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Impact of Single Nucleotide Polymorphisms of the Promoter of the *TNF* Gene on Adalimumab Treatment Responses in Hidradenitis Suppurativa

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Adalimumab · Hidradenitis suppurativa · Treatment response · Single nucleotide polymorphisms

Abstract
Background: Results of randomized clinical trials show great variation in response to treatment with adalimumab (ADA) in hidradenitis suppurativa (HS). This varied response may be associated with genetic polymorphisms. ***Objectives:*** The aim of the study was to study the association between carriage of single nucleotide polymorphisms (SNPs) in the promoter of the *tumor necrosis factor* (*TNF*) gene and their response to ADA. ***Methods:*** Patients with moderate to severe HS who received ADA treatment for at least 12 weeks were enrolled. SNPs were analyzed with PCR-restriction fragment length polymorphism. Hidradenitis Suppurativa Clinical Response (HiSCR) score, International Hidradenitis Suppurativa Severity Scoring System 4 (IHS4) score, inflammatory lesion (AN) count, and draining tunnel (dT) count were collected at weeks 0, 12, 24, 36, and 48. ***Results:*** HiSCR response after 12 weeks of ADA treatment was 71.8% among carriers of the common GGG haplotype and 50.0% among carriers of minor frequency SNP haplotypes (*p*: 0.031; odds ratio: 0.39). This significant difference persisted until week 36. Carriers of minor frequency SNP haplotypes also had a lower relative decrease of the AN count at weeks 12 and 24; the dT count and IHS4 were not statistically different between the two groups. ***Conclusions:*** Carriage of at least one minor frequency SNP haplotype of the promoter of the *TNF* gene is associated with a decreased response to ADA. This association may have an impact on treatment decision-making.

Introduction

Tumor necrosis factor-alpha (TNFα), a pro-inflammatory cytokine produced by a variety of skin cells including macrophages and keratinocytes, is found to be heavily deposited in the skin of patients with hidradenitis suppurativa (HS) [1, 2]. Blocking TNF with adalimumab (ADA), a fully humanized anti-TNF monoclonal antibody, results in significant clinical

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improvement in HS with HS Clinical Response (HiSCR) rates between 41.8% and 58.9% in randomized clinical trials [3, 4].

The reason for this wide variation in HS clinical response to anti-TNF is unclear. However, in a previous small pilot study of 32 patients receiving etanercept or infliximab, we found that carriage of at least one single nucleotide polymorphism (SNP) was correlated with 2.67 odds ratio (OR) for lack of treatment response to the anti-TNF therapy (95% confidence intervals [CIs]: 1.13–6.29; *p*: 0.025) [5]. In an effort to expand these findings, we developed the STAGE study (a multicenter clinical study to assesS the correlation of the Tumor necrosis factor-Alpha GEne and response to treatment with adalimumab in moderate to severe hidradenitis suppurativa) to investigate in a larger study population any possible association between carriage of SNPs of the *TNF* gene promoter and the response to ADA treatment.

Patients and Methods

Study Population and Data Collection

The study was conducted between February 2019 and June 2020. Participants were enrolled from 3 different study sites: the outpatient Department of Immunology of Infectious Diseases of ATTIKON University Hospital in Athens, Greece; the outpatient Department of Hidradenitis Suppurativa of Papageorgiou Hospital in Thessaloniki, Greece; and the Department of Dermatology of The Ohio State University in Ohio, USA. The study was approved by the Institutional Board of the hospitals (approvals EBD11/10-01-2019; A12/26-02-2019; and 2018H0314/26-09-2018, respectively).

The inclusion criteria were as follows: (1) age ≥18 years old; (2) written informed consent provided by the patients; (3) diagnosis of HS based on early onset after puberty, presence of subcutaneous nodules in skin areas rich in apocrine glands, and compatible history of recurrent pus drainage from the affected areas [6]; (4) Hurley stage II or III; (5) patients naïve to any previous biological treatment; and (6) at least 12 weeks of treatment with ADA. There were no exclusion criteria for this study.

The following data were collected: (1) demographics, i.e., age, gender, ethnicity, age of HS onset, and family history of HS; (2) comorbidities, i.e., body mass index and Charlson's Comorbidities Index (CCI); (3) physical examination and HS history, i.e., Hurley stage, number of exacerbations per month or per year, number of affected body areas, months of treatment with ADA, number of inflammatory nodules (IN), abscesses (Abs), draining tunnels (dT) at baseline and at weeks 12, 24, 36, and 48 of the treatment, HiSCR response at weeks 12, 24, 36, and 48 of ADA treatment, and relative change of IHS4 score from baseline at weeks 12, 24, 36, and 48 of ADA treatment. The International HS4 (IHS4) score was calculated at baseline, and at weeks 12, 24, 36, and 48 of ADA treatment using the following formula: (i) number of IN multiplied by 1, (ii) number of Abs multiplied by 2, (iii) number of dT multiplied by 4 [7]. The relative decreases of the inflammatory lesion (AN) count (sum of IN and Abs) and of dT count from baseline were also calculated.

The primary study endpoint was the comparison of HiSCR response after 12 weeks of treatment with ADA between carriers of the major frequency GGG SNP haplotype and carriers of at least one minor frequency SNP haplotype of the promoter of the *TNF* gene. The secondary study endpoints were the comparisons between carriers of the major frequency GGG SNP haplotype and carriers of at least one minor frequency SNP haplotype on (i) HiSCR response after 24, 36, and 48 weeks of treatment; and (ii) the relative changes of IHS4 and of the AN and dT counts from baseline after 12, 24, 36, and 48 weeks of treatment.

Blood Sampling and Genotyping

One sample of peripheral blood (3 mL) was collected from each patient into ethylenediamine tetra acetic acid anticoagulation tubes and stored at −80 °C until processed. Genomic DNA was extracted from all individuals using the Puregene Blood Core Kit C (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. The genotyping analysis was performed in a blinded phase for clinical data, with analyst being unaware of the patients' names. After extraction, the total DNA quality and concentration were assessed using NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). The absorbance ratios 260 nm/280 nm and 260 nm/230 nm were analyzed to determine the purity and concentration of total DNA.

In order to screen for the −376 (G/A) SNP (rs1800750), a 148-bp fragment was amplified with forward primer 5′-CCT CAG GAC TCA ACA CAG C-3′ and reverse primer 5′-GGG GAC CAG GTC TGT GGT CTG TTT CCT GTT AA-3′. The PCR cycling conditions consisted of one initial denaturation phase of 95°C for 10 min followed by 35 cycles; each cycle consisted of one annealing step of 95°C for 60 s, one polymerization step of 58°C for 1 min and one elongation step of 72°C for 1 min. Then, another cycle of 72°C for 5 min was done before termination. For the −308 G/A polymorphism (rs1800629), a 147-bp fragment was amplified with forward primer 5′-GAG GCA ATA GGT TTT GAG GGC CAT-3′ and reverse primer 5′-GGG ACA CAC AAG CAT CAA G-3′. The PCR cycling conditions consisted of one initial denaturation phase of 95°C for 10 min followed by 35 cycles; each cycle consisted of one annealing step of 95°C for 60 s, one polymerization step of 60°C for 1 min, and one elongation step of 72°C for 1 min. Then, another cycle of 72°C for 5 min was done before termination. For −238 G/A SNP (rs361525), a 165-bp fragment was amplified with forward primer 5′-CAG ACC ACA GAC CTG GTC-3′ and reverse primer 5′-AAG GAT ACC CCT CAC ACT CCC CAT CCT CCC GGA TC-3′. The PCR cycling conditions consisted of one initial denaturation phase of 95°C for 10 min followed by 35 cycles; each cycle consisted of one annealing step of 95°C for 60 s, one polymerization step of 58°C for 1 min, and one elongation step of 67°C for 1 min. Then, another cycle of 72°C for 5 min was done before termination. Then, 10 μL of each PCR product was treated with three restriction endonucleases *Hpa*I, *NCOI*, and *Bam*HI (New England Biolabs, USA) for rs1800750, rs1800629, and rs361525, respectively, according manufacturer's specifications. The pattern of digested products was analyzed using 2% agarose gel after ethidium bromide staining.

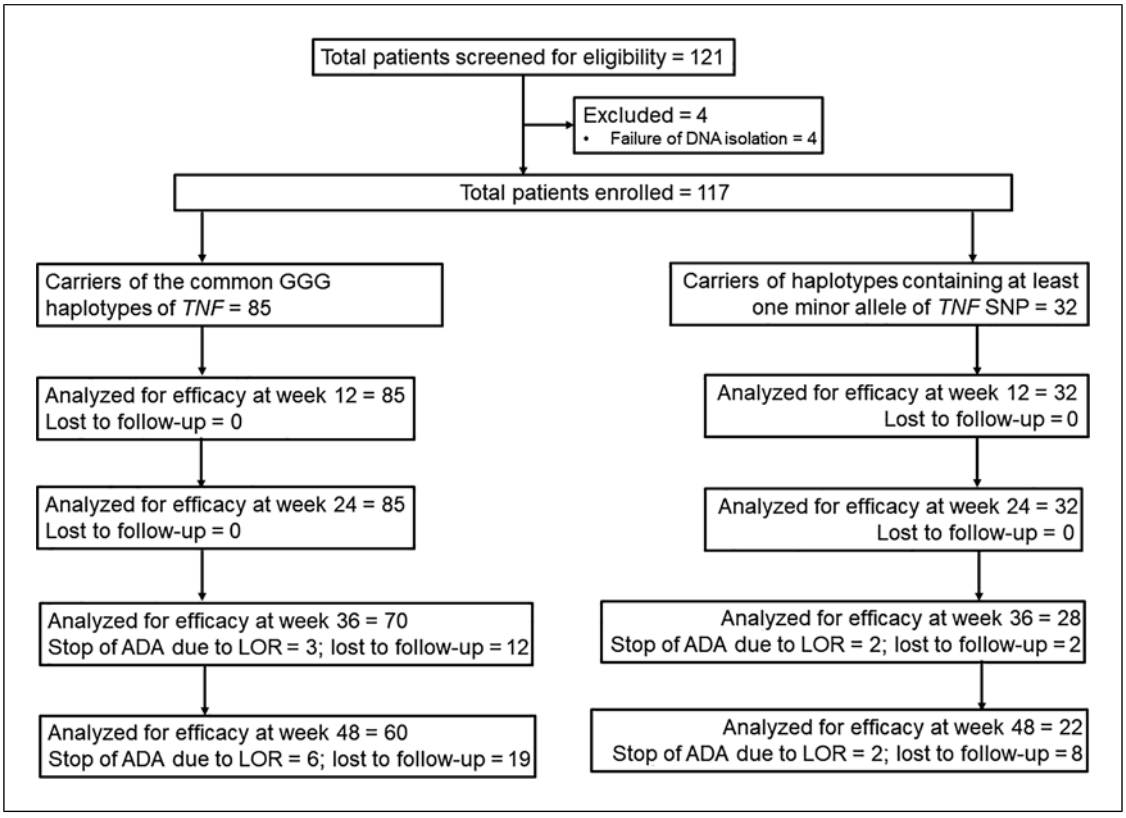

Fig. 1. Study flowchart. ADA, adalimumab; LOR, loss of response; SNP, single nucleotide polymorphisms.

Statistical Analysis

Patients were divided into a group who were carriers of the common GGG haplotype (i.e., bringing the G allele of all studied SNPs in both chromosomes) and a group who were carriers of haplotypes containing at least one minor frequency SNP allele. All comparisons between carriers of common haplotypes and of SNP haplotypes for the HiSCR response at weeks 12, 24, 36, and 48 were done by the Fisher's exact test. All respective comparisons for the relative changes of IHS4 score, AN and dT counts from baseline were done by the Student's *t* test. A 55% or more decrease in the baseline IHS4 has recently been suggested as an alternative efficacy endpoint [8, 9]. Comparisons for this endpoint were done by the Fisher's exact test. ORs and 95% CIs were calculated according to Mantel and Haenszel. Any p value <0.05 ($p < 0.005$) was considered statistically significant.

Results

A total of 117 patients were enrolled and analyzed; 85 patients were carriers of the common GGG haplotype; and 32 patients were carriers of haplotypes containing at least one minor frequency SNP allele (Fig. 1). Five patients (4.3%) were carriers of the minor frequency A allele of rs1800750; 17 patients (14.5%) were carriers of the minor frequency A allele of rs1800629; and 16 patients (13.7%) were carriers of the minor frequency A allele of rs361525.

A total of 77 patents achieved HiSCR response by week 12 (65.8%). The baseline characteristics of enrolled patients before start of ADA treatment are shown in Table 1. HiSCR responders had a lower frequency of Hurley stage III lesions, lower IHS4 score, and lower dT counts at baseline. All other characteristics between groups were not significant (Table 1).

HiSCR response after 12 weeks of ADA treatment was 71.8% among carriers of the common GGG haplotype and 50.0% among carriers of minor frequency SNP haplotypes (p: 0.031; OR: 0.39; 95% CI: 0.17–0.91) (Fig. 2). Similar differences between carriers of the common GGG haplotype and of SNP haplotypes were found in the achievement of HiSCR response after 36 weeks of treatment, and a trend toward significant difference was noted after 48 weeks of treatment.

Carriage of SNP haplotypes was associated with lower relative decrease in the AN count at weeks 12 and 24. The dT count and IHS4 score were not statistically different between groups (Fig. 3).

Table 1. Comparative demographics of study participants by HiSCR response to ADA after 12 weeks of treatment

	HiSCR nonresponders, $n = 40$	HiSCR responders, $n = 77$	p value
Female sex, *n* (%)	24 (60.0)	41 (53.2)	0.558
Age, mean (SD), years	41.2 (13.7)	38.9 (11.2)	0.383
Age at HS onset, mean (SD), years	27.7 (12.0)	25.3 (10.9)	0.308
Number of affected areas, mean (SD)	4.66 (2.02)	4.17 (1.98)	0.269
Family history of HS, *n* (%)	5 (12.5)	19 (24.7)	0.151
Exacerbations/year, mean (SD)	4.48 (4.36)	4.03 (4.34)	0.674
BMI, mean (SD), kg/m^2	30.3 (8.6)	29.2 (5.8)	0.482
IN count*, mean (SD)	7.88 (6.22)	6.43 (4.22)	0.159
Abs count*, mean (SD)	1.17 (1.58)	1.51 (2.31)	0.444
dT count*, mean (SD)	7.71 (6.23)	3.12 (3.07)	<0.0001
Hurley II/III stage, *n* (%)	10 (25.0)/30 (75.0)	39 (50.6)/38 (49.4)	0.010
IHS4 score*, mean (SD)	36.8 (28.5)	21.9 (17.6)	0.001
Race, *n* (%)			
Caucasian	38 (95.0)	75 (97.4)	0.605
Afro-American	2 (5.0)	1 (1.3)	0.342
Latino	0 (0)	1 (1.3)	1.00
Comorbidities, *n* (%)			
Acne	2 (5.0)	4 (5.2)	1.00
Hypothyroidism	5 (12.5)	6 (7.8)	0.507
Type 2 diabetes mellitus	4 (10.0)	5 (6.5)	0.489
Crohn disease	0 (0)	2 (2.6)	0.546
Pilonidal sinus	4 (10.0)	6 (7.8)	0.734
Dyslipidemia	0 (0)	3 (3.9)	0.550
Polycystic ovary syndrome	0 (0)	3 (3.9)	0.550
Arterial hypertension	1 (2.5)	2 (2.6)	1.00
Peptic ulcer	2 (5.0)	1 (1.3)	0.342
Charlson's Comorbidities Index, mean (SD)	0.44 (0.85)	0.43 (0.77)	0.940
Carriage of at least one SNP of *TNF*, *n* (%)	16 (40.0)	16 (20.8)	0.031

BMI, body mass index; HiSCR, Hidradenitis Suppurativa Clinical Response; IHS4, International Hidradenitis Suppurativa 4 score; *n*, number of patients; SD, standard deviation; TNF, tumor necrosis factor. *Data refer to 107 patients.

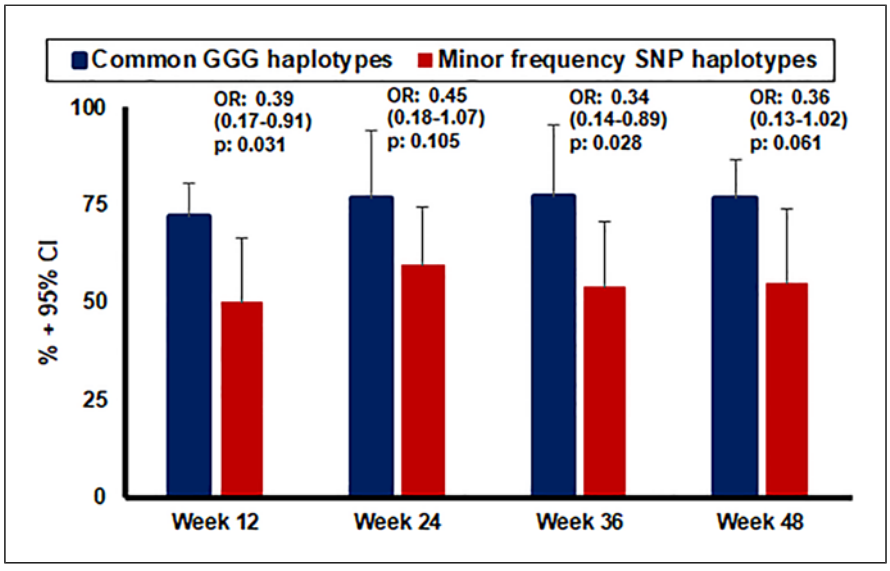

Fig. 2. Comparative HiSCR response after treatment with ADA between carriers of haplotypes of the *TNF* gene promoter containing only major alleles and carriers of haplotypes containing at least one SNP allele. The p values of the indicated comparisons by the Fisher's exact test are provided. The OR refers to the odds of positive response to ADA treatment among patients with any minor frequency SNP haplotype compared to the common GGG haplotype. Haplotypes consist of the alleles of each of rs1800750 (−376 G/A), of rs1800629 (−308 G/A), and of rs361525 (−238 G/A). CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response score; OR, odds ratio; SNP, single nucleotide polymorphism.

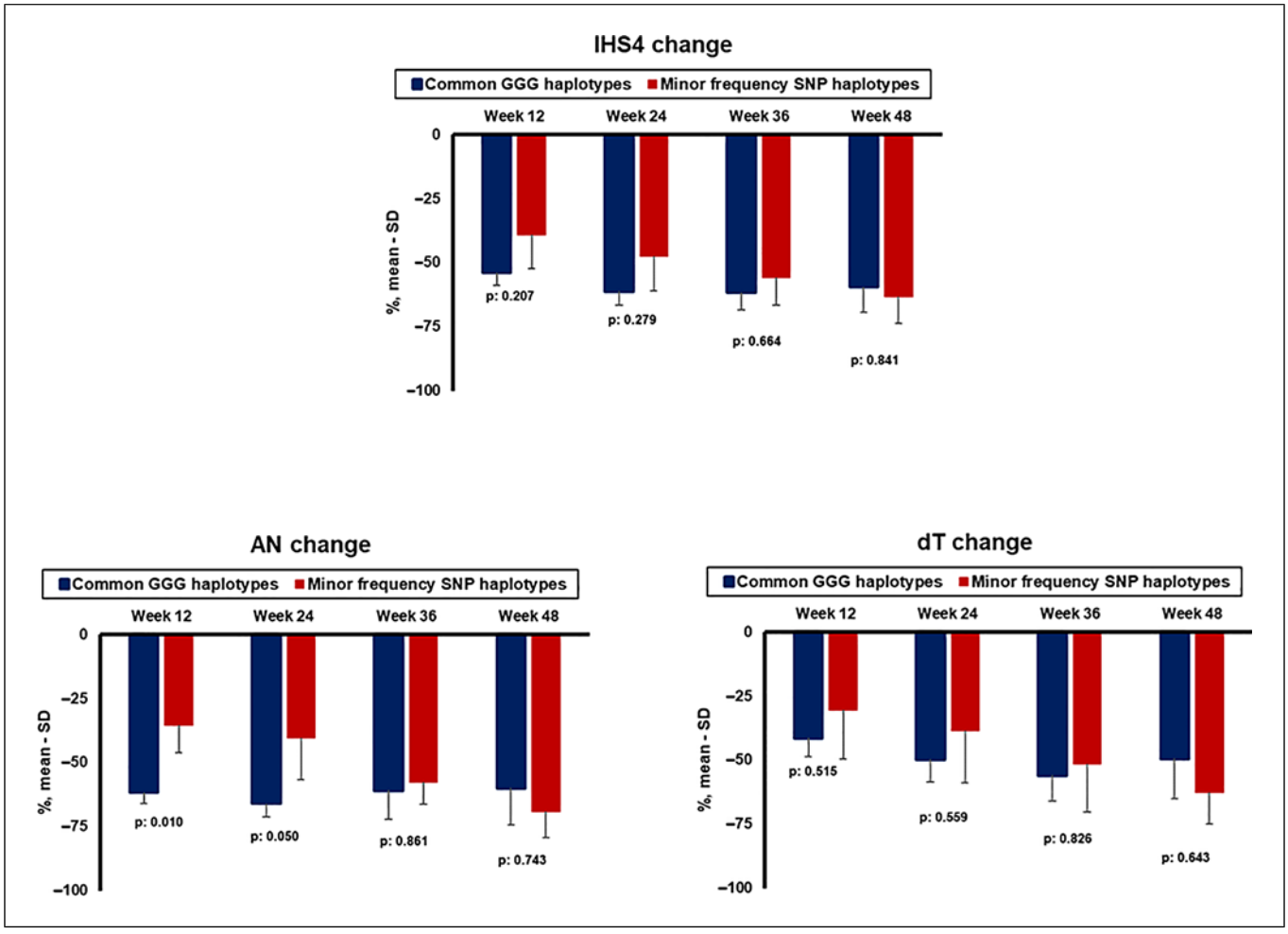

Fig. 3. Comparative changes of lesions after treatment with ADA between carriers of haplotypes of the *TNF* gene promoter containing only major alleles and carriers of haplotypes containing at least one SNP allele. The *p* values of the respective comparisons by the Student's *t* test are provided. Haplotypes consist of the alleles of each of rs1800750 (-376 G/A), of rs1800629 (-308 G/A), and of rs361525 (-238 G/A). AN, inflammatory lesions (IN and Abs); dT, draining tunnels; IHS4, International Hidradenitis Suppurativa Severity Scoring System 4 score; SD, standard deviation.

A 55% decrease in IHS4 score, a new efficacy endpoint for HS, was evident in 68.9% of week 12 HiSCR responders and only 12.1% of non-HiSCR responders. Carriers of the common GGG haplotype and carriers of minor frequency SNP haplotypes were not statistically different in the 55% decrease in IHS4 score (Fig. 4).

Discussion

The results of the present study suggest that carriage of minor frequency SNP haplotypes of the promoter of *TNF* decreases significantly the likelihood of HiSCR response to ADA after 12 weeks of treatment. This effect persists for at least 36 weeks. Carriage of A allele haplotypes impacts the efficacy of ADA on the AN count; no effect on the dT count is found. This also explains why the achievement of 55% or more decrease in the baseline IHS4 cannot be shown among carriers of minor frequency haplotypes, since the dT count impacts most on the HIS score [7]. This is the first study to our knowledge in HS which correlates the carriage of haplotypes containing SNPs of the minor frequency A alleles of *TNF* promoter with poor response to ADA. Our data offer a possible explanation for the wide range of published efficacies of ADA treatment in HS.

The gene SNPs which modulate response to treatment with anti-TNFs are involved in the activation of nuclear factor-kappaB. The impact of the carriage of SNPs in *TNF* on the response to anti-TNFs has been documented in other diseases. One seminal study from Chile showed that the

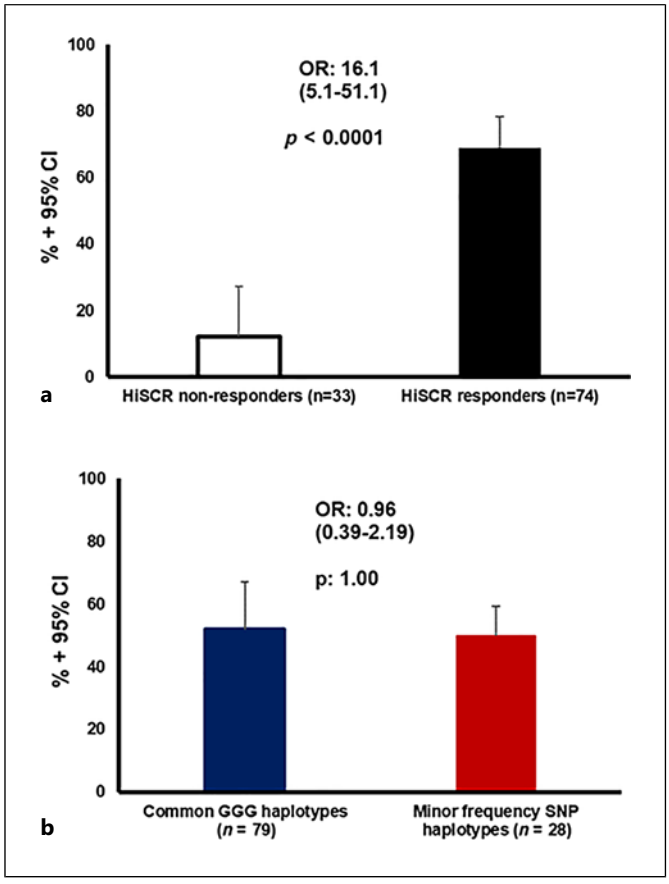

Fig. 4. Association of HiSCR response after 12 weeks of treatment with ADA and change in baseline IHS4 score. Results refer to 107 patients since for 10 patients lesion counts were not captured. **a** Achievement of 55% or more decrease in baseline IHS4 score among HiSCR responders and HiSCR nonresponders. **b** Achievement of 55% or more decrease in baseline IHS4 score among carriers of haplotypes containing only major frequency G alleles of the *TNF* gene promoter and carriers of haplotypes containing at least one minor frequency A allele of the *TNF* gene promoter. The p values of the respective comparisons by the Fisher's exact test are provided. Haplotypes consist of the alleles of each of rs1800750 (-376 G/A), of rs1800629 (-308 G/A), and of rs361525 (-238 G/A). CI, confidence interval; HiSCR, Hidradenitis Suppurativa Clinical Response score; OR, odds ratio; *n*, number of patients.

treatment response of patients with rheumatoid arthritis (RA) to ADA was 88.2% among carriers of G alleles of rs1800629 compared to 68.4% of carriers of A alleles [10]. This was confirmed in another study, where carriage of haplotypes by minor frequency alleles of rs1800629 and rs361525 decreased response to treatment [11]. A recent meta-analysis included 30 studies and aimed to unravel the association between the genetic make-up of the host and response of RA to treatment with anti-TNFs. Six of the included trials were genome-wide association studies, and 24 were candidate gene studies. Although several genotypes were correlated with treatment response, the findings were not consistent among studies. As a consequence, a specific genotype was not able to be suggested as prognostic of response to treatment [12].

Candidate gene studies have also shown that the carriage of the A allele of rs1800629 is associated with a poor response to ADA in juvenile idiopathic arthritis [13], inflammatory bowel disease, and spondyloarthritis [14]. The OR for response to treatment among carriers of A alleles was 0.43, which mirrors the 0.39 reported for HS in our study. The comparisons of the OR for response to ADA according to carriage of *TNF* SNP alleles to ADA should take into consideration that the dose regimen of ADA for RA and juvenile idiopathic arthritis was different than HS; in these patients, ADA was administered every other week [10, 13].

Similar to our results where carriers of the major frequency alleles had better response to ADA in HS, previous studies have demonstrated better anti-TNF efficacy for these common frequency carriers in psoriasis as well. In one study, 82.5% of carriers of G alleles of rs361525 and 58.8% of carriers of A alleles of rs361525 demonstrated more than 75% psoriasis area severity index (PASI) responses to anti-TNF after 6 months of treatment [15]. The second study analyzed 97 patients and reported that the frequency of the GG genotype of rs361525 was 92.5% of responders compared to 63.2% of nonresponders to etanercept. Similarly, the third study showed that the frequency of the GG genotype of rs1800629 was 81.4% among responders [16].

The two major strengths of our study are the prospective design and the enrollment of patients from three different study sites. Previously, the majority of studies associating treatment response of RA, inflammatory bowel disease, and psoriasis with the genetic make-up have been retrospective in design. The main limitation is the lack of information on the functional impact of the studied SNPs on the tissue expression of TNF in the lesions of HS. The poor effect on the AN count is indirect evidence that these SNPs are associated with the intensity of the inflammatory process.

In conclusion, our study is the first in HS to find an association between carriage of at least one minor frequency SNP haplotype of the promoter of the *TNF* gene and a poor response to treatment with ADA. These findings have important implications for further research to investigate if SNPs can be utilized to predict treatment response.

Key Message

Carriage of minor frequency SNP haplotypes in the *TNF* gene promoter decreases the likelihood of response to adalimumab in hidradenitis suppurativa.

Statement of Ethics

The STAGE study was approved by the Ethics Committees of ATTIKON University General Hospital (approval EBD11/10-01-2019); of Papageorgiou Hospital of Thessaloniki (approval A12/26-02-2019); and of the Ohio State University in Ohio, USA (approval 2018H0314/26-09-2018). Written informed consent was provided by all study participants.

Conflict of Interest Statement

J.K. is principal investigator for trials funded by AbbVie, Eli Lilly, Incyte, Janssen, Pfizer, Regeneron, and UCB.; and T.K. has received honorarium from XBiotech. E.G-B. has received honoraria from Abbott CH, bioMérieux, Brahms GmbH, GSK., InflaRx GmbH, Sobi, and XBiotech Inc.; independent educational grants from Abbott CH, Axis-Shield, bioMérieux Inc., InflaRx GmbH, Johnson & Johnson, MSD., Novartis, Sobi, and XBiotech Inc.; and funding from the Horizon 2020 Marie Skłodowska-Curie International Training Network "the European Sepsis Academy" (granted to the National and Kapodistrian University of Athens), and the Horizon 2020 European Grants ImmunoSep and RISCinCOVID (granted to the Hellenic Institute for the Study of Sepsis), and the Horizon Health grant EPIC-CROWN-2 (granted to the Hellenic Institute for the Study of Sepsis). The other authors have no conflict of interest to declare concerning this study.

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Author Contributions

M.A. drafted the study protocol, collected clinical data, drafted the manuscript, and approved the final version to be submitted. A.T., J.K., D.S., E.M., S.M., A.K., P.M., T.K., and E.L. collected clinical data, edited the manuscript, and approved the final version to be submitted. G.D. performed DNA isolation and SNP lab analysis, edited the manuscript the manuscript, and approved the final version to be submitted. E.G.B. conceived the study, supervised the study, analyzed the data, drafted the manuscript, and approved the final version to be submitted.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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