

*Key Indexing Terms:*
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The use of therapies targeting the key proinflammatory cytokine tumor necrosis factor-α (TNF-α) has greatly improved the standard of care for the treatment of psoriatic arthritis (PsA) and other immune-mediated inflammatory disorders. Currently, 4 TNF-α blockers are licensed to treat PsA: infliximab (a mouse/human chimeric monoclonal antibody),

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adalimumab and golimumab (human monoclonal antibodies), and etanercept (a fusion protein consisting of a dimer of the extracellular portion of the p75 TNF-α receptor linked to the Fc portion of human IgG1). The Fc portion of these biological agents binds specifically to cell-surface Fc-γ receptors (*FCGR*) and this may affect their half-life and certain innate and adaptive immune responses, such as phagocytosis and/or antibody-dependent cellular cytotoxicity. There are differences in the structural composition of monoclonal antibodies (which are composed of a whole IgG1 molecule) and soluble receptor (lacking the hinge region and CH1 of the IgG1 molecule). That means that etanercept is likely to begin complement activation but perhaps is not able to sustain it over time. On the other hand, these 4 molecules exhibit CH2 and CH3 regions that allow all 4 drugs to develop antibody-dependent cellular cytotoxicity responses, although once again experiments show that etanercept seems to need a higher concentration to reach the same responses as monoclonal antibodies. Together, these data point to a more profound effect of monoclonal antibodies on levels of TNF (transmembrane and soluble form)[1].

Three major classes of human FCGR have been reported, encompassing 8 genes (*FCGR1A*, *B* and *C*; *FCGR2A*, *B*, and *C*; *FCGR3A* and *B*), all mapping to chromosome 1[2]. Some of these genes display functional allelic polymorphisms generating further molecular heterogeneity and interindividual differences in the effector properties of the receptors. *FCGR2A* encodes for the most widely expressed FCGR (found in most myeloid cells and platelets), and presents a single-nucleotide polymorphism (SNP) in the membrane-proximal Ig-like domain, resulting in either arginine (R) or histidine (H) at position 131, which affects receptor affinity for IgG immune complexes[3]. Consequently, the most striking difference between the *FCGR2A*-131H and R alleles is in their affinity for human IgG2 and, to a lesser degree, for IgG1 and IgG3, which is higher for H alleles[4]. A similar situation applies to the *FCGR3A* receptor expressed mainly on macrophages and natural killer cells. An SNP resulting in either phenylalanine (F) or valine (V) at position 158 also affects binding to IgG; the *FCGR3A*-158V allele binds more avidly to the IgG1, IgG3, and IgG4 subclasses[5]. In addition, it has been reported that the *FCGR3A* polymorphism implies differences not only in receptor affinity but also in levels of surface receptor expression[6].

PsA, which occurs in up to one-third of patients with psoriasis, is a chronic immune-mediated inflammatory disease that can lead to damage of articular cartilage and bone. It is characterized by a heterogeneous range of clinical manifestations, including peripheral arthritis, enthesitis, dactylitis, sacroiliitis, and/or vertebral inflammation, together with nail and skin psoriasis[7]. It has been demonstrated that TNF-α blocker agents are effective for the whole range of PsA manifestations, slowing radiographic progression and improving patients' quality of life. However, > 30% of patients show low or no response[8]; this might be due, at least in part, to the heterogeneity of the *FCGR*. Polymorphisms resulting in a higher/lower affinity to the Fc region of TNF blockers may modulate both their half-life and cellular effects, and may therefore produce different therapeutic effects, as shown in patients with rheumatoid arthritis (RA)[9,10].

Our objective was to assess the influence of the *FCGR2A*-H131R and *FCGR3A*-V158F genetic polymorphisms on the European League Against Rheumatism (EULAR) response to biological therapy in patients with PsA.

## MATERIALS AND METHODS

*Study population*. This was an observational multicenter study. Patients diagnosed with PsA according to the CASPAR criteria[11], excluding the pure axial form, and treated with anti-TNF-α agents (infliximab, etanercept, or adalimumab; golimumab was still not approved for PsA) at 3 Spanish public hospitals (Hospital Clínic, Barcelona, Hospital Juan Canalejo, La Coruña, and Hospital Clínico, Salamanca) were included. The Ethics Committee of the Hospital Clínic approved the study and written informed consent was obtained from all participants.

All patients had PsA that was nonresponsive to conventional disease-modifying antirheumatic drug therapy (methotrexate 15–25 mg/week) and started anti-TNF-α therapy according to Spanish recommendations for the management of PsA[12]. All information provided referred to the first anti-TNF-α treatment. At inclusion, the Psoriasis Global Assessment (PGA) score was taken. At Months 3 and 6 of treatment, the number of tender and swollen joints, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP; mg/dl, by nephelometry) were recorded. Disease activity was evaluated by the 28-joint Disease Activity Score (DAS28) using 3 variables, including CRP (DAS28 3v-CRP).

At baseline, HLA-B27 typing by polymerase chain reaction (PCR) was performed, as well as quantification of rheumatoid factor (RF, by nephelometry; positive > 25 IU/ml) and anticitrullinated peptide antibodies (ACPA) by Immunoscan-RA Mark-2 ELISA (Eurodiagnostica, Malmö, Sweden) according to the manufacturer's instructions (positive > 50 IU/ml).

DAS28 response was analyzed by change from baseline, and the efficacy of therapy at 3 and 6 months was classified using the EULAR criteria response categories[13], which classify patients as good, moderate, or nonresponders using the individual amount of change in the DAS28 and the DAS28 final value. DAS28 improvement > 1.2 with final DAS28 ≤ 3.2 is considered indicative of a good response, an improvement of 0.6 with DAS28 final > 3.2 a moderate response, and an improvement ≤ 0.6 or > 0.6 and ≤ 1.2 with a DAS28 final value > 5.1 is considered no response[13].

*Determination of FCGR polymorphisms*. Genomic DNA was purified from EDTA blood samples using the Qiagen DNA blood kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. The biallelic polymorphism *FCGR2A*-H131R was assessed using a PCR sequencing-based typing method. Briefly, a 367-bp genomic DNA fragment was amplified by PCR using the intronic sense 5'- CTT TCA GAA TGG CTG GTG CT-3' and the antisense 5'-TTT GCT GCT ATG GGC TTTCT-3' primer pairs. The PCR reaction mix included 50–200 ng DNA, 10 pmol primers, 1 U Expand 20 kb Plus Taq DNA polymerase (Roche Diagnostics GmbH, Mannheim, Germany), and 0.5 mM dNTPs, diluted in Expand 20 kb Plus buffer at a final volume of 20 $\mu$l. The cycling conditions were 1 cycle of 94°C for 5 min; 10 cycles of 94°C for 30 s; 65°C for 30 s and 72°C for 60 s; 25 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 60 s; and 1 cycle of 72°C for 7 min. Five microliters of the resulting amplicons were treated with ExoSAP-IT (USB Corporation, Cleveland, OH, USA) and were directly sequenced using the BigDye Terminator version 1.1 cycle sequencing kit (Applied Biosystems, Warrington, UK) according to the manufacturer's instructions, with the sense gene-specific primers noted above. Sequencing reactions were analyzed by capillary electrophoresis in an ABI Prism 3100 Genetic DNA Analyser (Applied Biosystems). An allele-specific PCR method was used to genotype the biallelic functional *FCGR3A*-V158F polymorphism with some modifica-

tions[14]. Amplicons were visualized by electrophoresis on agarose gel with ethidium bromide staining and ultraviolet illumination.

*Statistical analysis*. Quantitative variables were described using medians and interquartile range (IQR) and qualitative variables using frequencies and percentages.

Comparisons between groups were made using the Kruskal-Wallis or Wilcoxon rank-sum test for quantitative variables and Fisher's exact test for qualitative variables.

Changes in the swollen joint count during the followup (dichotomized into none and ≥ 1) were analyzed using the generalized estimating equation model. Low/high-affinity alleles for *FCGR2A* or *FCGR3A* were also evaluated as independent variables and their interaction with the followup visits was assessed. Pairwise comparisons were used to assess the association between *FCGR2A* or *FCGR3A* and EULAR response at 3 and 6 months in patients treated with etanercept and those treated with infliximab or adalimumab. The random-effects regression model was used to estimate the change in CRP over time and whether the change differed between low/high affinity groups.

To evaluate whether CRP level (high/normal) had an effect on the relationship between *FCGR2A* and EULAR response we tested the interaction between EULAR response and CRP at 3 and 6 months using a logistic regression model.

For all tests, the level of significance was established as $p = 0.05$, except for pairwise comparisons, for which $p < 0.025$ was used. All statistical analyses were performed using Stata 10 (StataCorp., College Station, TX, USA).

## RESULTS

*Clinical and biological characteristics of the patient population*. A total of 103 patients with PsA were included. Clinical and demographic data and the distribution of *FCGR2A* and *FCGR3A* genotypes are shown in Table 1. Patients were treated with the TNF-α blockers etanercept (53.4%), infliximab (33%), and adalimumab (13.6%). Etanercept was administered subcutaneously (SC) 50 mg/week; adalimumab SC 40 mg/every other week; and infliximab intravenously 5 mg/kg at Weeks 0, 4, and 6, and then each 8 weeks.

Fifty-four percent of patients were male, with a median age at inclusion of 49 (IQR 41, 59) years, disease duration 12 (IQR 8, 17) years, CRP 1.3 (IQR 0.67, 2.84) mg/dl, ESR 26 (IQR 11, 46) mm/h, and DAS28 4.62 (IQR 3.78, 5.46). Twenty-four out of 103 patients (23.3%) were HLA-B27-positive. RF was positive in 6 patients (5.8%; all < 80 IU), and ACPA was positive in 4 patients (3.9%; all < 100 IU).

A total of 81.6% of patients had a peripheral arthritis pattern (30% oligoarthritis, ≤ 4 inflamed joints; and 51.6% polyarthritis, > 4 inflamed joints) without axial inflammation, and 18.4% had a mixed pattern (peripheral arthritis plus axial disease defined by radiological sacroiliitis and inflammatory back pain). The PGA score at inclusion was 23% clear, 20% minimal, 32% mild, 19% moderate, and 6% severe psoriasis.

*EULAR response*. A EULAR response (moderate plus good) was achieved by 85.4% of patients at 3 months and 87.4% at 6 months. A good response was reached by 61.2% and 62.1% of patients, respectively. Disease remission, defined as DAS28 < 2.6, was achieved by 42% of patients at 3 months and 65% at 6 months (Table 2).

*Association of FCGR2A/3A variant combinations with EULAR response*. The presence of the high-affinity *FCGR2A*-131H allele in either homozygous or heterozygous combinations (HH and HR) was associated with a EULAR response (moderate and/or good) at 6 months compared to patients homozygous for low-affinity variants (RR: 91% vs 73%; pairwise p = 0.030; Table 2). When we analyzed the association between EULAR moderate or good response at Month 3 and 6 and low-affinity variants (RR) of *FCGR2A* by logistic regression, a strong trend to significance remained (OR 0.273, 95% CI 0.070, 1.073, p = 0.063). No association

*Table 1*. Clinical and demographic data of patients with PsA according to FCGR genotypes. Data are expressed as median (interquartile range); qualitative data as frequency (%).

| Characteristic | All Patients, n = 103 | *FCGR2A* HH, n = 32 (31.1%) | HR, n = 49 (47.6%) | RR, n = 22 (21.4%) | *FCGR3A* VV, n = 21 (20.4%) | VF, n = 56 (54.4%) | FF, n = 26 (25.2%) |
|---|---|---|---|---|---|---|---|
| Age, yrs | 49.0 (41–59) | 47.5 (41–57) | 50.0 (43–56) | 45.5 (40–61) | 44.0 (38–49) | 49.0 (42.5–56) | 54.0 (42–62) |
| Female (%) | 49 (47.6) | 16 (50.0) | 19 (39.0) | 14 (64.0) | 9 (43.0) | 24 (43.0) | 16 (62.0) |
| PsA onset age, yrs | 35 (26–42) | 35 (27–42.5) | 36 (26–42) | 30.5 (24–50) | 30 (25–37) | 36.5 (26–42) | 37.5 (26–48) |
| PsA duration, yrs | 12 (8–17) | 13 (9–17) | 11 (8–17) | 12.5 (8–18) | 13 (10–15) | 11 (7–16.5) | 14 (10–20) |
| PsA pattern (%) | | | | | | | |
| Peripheral* | 84 (81.6) | 23 (72.0) | 43 (88.0) | 18 (82.0) | 16 (76.0) | 46 (82.0) | 22 (85.0) |
| Mixed** | 19 (18.4) | 9 (28.0) | 6 (12.0) | 4 (18.0) | 5 (24.0) | 10 (18.0) | 4 (15.0) |
| TNF-α blocker used (%) | | | | | | | |
| Infliximab | 34 (33.0) | 11 (34.0) | 15 (31.0) | 8 (33.0) | 9 (43.0) | 19 (34.0) | 6 (23.0) |
| Etanercept | 55 (53.4) | 16 (50.0) | 27 (55.0) | 12 (55.0) | 10 (48.0) | 28 (50.0) | 17 (65.0) |
| Adalimumab | 14 (13.6) | 5 (16.0) | 7 (14.0) | 2 (9.0) | 2 (10.0) | 9 (16.0) | 3 (12.0) |
| DAS28 | | | | | | | |
| Baseline | 4.62 (3.78–5.46) | 4.59 (3.75–5.53) | 4.67 (4.00–5.29) | 4.54 (3.43–5.46) | 4.37 (3.68–4.91) | 4.68 (3.86–5.46) | 4.73 (3.82–5.60) |
| 3 mo | 2.46 (1.82–3.49) | 2.37 (1.87–3.23) | 2.65 (1.93–3.54) | 2.09 (1.73–3.07) | 2.16 (1.55–3.24) | 2.62 (1.82–3.56) | 2.34 (2.10–3.10) |
| 6 mo | 2.26 (1.73–3.44) | 2.44 (1.53–3.37) | 2.24 (1.82–3.43) | 2.40 (1.53–3.97) | 2.19 (1.55–2.94) | 2.23 (1.74–3.52) | 2.46 (2.03–3.39) |

* Peripheral: PsA patients with peripheral arthritis but without radiological sacroiliitis and inflammatory back pain. ** Mixed: PsA patients with peripheral arthritis and axial inflammation (sacroiliitis and inflammatory back pain). PsA: psoriatic arthritis; TNF-α: tumor necrosis factor-α; DAS28: 28-joint Disease Activity Score.

*Table 2*. EULAR responses of patients with psoriatic arthritis at Months 3 and 6. Patients are classified by low-affinity and high-affinity *FCGR2A* and *FCGR3A* genotypes.

| EULAR Response | *FCGR2A*, n (%) | | | | *FCGR3A*, n (%) | | | |
|---|---|---|---|---|---|---|---|---|
| | HH + HR (High affinity) | RR (Low affinity) | Total | p* | VV + VF (High affinity) | FF (Low affinity) | Total | p* |
| 3 months, n = 103 | | | | | | | | |
| None | 10 (12) | 5 (23) | 15 (15) | 0.304 | 11 (14) | 4 (15) | 15 (15) | 1.000 |
| Moderate + Good | 71 (88) | 17 (77) | 88 (85) | | 66 (86) | 22 (85) | 88 (85) | |
| 6 months, n = 103 | | | | | | | | |
| None | 7 (9) | 6 (27) | 13 (13) | 0.030 | 10 (13) | 3 (12) | 13 (13) | 1.000 |
| Moderate + Good | 74 (91) | 16 (73) | 90 (87) | | 67 (87) | 23 (88) | 90 (87) | |

* Fisher's exact test. EULAR: European League Against Rheumatism.

*Table 3*. EULAR responses of patients with psoriatic arthritis at Months 3 and 6. Patients are classified by low-affinity and high-affinity *FCGR2A* genotype and stratified by type of TNF blocker.

| EULAR Response | *FCGR2A*, n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Infliximab or Adalimumab, n = 48 | | | | Etanercept, n = 55 | | | |
| | HH + HR (High affinity) | RR (Low affinity) | Total | p* | HH + HR (High affinity) | RR (Low affinity) | Total | p* |
| 3 months | | | | | | | | |
| None | 5 (13) | 1 (10) | 6 (13) | | 5 (12) | 4 (33) | 9 (16) | |
| Moderate + Good | 33 (87) | 9 (90) | 42 (88) | 1.000 | 38 (88) | 8 (67) | 46 (84) | 0.092 |
| 6 months | | | | | | | | |
| None | 4 (11) | 2 (20) | 6 (13) | | 3 (7) | 4 (33) | 7 (13) | |
| Moderate + Good | 34 (89) | 8 (80) | 42 (88) | 0.591 | 40 (93) | 8 (67) | 48 (87) | 0.034 |

* Fisher's exact test. Pairwise comparison significance level < 0.025. EULAR: European League Against Rheumatism; TNF: tumor necrosis factor.

*Table 4*. EULAR responses of patients with psoriatic arthritis at Months 3 and 6. Patients are classified by low-affinity and high-affinity *FCGR3A* genotype and stratified by type of TNF blocker.

| EULAR Response | *FCGR3A*, n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Infliximab or Adalimumab, n = 48 | | | | Etanercept, n = 55 | | | |
| | VV + VF (High affinity) | FF (Low affinity) | Total | p* | VV + VF (High affinity) | FF (Low affinity) | Total | p* |
| 3 months | | | | | | | | |
| None | 10 (10) | 2 (22) | 6 (13) | | 7 (18) | 2 (12) | 9 (16) | |
| Moderate + Good | 35 (90) | 7 (78) | 42 (88) | 1.312 | 31 (82) | 15 (88) | 46 (84) | 0.705 |
| 6 months | | | | | | | | |
| None | 5 (13) | 1 (11) | 6 (13) | | 5 (13) | 2 (12) | 7 (13) | |
| Moderate + Good | 34 (87) | 8 (89) | 42 (88) | 0.100 | 33 (87) | 15 (88) | 48 (87) | 0.100 |

* Fisher's exact test. Pairwise comparison significance level < 0.025. EULAR: European League Against Rheumatism; TNF: tumor necrosis factor.

between the *FCGR3A* polymorphism and response to TNF-α blockers was found (Tables 2, 3, 4).

*Association of FCGR2A variant combinations with EULAR response is mainly due to patients treated with etanercept*. We stratified the *FCGR* polymorphism analysis by type of TNF-α blocker used, based on the differences in structural composition between monoclonal antibodies (infliximab and adalimumab) and soluble receptor (etanercept) that might influence the EULAR response. The presence of the high-affinity *FCGR2A*-131H allele in either homo- or heterozygous combinations (HH and HR) in patients receiving etanercept showed a strong trend to a higher rate of EULAR response compared with those without a response (93% vs 67%; pairwise p = 0.034). Patients receiving infliximab or adalimumab showed similar percentages of EULAR response (89% vs 80%; pairwise p = 0.591; Table 3).

*Analysis of effects of CRP levels on interaction between EULAR response and high/low-affinity FCGR2A/3A alleles*. CRP binds specifically to Fc-γ receptors and therefore could interfere with interaction between these receptors and TNF-α

blockers[15]. In order to ascertain whether CRP had any effect on the relationship between EULAR response and high/low-affinity alleles, we stratified patients by level of CRP (high/normal, taking normal as ≤ 1 mg/dl). Eighty-one of 103 (78.6%) patients had normal CRP, and only in this group did we find a higher number of patients with a EULAR response who had high-affinity *FCGR2A* alleles (94% HH+HR vs 69% RR; pairwise p = 0.013). No differences were found in the analysis of *FCGR3A* (data not shown).

To determine whether CRP had an effect on the relationship between EULAR response and *FCGR2A/3A*, we estimated the OR of EULAR response and CRP at 3 and 6 months and the interaction for each polymorphism using logistic regression. We found no association between CRP and *FCGR2A* or *3A* (Table 5). However, the logistic regression analysis showed a significant negative association between EULAR response at 6 months and the low-affinity *FCGR2A* alleles (RR; OR 0.138, 95% CI 0.024–0.800, p = 0.027; Table 5).

Finally, we found no evidence that disease duration (< 6 months, n = 15 vs > 6 months, n = 88) had an effect on the EULAR response (data not shown).

## DISCUSSION

The effect of *FCGR2A* and *FCGR3A* polymorphisms on clinical response to TNF-α blockers was analyzed in a cohort of patients with PsA followed for 6 months in search of genetic biomarkers of clinical response to these agents. Overall, around 85% of patients achieved a EULAR response and 60% a good EULAR response during the study period. Disease remission, defined as DAS28 < 2.6, was around 60% at 6 months, similar to values in another study[16].

*Table 5.* Interaction between EULAR response and CRP at 3 and 6 months in the logistic regression model, *FCGR2A* (low affinity vs high affinity).

| Variable | OR (95% CI) | p |
|---|---|---|
| EULAR response at 3 mo | | |
| None | 1 | |
| Moderate + good | 1.418 (0.196–10.279) | 0.730 |
| CRP at 3 mo | | |
| ≤ 1 | 1 | |
| > 1 | 0.699 (0.060–8.202) | 0.775 |
| Interaction: EULAR response with CRP (Month 3) | | |
| 0 | 1 | |
| 1 | 0.196 (0.007–5.168) | 0.329 |
| EULAR response at 6 mo | | |
| None | 1 | |
| Moderate + good | 0.138 (0.024–0.800) | 0.027 |
| CRP at 6 mo | | |
| ≤ 1 | 1 | |
| > 1 | 0.291 (0.017–4.831) | 0.389 |
| Interaction: EULAR response with CRP (Month 6) | | |
| 0 | 1 | |
| 1 | 13.527 (0.551–331.807) | 0.111 |

Significance: p < 0.05. EULAR: European League Against Rheumatism; CRP: C-reactive protein.

We found that presence of the high-affinity *FCGR2A*-131H allele in either HH or HR combinations was strongly, but non-significantly, associated with a EULAR response at 6 months, compared to homozygosity for low-affinity alleles (RR), in the pairwise comparison setting. No association was found between the *FCGR3A* polymorphism and response to TNF-α blockers.

When TNF-α blockers were stratified by structural composition, patients with high-affinity alleles of *FCGR2A* treated with etanercept (n = 55), but not those treated with monoclonal antibodies (n = 48), had higher rates of EULAR response at 6 months (pairwise p = 0.034).

Logistic regression analysis including the interaction between EULAR response, CRP level, and *FCGR2A* and *FCGR3A* polymorphisms showed a positive, statistically significant association between EULAR response at 6 months and high-affinity alleles of *FCGR2A*.

These results suggest a potential association between EULAR response at 6 months and high-affinity variants of *FCGR2A*, mainly due to the patients treated with etanercept. Demonstration of this association was difficult in our study because of the relatively small number of patients and the high rate of EULAR response achieved, which left a small margin to detect other effects on the EULAR response beyond treatment. Further, the possible effect of the *FCGR* polymorphism on the EULAR response would be rather small, as found in RA[9].

To our knowledge, no previous studies have analyzed the association between the *FCGR2A* polymorphism and the response to TNF-α blocker in patients with PsA, and there is only 1 limited study on the *FCGR3A* polymorphism[17]. That study analyzed the specific distribution of the *FCGR3A* V158F polymorphism in relation to infliximab response at 3, 6, and 12 months in 16 patients with PsA, and found that more patients with a high-affinity genotype (FV+VV) reached a EULAR response at 3 months (20% FF vs 83.3% FV-VV; p = 0.036, Fisher's test p = 0.067)[17]. Similarly, a significant association was observed between the high-affinity V allele and better response in 33 patients with ankylosing spondylitis (AS) at 6 months in terms of both genotype and allele distributions (33.3% FF vs 84.6% FV-VV; p = 0.008; and 45.4% F vs 88.2% V; p = 0.003, respectively)[17]. In accord with these results, the rs767455 polymorphism in *TNFR1A* seems to have opposite effects on the response to TNF-α blockers in PsA and RA (Conesa-Zamora P, personal communication). These findings suggest that substantial differences between PsA and RA may exist regarding the interaction with TNF-α blockers.

PsA and AS belong to the group of spondyloarthropathies (SpA), a heterogeneous group of disorders with similar clinical features including axial and peripheral arthritis, uveitis, psoriasis, and inflammatory bowel diseases, such as Crohn's disease (CD) and ulcerative colitis. These disorders also share immunogenetic and pathogenic characteristics that differ from

those of RA[18]. Interestingly, a study found that PsA and CD share common genetic control of certain inflammation pathways[19]. In CD, the genotype combinations including the high-affinity genotype (VV+VF) have been associated with a greater reduction in CRP levels in response to infliximab therapy[20], which is in agreement with our results as well as with the idea that CD and PsA share a number of pathogenetic features.

We found no association between the *FCGR3A* polymorphism and response to TNF-α blockers in PsA. Together with the results of other studies on PsA, AS, and CD[17,20], this stands in contrast to the results in RA, where 3 out of 4 published studies have found a better response in patients homozygous for low-affinity *FCGR3A* (FF) alleles[9,10,17,21]. In our previous study on RA, which had a similar sample size to our present study, low-affinity *FCGR3A* and *FCGR2A* alleles were associated with a better response to infliximab therapy[9]. We thus hypothesized that, in RA, low-affinity polymorphisms were associated with a longer half-life of infliximab and, consequently, with greater efficacy. Our results for *FCGR2A* and from the previous smaller study with *FCGR3A*[17] showing an association between higher rate of EULAR response and high-affinity alleles suggest a different type of interaction between cell-surface Fc-γ receptors and TNF-α blockers in RA compared with PsA and, probably, with other SpA. Indeed, the association between the high-affinity *FCGR2A* polymorphism and EULAR response to TNF-α blockers (mainly to etanercept) in PsA evokes that of the *FCGR2A/3A* polymorphism and good response to rituximab in patients with indolent non-Hodgkin's lymphoma (NHL), including follicular NHL and Waldenström's macroglobulinemia[22]. However, this is not the case for other associated diseases such as chronic lymphocytic leukemia or aggressive NHL, suggesting that other pathogenic disease factors influencing rituximab response could contribute to the overall outcome[23,24]. This might also be the case for the observed differences in correlation between the *FCGR2A/3A* polymorphism and response to anti-TNF-α therapy in PsA and RA.

It is feasible that binding of TNF-α blockers to high-affinity Fc-γ receptors could promote beneficial cell responses (i.e., in natural killer cells) relevant to the pathogenesis of psoriatic but not rheumatoid synovitis. In fact, a predominant macrophage type 2 (M2, alternative) response has been reported in SpA, including PsA, compared to a predominant macrophage type 1 (M1, classical) response in RA[18], which could explain the different genetic associations between the 2 diseases and the response to biological therapies.

The lack of association found with the *FCGR3A* polymorphism in our study may be partly because the efficacy of TNF-α blockers in our PsA cases was much higher than that reported for RA[9,16], and therefore the potential for the influence of the *FCGR2A* and *FCGR3A* polymorphisms on the response is lower in PsA than in RA.

We found that in PsA, in contrast to RA, high-affinity *FCGR2A* polymorphisms may be associated with a better response to TNF-α blockers, mainly etanercept. Our present and previous results suggest that, in PsA and probably also in other SpA, high-affinity interactions of TNF-α blockers with Fc-γ receptors present on certain cell populations (probably M2) would be beneficial, while the same interactions would be detrimental in RA. Further studies are needed to confirm this possibility.


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