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RESEARCH ARTICLE

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Drug survival of omalizumab in atopic asthma: Impact of clinical and genetic variables

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ABSTRACT

It is estimated that 40–50% of severe asthma has an atopic basis, representing a clinical challenge and a significant economic burden for healthcare systems. The most effective treatment has emerged with the use of biologic therapies such as omalizumab; however, the rate of therapy switching due to loss of efficacy is high, which has a negative impact on the healthcare system. The aim was to evaluate the influence of genetic polymorphisms as predictors of omalizumab survival. We conducted a retrospective observational cohort study of 110 patients with uncontrolled severe allergic asthma treated with omalizumab in a tertiary hospital. We analyzed *FCER1A* (rs2251746, rs2427837), *FCER1B* (rs1441586, rs573790, rs1054485, rs569108), *C3* (rs2230199), FCGR2A (rs1801274), *FCGR2B* (rs3219018, rs1050501), *FCGR3A* (rs10127939, rs396991), *IL1RL1* (rs1420101, rs17026974, rs1921622) and *GATA2* (rs4857855) by real-time PCR using Taqman probes. Drug survival was defined as the time from initiation to discontinuation of omalizumab. Cox regression analysis adjusted for the presence of respiratory disease, GERD, SAHS and years with asthma showed that the SNPs *FCER1B* rs573790 - CT ($p < .001$; HR = 3.38; CI95% = 1.66–6.87), *FCGR3A* rs10127939-AC ($p = .018$; HR = 3.85; CI95% = 1.25–11.81) and *FCGR3A* rs396991-CC ($p = .020$; HR = 2.23; CI95% = 1.14–4.38) were the independent variables associated with worse survival in patients diagnosed with asthma. A trend toward statistical significance was also found between and *FCGR3A* rs10127939-CC ($p = .080$; HR = 0.13; CI95% = 0.01–1.28) and longer drug survival. The results of this study demonstrate the potential influence of the polymorphisms studied on omalizumab survival and the clinical benefit that could be achieved by defining predictive biomarkers of drug survival.

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Introduction

Between 3–10% of the population with asthma suffers from severe asthma, characterized by persistent symptoms, frequent exacerbations, and a poor response to conventional therapy.[1] It is estimated that 40–50% of individuals with severe asthma have an atopic basis.[1,2] Therefore, severe asthma not only poses a clinical challenge but also generates a significant economic burden on healthcare systems. Frequent medical visits, hospitalizations, and the use of biologic therapies, contribute to an increase in healthcare costs associated with severe asthma.[1,2]

Asthma is a respiratory condition with complexity shaped by a blend of genetic, immunological, and environmental factors. From a genetic standpoint, it is suggested that 35–95% of the phenotypic variability of the disease is due to genetic inheritance. Several genes have been linked to an elevated risk of experiencing the disease.[3] Immunologically, asthma involves the activation of the immune system, leading to chronic inflammation in the airways, frequently triggered by type 2 cytokines produced by Th2 or ILC2 cells. These cytokines, including IL-4, IL-5, and IL-13, stimulate the B lymphocytes to undergo isotype switching, resulting in the production of IgE.[4] In allergic asthma, the pathogenic role of IgE depends on its binding (via the CƐ3 domains) to high-affinity (FcƐRI) and low-affinity (FcƐRII) receptors expressed by numerous cell types.[5,6]

Biologic therapies, such as omalizumab, are used to treat atopic patients with uncontrolled severe asthma. Omalizumab is a humanized IgG1 monoclonal antibody that selectively binds to IgE through the CƐ3 domain.[7] It is indicated for the treatment of uncontrolled severe asthma with an allergic phenotype in patients over 6 years of age with total IgE levels between 30–1500 IU and a forced expiratory volume in one second (FEV1) < 80%. It is administered subcutaneously in varying doses based on the patient's IgE levels and body weight.[8] Randomized clinical trials have extensively demonstrated the effectiveness of omalizumab, showing significant improvements in

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patient quality of life, reduced exacerbations, lowered systemic corticosteroid use, and diminished symptom intensity.[9–13] Although there is strong scientific evidence supporting its effectiveness and enhanced patients' quality of life, there is a high rate of switching from omalizumab biological therapy due to a loss of efficacy.[14] This has a negative impact on the healthcare system.

Pharmacogenetics could be the key to a precision medicine model that predicts drug survival (DS) in patients before treatment initiation. This is because genes involved in both the metabolism of drugs and their mechanism of action may have small abnormalities or variations that affect their proper functioning.

Pharmacogenetic studies linking allelic variants or single nucleotide polymorphisms (SNPs) to the efficacy, toxicity, or DS in asthmatic patients undergoing omalizumab treatment are limited. However, given the metabolism and mechanism of action of omalizumab, primary areas of investigation can be directed toward polymorphisms in the CƐ3 domain gene (*C3*), which is crucial for the binding of omalizumab to IgE.[7] Similarly, SNPs in genes encoding IgE receptors (*FCER1A*, *FCER1B*) may potentially induce cross-linking with IgE-FcƐR, thereby affecting its intracellular signaling. Furthermore, these SNPs may alter the expression of CƐ complement to which omalizumab binds.[15–17] SNPs in genes regulating or triggering the cytokine cascade, such as *FCGR2A*, *FCGR3A*, or *IL1RL1*, are also of interest for investigation. Omalizumab, an IgG1, selectively binds to Fc-gamma receptors (FCGR) located on the surface of B lymphocytes, dendritic cells, and macrophages. These membrane glycoproteins exert complex activation or inhibitory effects on the cellular functions of the antibody following IgG aggregation.[18,19] Finally, SNPs in transcription factor genes, such as *GATA2*, which regulates the expression of FcƐR receptors and activates IgE-mediated degranulation, may also impact omalizumab response.[20]

Currently, there are few studies exploring genetic biomarkers that predict the duration of response to omalizumab in asthmatic patients. Further studies are required to validate the potential genetic implications of these polymorphisms on the effectiveness of the treatment. Pharmacogenetics is a simple and useful tool, making this approach a promising way to address this question. Therefore, the aim of the study was to assess the influence between polymorphisms in the above-mentioned genes and omalizumab survival.

Materials and methods

We followed the methods of Cristina Membrive-Jiménez, et al. 2023[21] and the present research article was part of the thesis 'Influencia Gentica En La Respuesta A Terapias Biologicas En Pacientes Con Asma Grave No Controlada' by Dr. Rojo-Tolosa.[22]

Study design

A retrospective observational cohort study was conducted.

Ethics statement

The study was conducted with the approval of the Ethics and Research Committee of the Andalusian Health System (SAS: Andalusian Health System) in accordance with the Declaration of Helsinki (code: 0201-N-23). Participants in the study signed an informed consent for the collection and genetic analysis of saliva samples and their donation to the Biobank of the Public Health Service of Andalusia. Samples were identified using alphanumeric codes.

Study population

The study included 110 Caucasian patients from southern Spain diagnosed with severe asthma at the Respiratory Medicine Department of the Virgen de las Nieves University Hospital (HUVN) who were treated with omalizumab between 2007 and 2023 were included in the study. The duration of treatment varied among patients, with follow-up continuing until September 2023. Inclusion criteria were individuals aged 18 years or older, diagnosed with severe asthma, treated with omalizumab, and with available clinical and genetic data. After a thorough review and assessment of the inclusion criteria, 33 patients were excluded from the analysis, resulting in a study cohort of 77 patients.

Socio-demographic and clinical variables

Sociodemographic and clinical data were collected by reviewing medical records using the *Diraya Estación Clínica* software. The sociodemographic variables collected included age, sex, body mass index (BMI), smoking status, years with the disease, nasal polyps, previous respiratory disease, allergies, gastroesophageal reflux disease (GERD), sleep apnea-hypopnea syndrome (SAHS), chronic obstructive pulmonary disease (COPD), years with omalizumab, omalizumab discontinuation and the reasons for discontinuation. Patients were categorized as smokers if they had smoked or were currently smoking 100 or more cigarettes in their lifetime, as former-smokers if they had smoked 100 or more cigarettes in their lifetime but were not currently smoking, and as nonsmokers if they had never smoked or had smoked less than 100 cigarettes in their lifetime.[23]

The clinical variables collected 12 months prior to starting omalizumab treatment included doses of oral (OCS) and inhaled corticosteroids (ICS), blood eosinophil count, exacerbations requiring emergency treatment or hospitalization, baseline IgE levels, and baseline lung function measured as FEV1. OCS were recorded as cycles of OCS received by the patient in the year prior to starting omalizumab. Lung function was classified as %FEV1 < 80% or %FEV1 ≥ 80%, with values greater than 80% considered good lung function. Eosinophil counts were classified as low (<300 cells/mL) and high (≥300 cells/mL), and years of treatment with omalizumab were defined as less than 5 years or greater than or equal to 5 years, as the use of omalizumab was often discontinued after this time. Discontinuation of omalizumab was defined as discontinuation of treatment for any reason, recorded as reasons for discontinuation of omalizumab.

Genetic variables

DNA isolation

After patients were enrolled and provided informed consent, saliva samples were collected using oral swabs (OCR-100 kit). DNA was extracted using the QIAamp DNA Mini extraction kit (Qiagen GmbH, Hilden, Germany) following the manufacturer's guidelines for saliva DNA purification and stored at −40°C. The DNA concentration and purity were evaluated using a UV NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA) by measuring the absorbance ratios of 260/280 and 260/230.

Detection of gene polymorphisms

The selection of SNPs was based on their involvement in the pharmacodynamics and mechanism of action of omalizumab. Specifically, we focused on genetic variants in Fc receptors (*FCER1A*, *FCER1B*, *FCGR2A*, *FCGR2B*, and *FCGR3A*), as they play a key role in IgE-mediated immune responses and have been implicated in the modulation of omalizumab efficacy. Additionally, we included polymorphisms in the *C3* gene, which encodes a key component of the complement system involved in immune regulation, as well as *IL1RL1* and *GATA2*, which influence cytokine signaling and immune cell activation. While other genetic markers could provide valuable insights into omalizumab response, our study was designed as an initial exploratory analysis focused on genes directly involved in the drug's mechanism of action. The genetic polymorphisms were analyzed using real-time polymerase chain reaction (PCR) with TaqMan™ probes (ABI Applied Biosystems, 7300 Real-Time PCR System). The ID assays used for the polymorphisms were as follows: C___1840470_20 and C___16233438_20 for *FCER1A* (rs2251746, rs2427837); C___1842226_10, C____900105_20, C___2932371_10 and C____900116_10 for *FCER1B* (rs1441586, rs573790, rs1054485, rs569108); C__26330755_10 for *C3* (rs2230199); C___9077561_20 for *FCGR2A* (rs1801274); C___57480226_10 and C___25815666_10 for *FCGR3A* (rs10127939, rs396991); C___8906009_20, C___33551182_10 and C___1226146_10 for *IL1RL1* (rs1420101, rs17026974, rs1921622); and C___11231076_10 for *GATA2* (rs4857855). The *FCGR2B* polymorphisms (rs3219018, rs1050501) were analyzed using a customized assays by ThermoFisher Scientific (Waltham, MA, USA) coded as ANPRZAZ and ANRWUVX. The genetic variables were determined using QuantStudio 3™ software (Applied Biosystems, 96 wells) at the Pharmacogenetics Unit of HUVN. Quality control criteria for SNPs included (1) missing genotype rate per SNP < .05, (2) minor allele frequency (MAF) > 0.01, (3) p-value in the Hardy-Weinberg equilibrium test > 0.05, and (4) missing genotype rate between cases and controls < 0.05. The variants included in the study were selected based on their frequency in the Caucasian population and previous findings from similar studies in the scientific literature.

Survival variable

The primary endpoint of drug survival (DS) was defined as the time from initiation of omalizumab treatment to discontinuation for any cause. While DS does not directly measure treatment efficacy, it reflects treatment persistence in real-world clinical practice, a methodology commonly used in studies on biologic therapies. Reasons for discontinuation were recorded and categorized according to the information available in the clinical registries, establishing the following main categories:

- Clinical inefficacy: lack of improvement in asthma symptoms or need to switch to another biologic therapy due to insufficient disease control.
- Clinical stability: discontinuation of treatment after reaching a stable state without exacerbations or sustained improvement, according to medical judgment.
- Adverse effects: discontinuation due to adverse reactions attributed to omalizumab, including systemic or local effects at the injection site.
- Completion of the recommended treatment period: in some cases, treatment was discontinued after completion of the 5-year period of therapy, according to established clinical recommendations.
- Other causes: reasons not related to the efficacy or safety of the drug, such as patient choice, changes in health coverage or transfer to another health care facility.

This categorization made it possible to differentiate the different discontinuation scenarios and their impact on omalizumab treatment survival.

Statistical analysis

Quantitative variables that followed a normal distribution were expressed using mean and standard deviation, while variables that did not adhere to a normal distribution were expressed using median and percentiles (25th and 75th). Normality was confirmed using the Kolmogorov-Smirnov test.

The Kaplan-Meier method and the log-rank test were used to analyze the association between DS and sociodemographic, clinical, and genetic variables. The Cox regression model (backward elimination method) was used for the multivariate analysis. The model provided the adjusted Hazard Ratio (HR) and 95% confidence interval (95%CI) for potential survival prognostic factors.

All tests were two-sided, and a significance level of 0.05 or lower was considered statistically significant. Descriptive, bivariate, and multivariate analyses were conducted using R software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).[24]

Hardy-Weinberg equilibrium, MAF, and linkage disequilibrium (LD) were determined. Linkage disequilibrium coefficient (r^2) and Lewontin's D prime values (D') were calculated using the genome association analysis programs PLINK 1.9 and Haploview 4.2.[25,26] Haplotype survival analysis was

Table 1. Demographic and clinical characteristics of patients undergoing omalizumab treatment.

Characteristic	N	%	Mean ± SD/p50(p25, p75)
Sex			
Female	51	66.23	
Male	26	33.77	
Age at omalizumab initiation (years)	77		47 ± 15
Years with asthma	77		8 (5,14)
BMI (kg/m^2)			
Normal weight	19	24.68	
Overweight	28	36.36	
Obesity	30	38.96	
Previous respiratory disease			
Yes	20	25.97	
No	57	74.03	
Tobacco consumption			
Non-smoker	58	75.32	
Current smoker	3	3.90	
Former smoker	16	20.78	
Polyps			
Yes	19	24.68	
No	58	75.32	
Allergies			
Yes	59	76.62	
No	18	23.38	
GERD			
Yes	24	31.17	
No	53	68.83	
SAHS			
Yes	20	25.97	
No	57	74.03	
COPD			
Yes	14	18.18	
No	63	81.82	
Age at asthma diagnosis (years)	77		42 ± 17
<18	11	14.29	
>18	66	85.71	
ICS (µg/day)	77		500 (250,1000)
OCS cycles per year			
Yes	57	74.03	
No	20	25.97	
Baseline FEV1%)			
<80	46	59.74	
≥80	31	40.26	
Exacerbation in previous year			
Yes	49	63.64	
No	28	36.36	
Basal blood eosinophils (cell/mcl)			
<300	42	54.55	
≥300	35	45.45	
Baseline IgE (IU/Ml)	77		383 (161,789)
Years with Omalizumab	77		4 (2,6)
<5	53	68.83	
≥5	24	31.17	
Discontinuation of omalizumab			
Yes	49	63.64	
No	28	36.36	
Reasons for omalizumab discontinuation*			
Clinical ineffectiveness	23	29.89	
Adverse events	5	6.49	
Clinical stability	15	19.48	
5-year compliance	5	6.49	
Other reasons	13	16.88	

BMI, body mass index; GERD, gastroesophageal reflux disease; SAHS, sleep apnea-hypopnea syndrome; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; OCS, oral corticosteroids; FEV1, maximum expiratory volume in the first second of forced expiration; IgE, immunoglobulin E. Qualitative variables are shown as numbers (percentage, %). Quantitative variables with a normal distribution are shown as mean ± standard deviation (SD). Quantitative variables with a non-normal distribution are shown as p 50 (p 25, p 75).
*Some patients had more than one reason for discontinuation.

conducted using Thesias 3.1 software, which applied Cox regression analysis.[27]

Results

Patient characteristics

Table 1 presents the sociodemographic and clinical characteristics of the 77 patients included in the study, who underwent omalizumab treatment. The mean age of the patients was 47 ± 15 years, with 66.23% (51/77) being female.

Survival of omalizumab and reasons for discontinuation

The median duration of omalizumab treatment was 4 (2, 6) years (Table 1, Figure 1). Of the total patients, 63.64% (49/77) discontinued treatment. The main reasons for discontinuing omalizumab were ineffectiveness (29.89%), clinical stability (19.48%), completion of 5 years of treatment (6.49%), and adverse events (6.49%) (Table 1).

Influence of sociodemographic and clinical characteristics on drug survival

Median DS was higher in patients without previous respiratory pathologies ($p_{long\text{-}rank} = 0.020$; 71.1 vs. 51.3 months; Table S1; Figure S1) and in patients without GERD and SAHS prior to the asthma diagnosis ($p_{long\text{-}rank} = 0.010$; 71.1 vs. 44.4 months; Table S1; Figure S2, and $p_{long\text{-}rank} = 0.060$; 69.7 vs. 35.5 months; Table S1; Figure S3, respectively). No association with SD was found for all other sociodemographic and clinical variables.

Genotype distribution

All studied polymorphisms had a MAF greater than 1% and were included in the analysis (Table S2). The distribution of genetic polymorphisms aligned with expected values according to the Hardy-Weinberg equilibrium model, except for the *IL1RL1* rs1921622 polymorphism ($p = .011$) (Table S3). However, there were no statistically significant differences compared to the frequencies described in the Iberian population for this polymorphism (*IL1RL1* rs1921622 A allele: 0.6494 vs. 0.4770; $p = .806$).[28] The LD values D' and r^2 are shown in Table S4. Strong LD was observed for the following polymorphisms pairs: *IL1RL1* rs17026974/rs1420101, *IL1RL1* rs17026974/rs1921622, *FCER1A* rs2427837/rs2251746, and *FCER1B* rs573790/rs1441586 (Figure 2). The SNPs rs1420101, rs17026974, and rs1921622 were included in the *IL1RL1* haplotype block, the SNPs rs2251746 and rs2427827 were included in the *FCER1A* haplotype block, and the SNPs rs1441586 and rs573790 were included in the *FCER1B* haplotype block. Tables S5, S6 and S7 provide the estimated haplotype frequencies. The CGG haplotype was the most frequent for the *IL1RL1* block (total frequency = 0.508), while the TG haplotype was the most frequent for the *FCER1A* block (total frequency = 0.805), and the CC haplotype was the most frequent for *FCER1B* block (total frequency = 0.492).

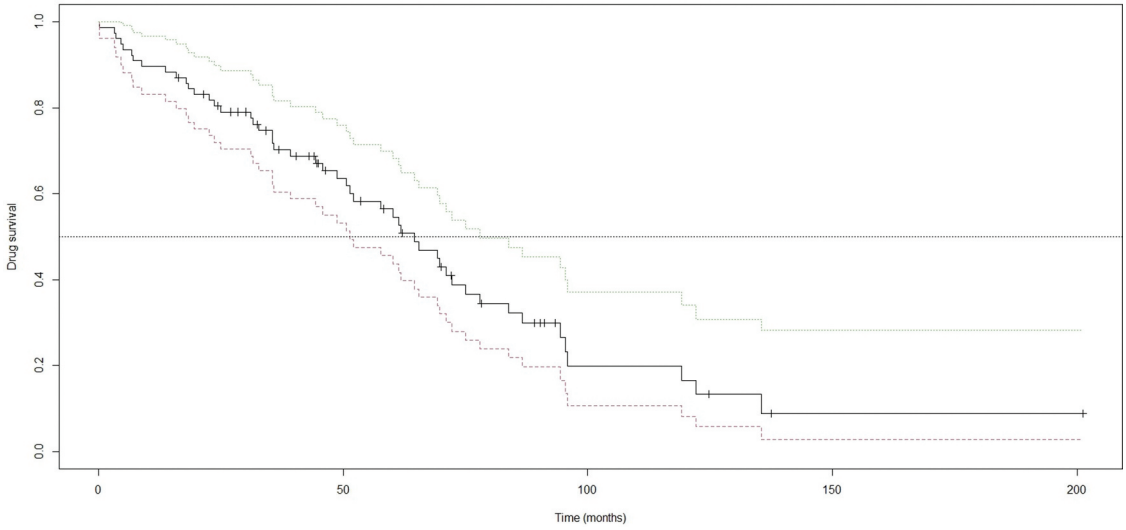

Figure 1. Kaplan-Meier curve for omalizumab survival to omalizumab.

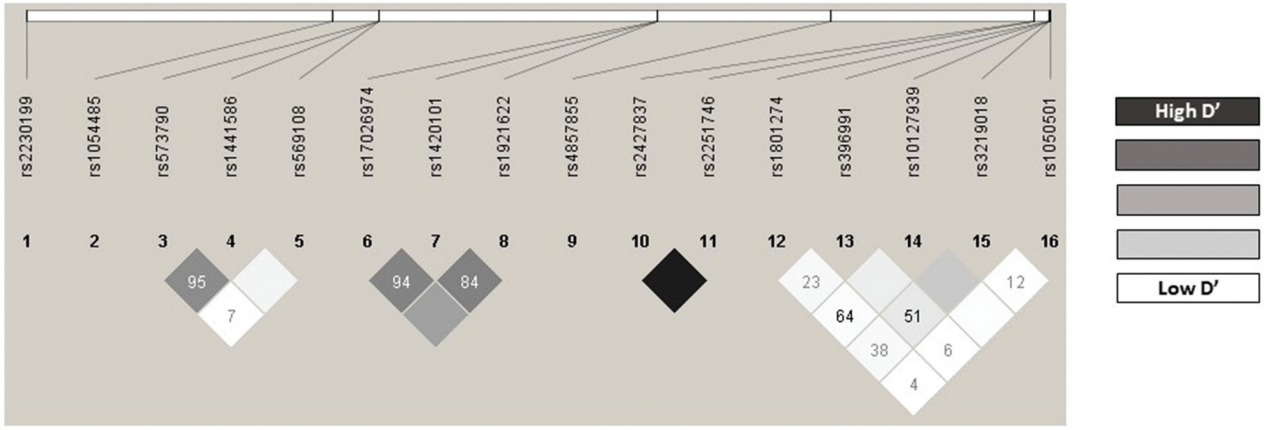

Figure 2. Linkage disequilibrium.

Influence of gene polymorphisms and haplotypes on drug survival

The bivariate analysis revealed an association between DS and the polymorphisms *FCER1B* rs573790, *FCGR2A* rs1801274, *FCGR3A* rs10127939, *and FCGR3A* rs396991 (Table S8).

Patients with the *FCER1B* rs573790 - TT genotype had a longer drug survival compared to those with the CC genotype ($p = .041$; HR = 0.72; 95%CI = 0.27–1.94). Figure 3 shows the Kaplan-Meier survival curves for DS according to SNP *FCER1B* rs573790 ($p_{long\text{-}rank} = 0.040$). The median DS for the TT genotype was 94.4 months (95%CI = 83.8-NR), while for the CC genotype it was 69.7 months (95%CI = 50.6-NR).

Carriers of the *FCGR2A* rs1801274 - G allele exhibited higher DS compared to carriers of the AA genotype ($p = .028$; HR = 0.52; 95%CI = 0.29–0.93). The median DS was 72.1 months (95%CI = 57.7–95.8) for the G allele, in contrast to 44.3 months (95%CI = 23.7–71.1) for the AA genotype. Similarly, an association was observed for the *FCGR2A* rs1801274 - AG genotype with higher DS ($p = .012$; HR = 0.44; 95%CI = 0.23–0.83). The median DS was 77.9 months (95%CI = 64.5-NR) for the AG genotype and 44.3 months (95%CI = 23.7–71.1) for the AA genotype. Figure 4 illustrates Kaplan-Meier survival curves for DS based on *FCGR2A* rs1801274 ($p_{long\text{-}rank} = 0.030$).

Patients carrying the *FCGR3A* rs10127939 - AC genotype had lower DS than those with the AA genotype ($p = .015$; HR = 3.37; 95%CI = 1.27–8.98). The Kaplan-Meier survival curves for DS according to *FCGR3A* rs10127939 are shown in Figure 5 ($p_{long\text{-}rank} = 0.020$). The median DS was 52.1 months (95%CI = 35.5–72.1) for the AC genotype and 86.6 months (95%CI = 60.2-NR) for the AA genotype.

Carriers of the *FCGR3A* rs396991 - C allele were associated with decreased DS compared to carriers of the AA genotype ($p = .028$; HR = 2.02; 95%CI = 1.08–3.79). Figure 6 shows the Kaplan-Meier survival curves for DS based on *FCGR3A* rs396991 ($p_{long\text{-}rank} = 0.020$). The median DS was 37.3 months (95%CI = 35.5-NR) for the C allele, compared to 69.3 months (95%CI = 57.7–86.6) for the AA genotype. Likewise, a significant association was found between the *FCGR3A* rs396991 - CA genotype and decreased DS ($p = .018$; HR = 2.20; 95%CI = 1.14–4.23). Figure 6 shows Kaplan-Meier survival curves for DS according to *FCGR3A* rs396991 ($p_{long\text{-}rank} = 0.050$). The median DS for the CA genotype was 35.5 months

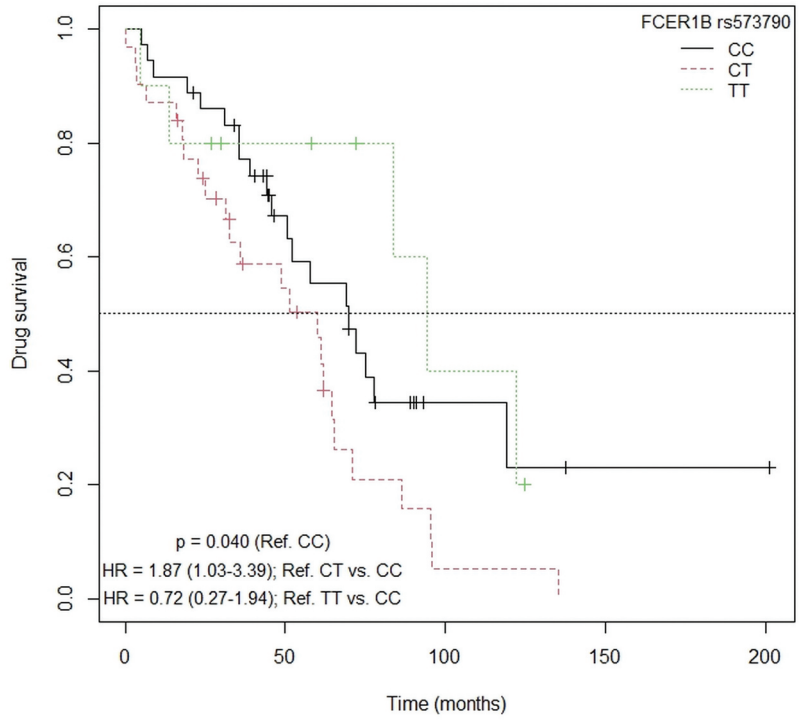

Figure 3. Kaplan-Meier curve for drug survival according to SNP *FCER1B* rs573790.

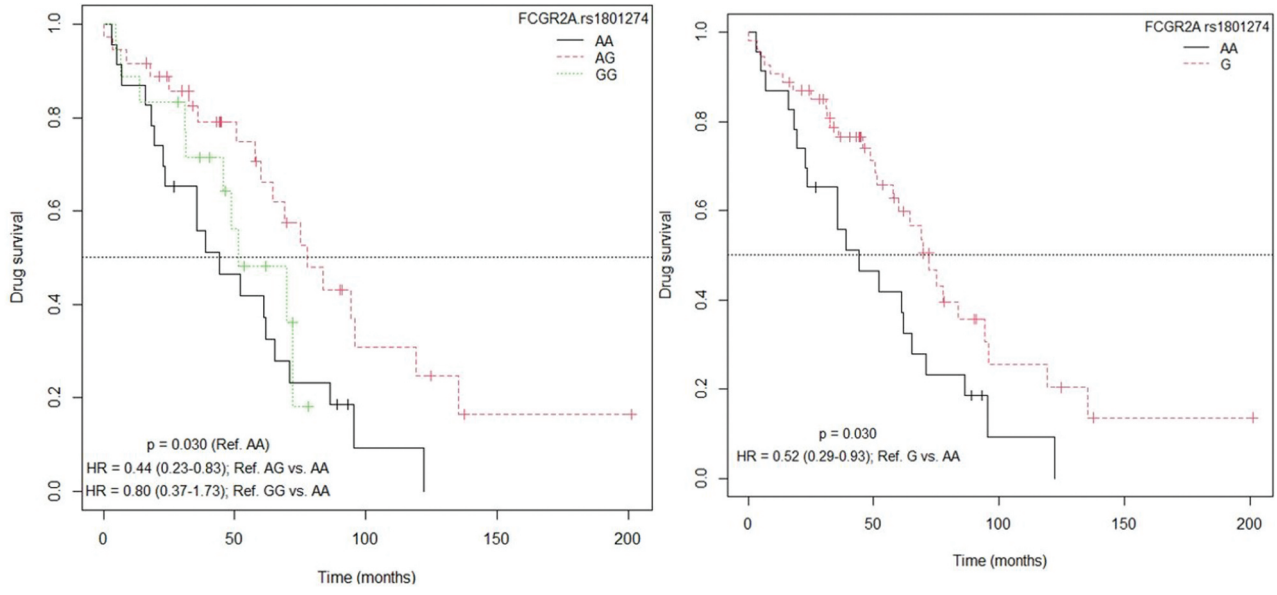

Figure 4. Kaplan-Meier curve for drug survival according to SNP *FCGR2A* rs1801274. a) *FCGR2A* rs1801274 and b) *FCGR2A* rs1801274-G allele.

(95%CI = 35.5-NR), while for the AA genotype, it was 69.3 months (95%CI = 57.7–86.6).

In the bivariate analysis, no statistically significant associations were found between *IL1RL1*, *GATA2*, *FECER1A*, *C3* and *FECGR2B* gene polymorphisms and DS. *

Cox regression analysis adjusted by the variables presence of respiratory diseases, GERD and SAHS before diagnosis, and years with asthma revealed that the SNPs *FCER1B* rs573790 - CT ($p < .001$; HR = 3.38; 95%CI = 1.66–6.87), *FCGR3A* rs10127939 - AC ($p = .018$; HR = 3.85; 95%CI = 1.25–11.81), and *FCGR3A* rs396991 - CC ($p = .020$; HR = 2.23; 95%CI = 1.14–4.38) were the independent variables associated with lower DS in patients diagnosed with asthma (Table 2). Similarly, a trend toward statistical significance was found between and *FCGR3A* rs10127939 - CC ($p = .080$; HR = 0.13; 95%CI = 0.01–1.28) and increased DS (Table 2).

Regarding haplotype analysis, the frequencies of the *IL1RL1*, *FECER1A*, and *FCER1B* haplotypes in censored and non-censored patients are shown in Tables S5, S6 and S7, respectively. Furthermore, the results of Cox regression

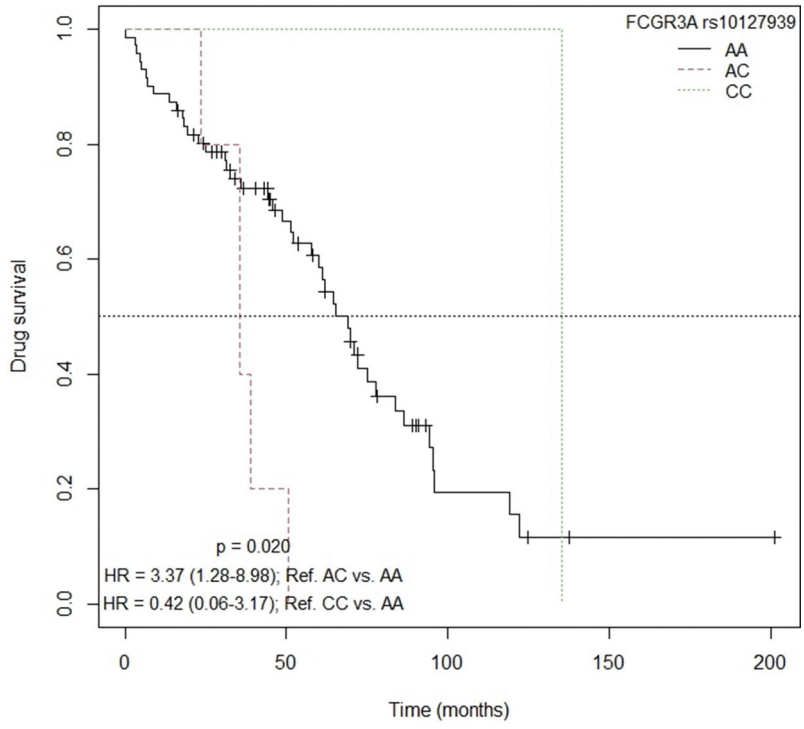

Figure 5. Kaplan-Meier curve for drug survival according to SNP *FCGR3A* rs10127939.

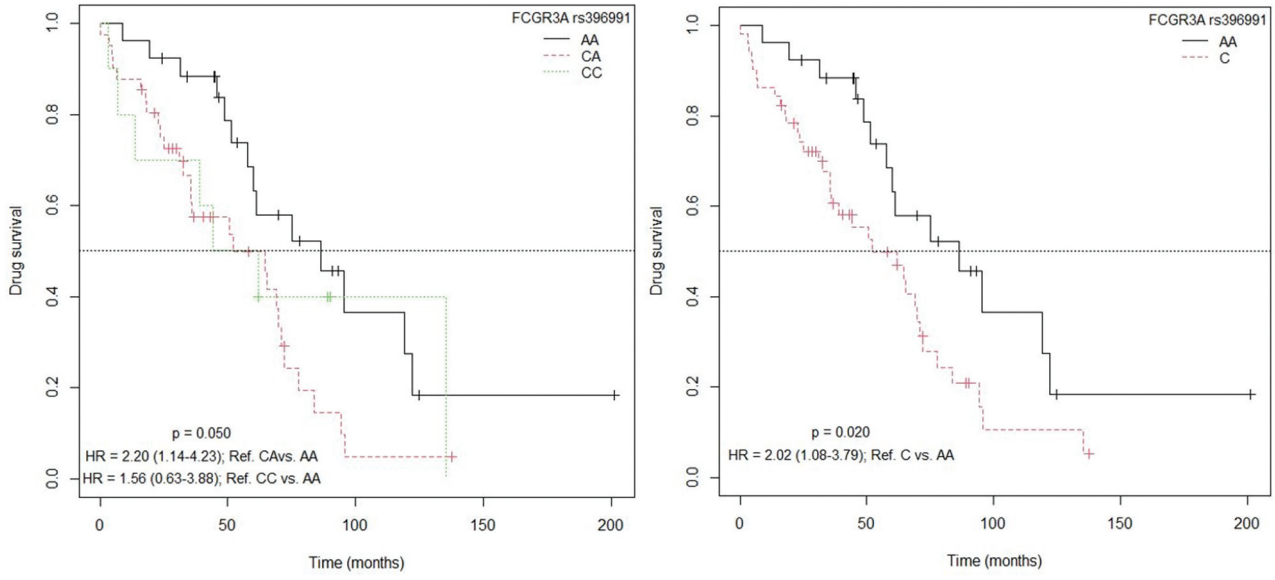

Figure 6. Kaplan-Meier curve for drug survival according to SNP *FCGR3A* rs396991. a) *FCGR3A* rs396991 and b) *FCGR3A* rs396991-C allele.

Table 2. Influence of gene polymorphisms and clinical-pathological characteristics on drug survival (multivariate analysis).

	Overall Drug Survival	
Independent variables	HR (95% CI)	p-value
Previous respiratory disease (Yes)	2.71 (1.32–5.54)	0.006
FCER1B rs573790 (CT vs. CC)	3.38 (1.66–6.87)	<0.001
FCGR3A rs10127939 (AC vs. AA)	3.85 (1.25–11.81)	0.018
FCGR3A rs10127939 (CC vs. AA)	0.13 (0.01–1.28)	0.080
FCGR3A rs396991 (CC vs. AA)	2.23 (1.14–4.38)	0.020

HR: hazard ratio; 95%CI: 95% confidence interval.

analysis for haplotypes and DS showed no significant findings for any of the three haplotype blocks ($p > .05$, Table S9, S10 and S11).

Discussion

Biologic therapies indicated for uncontrolled severe asthma with an allergic phenotype, such as omalizumab, are highly effective and safe. However, a subset of these patients experiences a high rate of biologic therapy switching due to loss of efficacy, resulting in a negative impact on the healthcare system. Switching from one biologic therapy to another is costly for healthcare systems, as these treatments are expensive and their replacement requires additional clinical evaluations, biomarker testing, and medical follow-up to assess response. Additionally, treatment discontinuation can lead to a period of disease instability, increasing the use of healthcare resources such as hospitalizations, emergency visits, and systemic corticosteroid treatment. There are also administrative costs associated with authorization, procurement, and potential delays in access to the new therapy. Optimizing treatment selection from the outset, based on predictive biomarkers, could help reduce unnecessary switches and their economic impact. The variability in response may be due to genetic factors, as alterations in genes involved in disease metabolism or drug mechanism of action may influence the efficacy of omalizumab. However, to date, there are no previous studies reporting associations between genetic markers and survival to omalizumab in patients with severe asthma. The main targets of this study are SNPs in omalizumab metabolism and mechanism of action genes, including *C3* encoding the binding domain of omalizumab to IgE; *FCER1A* and *FCER1B* encoding IgE receptors; *FCGR2A* and *FCGR3A* encoding specific receptors for omalizumab binding; *IL1RL1* regulating the cytokine cascade; *GATA2, a* transcription factor regulating the expression of FcƐR receptors and activating IgE-mediated degranulation.

In our cohort, the prevalence of nasal polyps was slightly higher than expected. While nasal polyps are frequently associated with type 2 inflammation and can be an indication for other biologic therapies such as dupilumab, omalizumab remains a viable option for patients with severe allergic asthma when their predominant phenotype aligns with its approved indications. In clinical practice, the selection of a biologic therapy is influenced by multiple factors, including the patient's overall clinical profile, comorbid conditions, physician preference, and accessibility to treatment. Additionally, during the early years of biologic therapy introduction (prior to the approval of alternative options), omalizumab was one of the few available choices for patients with severe allergic asthma, regardless of the presence of nasal polyps.

In this study, we initially evaluated DS, which had a median duration of 4 years. Ineffectiveness was identified as one of the primary reasons for omalizumab discontinuation or therapy change. Our findings align with a study conducted in the Caucasian population (France), which reported a median omalizumab treatment persistence of 4.2 years before discontinuation (95%CI = 4.1–4.5).[29] Other studies conducted in the Caucasian population (Poland and France) evaluated the persistence of omalizumab before discontinuation, define as median interval between discontinuation and loss of control, using different methods and smaller patient samples. These studies demonstrated an omalizumab persistence of 6.2 and 1.9 (95%CI = 0.2–4.9) years, respectively.[30,31]

After investigating the potential of SNPs involved in the metabolism and mechanism of action of omalizumab in 77 Caucasian patients (Spain), we found in multivariate analysis that the genotypes *FCER1B* rs573790-CT, *FCGR3A* 10127939-AC, and *FCRGR3A* rs396991-CC were associated with lower DS. Conversely, the *FCGR3A* 10127939-CC genotype was associated with higher DS. In bivariate analysis, an association was found between the *FCGR2A* rs1801274-G allele and higher DS, but this association was not maintained in multivariate analysis. No significant associations were found between omalizumab DS and the remaining SNPs located in the genes *IL1RL1*, *C3*, *GATA2*, *FCER1A*, and *FCGR2B*. *

The *FCER1B* gene, located on chromosome 11q12.1, encodes the beta subunit of the high-affinity immunoglobulin epsilon receptor, which acts as a signal amplifier for FcεRI. Several SNPs in this gene have been studied, including rs1441586 (*T* > C), rs573790 (*T* > C), rs1054485 (*T* > G), and rs569108 (A > G). These SNPs are commonly found in individuals with asthma and atopy and are linked to elevated levels of IgE and the expression of FcεRI.[32] Our study found a relationship between the *FCER1B* rs573790-CT genotype and reduced DS to omalizumab. To our knowledge, no studies have evaluated these SNPs in relation to drug survival to omalizumab. However, a previous study in the Caucasian population (Spain) showed a trend between the *FCER1B* rs573790-CC genotype (OR = 4.26; 95%CI = 1.01–26.98; p = .063) and a better response in reducing exacerbations.[33] Another author also associated this genotype with asthma and aspirin-exacerbated respiratory disease in a mestizo population (Mexico).[34]

The Fc region of IgG enhances drug stability and prolongs its half-life, improving its pharmacokinetics.[35] The Fc region of human IgG1 binds selectively to Fc-gamma receptors (FcγR) on the surface of B lymphocytes, dendritic cells (DCs), and macrophages. These receptors are integral membrane glycoproteins that exhibit complex activation or inhibitory effects on cellular functions of the antibody upon binding to IgG.[18,19] FcγRII is expressed in neutrophils, macrophages, and monocytes. SNPs in the *FCGR2A*, *FCGR2B*, and *FCGR3A* genes (chromosome 1q23.3) have been studied for their potential impact on the binding stability of the Fc region in biologic therapies, such as omalizumab.[18]

The SNP *FCGR2A* rs1801274 (A > G) results in a histidine-to-arginine substitution at position 131 (His131Arg).[36,37] Our study revealed a statistical association between the *FCGR2A* rs1801274-AG genotype and increased omalizumab DS. However, this association was not significant in the multivariate analysis. Previous studies in other pathologies have shown that *FCGR2A* rs1801274-p.131His results in a higher affinity for IgG1, which could explain increased DS.[38]

The *FCGR3A* SNP rs396991 (A > C) results in a phenylalanine-to-valine substitution at position 158 (Phe158Val).[38] Our findings indicate that the *FCGR3A* rs396991-C allele is associated with lower omalizumab DS. This could be explained by previous research on other biologic

therapies, demonstrating that the low-affinity variant *FCGR3A*-p.158Phe is associated with lower drug clearance and consequently, a better therapeutic response.[38] The second polymorphic site, *FCGR3A* rs10127939, is located in the extracellular domain of FcγRIIIa at amino acid residue 66 and is triallelic, resulting in a leucine-to-arginine or histidine change (Leu66Arg/His).[39] Our study found that the *FCGR3A* rs10127939-AC genotype was associated with lower DS. This could be attributed to the Leu to Arg or His change, which inhibits glycosylation. This can influence the ligand binding affinity to FcγRIIIa. Reduced binding affinity may alter the response to omalizumab, affecting DS.[39]

This is the first study in which SNPs involved in both the metabolism and mechanism of action of omalizumab are examined as potential genetic biomarkers for DS. One of the main strengths of the study lies in its robust patient recruitment and variable collection, as it was conducted by the same personnel, with all patients recruited from the same hospital following identical protocols. However, the lack of prior studies that could help validate these results and the limited sample size require replication in larger cohorts to firmly establish these associations or other potential ones that may not have been detected due to cohort limitations. In conclusion, an association was found between SNPs related to the metabolism and mechanism of action of omalizumab and DS. Specifically, our results suggest that *FCER1B* rs573790-CT, *FCGR3A* 10127939-AC, *FCGR3A* 10127939-CC and *FCRGR3A* rs396991-CC may act as predictors of DS in patients with uncontrolled severe asthma undergoing omalizumab treatment.

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Disclosure statement

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S.R.T. conceived and designed the experiments; S.R.T. performed the experiments; S.R.T. collected samples; S.R.T. and L.E.P.L, analyzed the data; M.V.G.G., J.A.S.M., G.J.G. and A.C.V. contributed materials and analysis tools; S.R.T. prepared the original draft; C.M.G., A.J.M. and S.R.T. reviewed and edited the draft; S.R.T., A.J.M. and C.M.G. reviewed the analysis and interpretation; A.J.M. and C.M.G. supervised funding acquisition. All the authors participated in critically re-viewing the manuscript and improving its intellectual content. All the authors read and approved the final version of the manuscript.

Informed consent statement

All subjects involved in the study signed the written informed consent form.

Institutional review board statement

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