

ADAM17 Genetic Variants and the Response of TNF- α Inhibitor in Rheumatoid Arthritis Patients

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Purpose: TNF- α is a transmembrane protein which requires cleavage by ADAM17 in order to act systemically. The activation of ADAM17 to generate soluble TNF- α results in an increased inflammatory activity. We hypothesized that variants spanning the ADAM17 gene contribute towards the observed variation in patient response defined by the number of changes in TNF- α inhibitors.

Patients and Methods: Seven single-nucleotide polymorphisms (SNPs) of ADAM17 in 63 patients with rheumatoid arthritis who received TNF- α inhibitors were analyzed: rs57467365, rs62117540, rs117645314, rs6432013, rs532704607, rs117179141, and rs12692386. Univariate and multivariate regression analysis were employed to investigate the independent predictable factors for changes in TNF- α inhibitors.

Results: ADAM17 rs117645314 and rs117179141 showed significant association with the number of changes in TNF- α inhibitors. Patients with GA in rs117645314 and AT in rs117179141 had significantly higher chance of two or more changes of TNF- α inhibitors than those with wild homozygous alleles. Multivariate analysis showed that rs117179141 explained 5.7% of the 23.8% variability in TNF- α inhibitor response.

Conclusion: This study showed that the number of changes in TNF- α inhibitor is associated with ADAM17 SNPs.

Keywords: rheumatoid arthritis, TNF- α inhibitor, ADAM17, single-nucleotide polymorphism

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation that mainly affects the joints. RA is an intricate, polygenic and heterogeneous disease characterized by complex interactions between genetic and environmental factors. The immune-mediated background is validated by the critical role of immune-suppressive therapies. Since the introduction of the first drugs of this class, the Tumor Necrosis Factor- α inhibitor (TNFi), the prognosis is much better than before. Recently, more immune mediators are under development, drugs targeting B cells, T cells or intracellular kinases.^{1,2} This choice of drugs is welcomed because none of them is effective in all patients. Typically, about 30% of the patients fail to respond to any of the drugs, and an additional 30% of patients show only a partial response. This variability in response drives rheumatologist to change from one drug to another, and by combining them with conventional antirheumatic drugs.³

Gene studies had been performed in order to investigate genetic biomarkers which could play an integral part in disease susceptibility and treatment. In regards

to TNFi, most studies included small number of patients with inconsistent results.^{4–8} Previously investigated genes in associations with TNFi include tumor necrosis factor gene, PDE3A-SLCO1C1, protein tyrosine phosphatase receptor type C, fragment C gamma receptor, and mitogen-activated protein kinase 14.^{9–13} More than 40 candidate gene studies and 6 GWAS regarding the response to TNFi have been performed previously.^{14,15} However, much of the research conducted has been focused on candidate genes related to susceptibility of the disease that are not necessarily the same as those involved in the treatment response. Also, in many cases, results of different studies show contradictory or inconclusive conclusions making it difficult to apply the pharmacogenetics of TNFi into clinical practice.

In an effort to discover genetic markers of TNFi response, we investigated a gene with a close relation to TNF- α pathway. TNF- α is a pro-inflammatory cytokine which undergoes proteolysis by TNF- α converting enzyme (TACE).¹⁶ A disintegrin and metalloproteinase 17 (ADAM17), also known as TACE, is a membrane bound enzyme that cleaves immune cell surface cytokine and cytokine receptor, such as TNF α and IL-6. Here, we examined the influence of ADAM17 genetic polymorphisms on the treatment response of TNFi.

Methods

Patients

The study population consisted of 63 patients with rheumatoid arthritis who were prescribed TNFi in Ajou University Hospital and Chungbuk National University Hospital between January 2008 and December 2018. Patients' data were collected from electronic medical records from both hospitals. This study was approved by the ethics committees (Ajou University Hospital: AJIRB-BMR-OBS-17-153 and Chungbuk National University Hospital: 2017-06-011-004) and patients gave their written informed consent. The study was conducted according to the principles of the Declaration of Helsinki (2013).

Genotyping

Seven single-nucleotide polymorphisms (SNPs) of ADAM17 (rs57467365, rs62117540, rs117645314, rs6432013, rs532704607, rs117179141, rs12692386) were selected based on <http://grch37.ensembl.org/index.html> with minor allele frequency of greater than 10% in Japanese and Han Chinese in Beijing. Genotyping was

conducted by SNaPshot assay in six SNPs and TaqMan Genotyping assay was used for rs12692386. Genomic DNA was purified from blood sample or buffy coat samples using the QIAamp DNA Blood Mini Kit (QIAGEN GmbH, Hilden, Germany) in accordance with the manufacturer's protocol. All seven SNPs were in concordance with the Hardy–Weinberg equilibrium.

Statistical Analysis

We examined the number of changes in TNFi for the primary outcome reflecting the response of TNFi. The criteria for change in TNFi were lack of efficacy, presence of adverse events or noncompliance. We have divided the number of changes in TNFi into three groups as none, once, and two or more changes. The Pearson's χ^2 -test or Fisher's exact test was used for categorical and multinomial logistic regression was used to compare continuous variables. Stepwise linear regression analysis was used to assess multivariate relationships between demographic, clinical, and genetic variables and changes in TNFi. Factors having P-values < 0.05 from univariate analysis along with age and sex were included in the multivariate analysis. Variables were entered by stepwise selection for P < 0.05 and were removed for P > 0.1. P-values < 0.05 were considered statistically significant. Statistical Package for Social Sciences version 25.0 for Windows (SPSS, Chicago, IL, USA) was used for all analyses. The Haploview 4.2 software package was used to estimate pairwise linkage disequilibrium (LD), detect departure from the Hardy–Weinberg equilibrium, and construct haplotypes. The haplotype block was created based on the default algorithm of Burmester et al.^{17,18}

Results

A total of 63 patients were included in the analysis and 17 patients showed one or more changes of therapy in TNFi. The median age of patients was 56 years, ranging from 19 to 78, and 77.8% were females. Most patients denied alcohol use or smoking (79.4% and 76.2%, respectively). Except three patients without the record of tuberculosis test, 20.7% of patient revealed pulmonary tuberculosis or positive interferon-gamma release assay (IGRA) or positive PPD test.

The number of changes in TNFi was associated with a significant increase in disease duration (p= 0.038). Nine patients had a history of hypertension, which showed statistical significance in relation to the number of changes in TNFi. (p= 0.042). Each component of disease activity

Table I Baseline Characteristics of Patients

	Number of Changes in TNF- α Inhibitors			P value
	None	Once	Two or More	
Age, years	53 \pm 15	55 \pm 11	54 \pm 18	0.712
Height, cm	159.8 \pm 7.6	160.4 \pm 10	161.8 \pm 9.2	0.656
Weight, kg	59 \pm 9.9	61.6 \pm 13.9	47.3 \pm 6.8	0.079
Sex, n (%)				0.367
Male	12 (85.7)	2 (14.3)	0	
Female	34 (69.4)	9 (18.4)	6 (12.2)	
Alcohol, n (%)				0.312
Yes	4 (57.1)	3 (42.9)	0	
No	38 (76.0)	7 (14.0)	5 (10.0)	
Unknown	4 (66.7)	1 (16.7)	1 (16.7)	
Smoking, n (%)				0.880
Current	5 (71.4)	1 (14.3)	1 (14.3)	
Former	3 (100)	0	0	
Never	35 (72.9)	9 (18.8)	4 (8.3)	
Unknown	3 (60.0)	1 (20.0)	1 (20.0)	
Tuberculosis, n (%)				0.903
Interferon-gamma Release Assay -				
Pulmonary tuberculosis	3 (100.0)	0 (0)	0 (0)	
IGRA + or PPD +	8 (80.0)	2 (20.0)	0 (0)	
IGRA indeterminate	3 (75.0)	1 (25.0)	0 (0)	
Unknown	2 (66.7)	1 (33.3)	0 (0)	
Duration of rheumatoid arthritis, month	93 \pm 61	89 \pm 54	177 \pm 153	0.038
Comorbidities, n (%)				0.720
Type 2 Diabetes Mellitus				
Yes	4 (100)	0	0	
No	42 (71.2)	11 (18.6)	6 (10.2)	
Hyperlipidemia				0.688
Yes	6 (75.0)	2 (25.0)	0	
No	40 (72.7)	9 (16.4)	6 (10.9)	
Hypertension				0.042
Yes	5 (55.6)	1 (11.1)	3 (33.3)	
No	41 (75.9)	10 (18.5)	3 (5.6)	
Osteoporosis				0.408
Yes	6 (66.7)	1 (11.1)	2 (23.2)	
No	40 (74.1)	10 (18.5)	4 (7.4)	
Disease activity score				
28 tender joint count	9 \pm 7	9 \pm 7	13 \pm 9	0.302
28 swollen joint count	7 \pm 7	6 \pm 4	5 \pm 4	0.437
C-Reactive Protein	2.59 \pm 3.73	1.65 \pm 1.18	1.24 \pm 0.98	0.242
General Health	59 \pm 20	65 \pm 17	58 \pm 31	0.774
Disease activity score 28	5.63 \pm 1.21	5.89 \pm 1.01	6.05 \pm 1.67	0.347
Rheumatoid factor, n (%)				0.862
Positive	38 (71.7)	10 (18.9)	5 (9.4)	
Negative	8 (80.0)	1 (10.0)	1 (10.0)	

(Continued)

Table 1 (Continued).

	Number of Changes in TNF- α Inhibitors			P value
	None	Once	Two or More	
Anti-cyclic citrullinated peptide antibody, n (%)				0.296
Positive	32 (71.1)	10 (22.2)	3 (6.7)	
Negative	10 (71.4)	1 (7.1)	3 (21.4)	
Unknown	4 (100)	0	0	

Abbreviations: IGRA, interferon-gamma release assay; PPD, purified protein derivative.

score (DAS) as well as the total DAS28 score at baseline did not differ among the groups. Fifty-three patients (84.1%) were positive for rheumatoid factor (RF) and 45 patients (71.4%) were positive for anti-cyclic citrullinated peptide antibody (ACPA). Both tests of RF and ACPA were not statistically significant among the groups (Table 1).

The most frequently prescribed TNFi was adalimumab (n=25), followed by golimumab (n=13). Non-TNF inhibitors, which were used prior to TNFi or concurrently, include conventional disease-modifying anti-rheumatic drugs such as methotrexate, leflunomide, sulfasalazine and hydroxychloroquine and newer agent such as tofacitinib. There were 18 patients who used hydroxychloroquine

Table 2 TNF- α Inhibitors and Non-TNF- α Inhibitors Used for Study Subjects

	Number of Changes in TNF- α Inhibitors			P value
	None	Once	Two or More	
Duration of TNF- α inhibitor, month	31.59 \pm 31.20	17.18 \pm 19.88	15.67 \pm 15.11	0.190 0.454
TNF- α inhibitor, n (%)				
Adalimumab	19 (76.0)	4 (16.0)	2 (8.0)	0.093
Etanercept	8 (66.7)	1 (8.3)	3 (25.0)	
Golimumab	11 (78.6)	2 (14.3)	1 (7.1)	
Infliximab	8 (66.7)	4 (33.3)	0	
Non-TNF inhibitor, n (%)				1.000
Tofacitinib				
Yes	4 (50.0)	2 (25.0)	2 (25.0)	0.424
No	42 (76.4)	9 (16.4)	4 (7.3)	
Methotrexate				0.003
Yes	39 (73.6)	9 (17.0)	5 (9.4)	
No	7 (70.0)	2 (20.0)	1 (10.0)	1.000
Leflunomide				
Yes	12 (66.7)	5 (27.8)	1 (5.6)	1.000
No	34 (75.6)	6 (13.3)	5 (11.1)	
Hydroxychloroquine				1.000
Yes	8 (44.4)	6 (33.3)	4 (22.2)	
No	38 (84.4)	5 (11.1)	2 (4.4)	1.000
Sulfasalazine				
Yes	3 (100)	0	0	1.000
No	43 (71.7)	11 (18.3)	6 (10)	
Steroid				1.000
Yes	36 (72.0)	9 (18.0)	5 (10.0)	
No	10 (76.9)	2 (15.4)	1 (7.7)	

and these users were statistically more likely to fail the first TNFi ($p=0.003$). Steroids were used in all patients showing no statistical difference among the groups (Table 2).

Of the 7 SNPs analyzed, no mutation was detected in rs532704607 SNP in our patients. For three SNPs, rs117645314, rs6432013, and rs117179141, homozygous variant allele carriers did not exist. Two SNPs showed statistical differences in number of changes in TNFi: rs117645314 and rs117179141 (Table 3). In rs117645314 SNP, GG-carriers had significantly lower chance of two or more changes in TNFi than those with GA genotypes (OR=0.12, 95% CI 0.02–0.78). For rs117179141 allelic variation, patients with AA genotype showed significantly lower chance of two or more changes in TNFi than those with AT-carriers (OR=0.12, 95% CI 0.02–0.78).

Haplotype analyses were performed for 6 SNPs in ADAM17 gene with mutations in our patients. LD was observed across rs117645314, rs6432013 and rs117179141 ($D^2=1$ among all three SNPs, $r^2=1$ between rs117645314 and rs117179141, and $r^2=0.33$ between rs6432013 and

other two SNPs). There was a strong LD between rs6432013 and rs12692386 ($D^2=0.79$, $r^2=0.63$) (Figure 1).

Stepwise linear regression analysis was used to determine the independent effects of the possible genetic factors of TNFi response. Age and sex were fixed inclusion factors, and variables with $p < 0.05$ from univariate analysis, including two statistically significant SNPs, were included in our model. Multicollinearity was checked which showed variance inflation factor values from 1.00 to 1.13, indicating a low correlation of predictor variables. In the final model, hydroxychloroquine use accounted for 16.1% and rs117179141 accounted for 5.7% of the total 23.8% variability in observed number of changes in TNFi (Table 4).

Discussion

Despite the proven efficacy of anti-TNF drugs in the treatment of rheumatoid arthritis, a significant inadequate response rate is exhibited.¹⁹ Current clinical factors provide little power for predicting response; therefore, “trial

Table 3 Univariate Analysis of Genetic Polymorphisms of ADAM17 with Number of Changes in TNF- α Inhibitors

ADAM17 SNPs	TNF- α Inhibitor Switch			P value
	None	Once	Two or More	
rs12692386				0.299
AA	33 (76.7)	8 (18.6)	2 (4.7)	
AG	12 (63.2)	3 (15.8)	4 (21.1)	
GG	1 (100)	0	0	
rs57467365				0.629
AA	23 (79.3)	3 (10.3)	3 (10.3)	
AT	20 (66.7)	7 (23.3)	3 (10.0)	
TT	3 (75.0)	1 (25.0)	0	
rs117645314				0.018
GG	41 (74.5)	11 (20.0)	3 (5.5)	
GA	5 (62.5)	0	3 (37.5)	
rs62117540				0.916
AA	35 (72.9)	8 (16.7)	5 (10.4)	
AG	10 (71.4)	3 (21.4)	1 (7.1)	
GG	1 (100)	0	0	
rs6432013				0.180
GG	33 (76.7)	8 (18.6)	2 (4.7)	
GT	13 (65.0)	3 (15.0)	4 (20.0)	
rs117179141				0.018
AA	41 (74.5)	11 (20.0)	3 (5.5)	
AT	5 (62.5)	0	3 (37.5)	

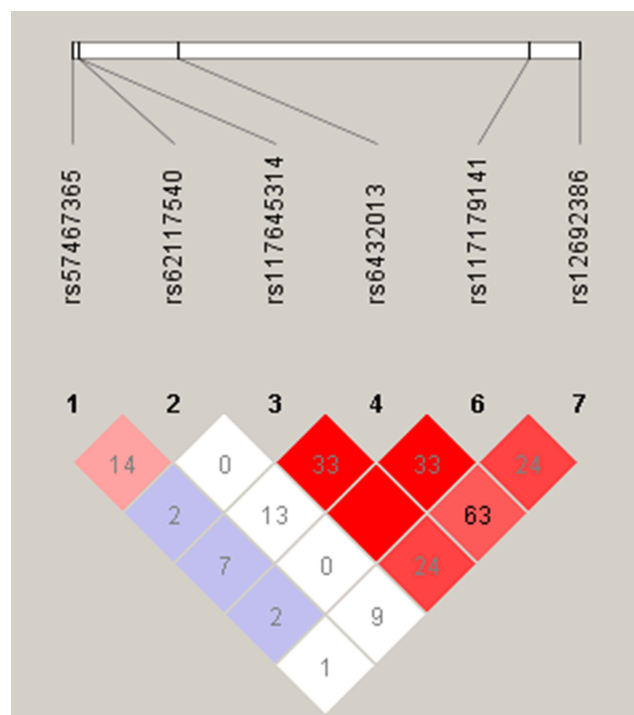


Figure 1 Relative positions and linkage disequilibrium (LD) estimates in ADAM17 polymorphisms in the analyzed population.

Notes: Colored squares correspond to r^2 values with numerical estimates given within the squares. The squares without a number correspond to $r^2 = 1$. Shading represents the magnitude and significance of pairwise LD, with a red-to white gradient reflecting higher to lower LD values.

and error” approach governs therapeutic decisions. In order to investigate clinically meaningful genetic polymorphism associated with TNFi, we examined ADAM17 SNPs. We found that rs117179141 and rs117645314 were statistically significant SNPs associated with the number of changes in TNFi.

The ADAM is a transmembrane protein, which is crucial for various biological processes, such as inflammation, migration and immunity. ADAM17, also recognized

Table 4 Multivariable Regression Model Predicting Number of Changes in TNF- α Inhibitors

Step	Predictors	Parameter	R ² value	p-value
0	Intercept	0.934		
1	Hydroxychloroquine	0.542	0.161	0.001
2	rs117179141 (AA=0, AT=1)	0.519	0.057	0.020
3	Disease duration, month	0.002	0.057	0.036
			Total 0.238	

as TACE, is responsible for the shedding of many substrates including TNF- α and IL-6R which mediate various inflammation-promoting biological activities.^{20,21} TACE expressions were up-regulated in rheumatoid arthritis patients and TACE was shown to be an important regulator of the secretion of TNF- α in previous studies.^{22,23}

Among the small number of studies examining the relationship between ADAM17 and pharmacotherapy, Umemura et al reported that suppression of ADAM17 can be a crucial therapeutic target in the treatment of abatacept in patients with rheumatoid arthritis.²⁴ Another study showed that ADAM17 haplotype was associated with a clinical response to infliximab in Crohn’s disease patients.²⁵ This haplotype included 11 SNPs spanning from the rs2001658 to the rs11684747, but none of the SNPs overlapped with our SNPs of interest. There was a study using a UK cohort which evaluated the association of TACE polymorphism with TNFi treatment response, but showed no significance in the 10 SNPs included.²⁶ Seven SNPs in our study did not overlap with the UK study due to the ethnic difference although similar selection criteria of minor allele frequency was used.

Of the seven SNPs from our study, two SNPs, rs117645314 and rs117179141, were shown to be statistically significantly associated with TNFi response. Unfortunately, studies including these two SNPs are scarce, making it difficult to clarify the underlying mechanism accordingly. We can speculate about the possible influence of SNPs on the response of TNFi as an association with other regulatory SNPs in LD.²⁷ One of the regulatory SNPs that may influence gene expression was found to be rs76947488 which was in strong LD with rs117179141. SNPs in strong LD with rs76947488 were rs72777025 in intergenic region and rs12692387 in regulatory region. But, rs117645314 was not in a strong LD with rs76947488 nor rs72777025, suggesting the putative functional role would be in rs117179141 and not rs117645314.²⁸

In order to examine the effects of SNPs on ADAM17 gene expression, we examined the expression profiling using GTEx datasets.²⁹ Unfortunately, two statistically significant SNPs (rs117179141 and rs117645314) were not found in GTEx datasets. We observed significant expression quantitative trait loci eQTL for linked SNPs of rs76947488, rs72777025 and rs12692387 in skeletal muscle tissue, which revealed significantly higher expressions with variant type alleles ($p = 4.4 \times 10^{-5}$, $p = 1.8 \times 10^{-11}$ and $p = 1.6 \times 10^{-17}$, respectively). Given these

findings of statistically different gene expression profile of SNPs in LD with the significant SNPs of our interest, involvement of ADAM17 in the treatment response of TNFi warrants further studies in different patient groups and populations.

The limitation of this study is the small sample size due to the limited number of rheumatoid arthritis patients in epidemic aspect. Thus, the effect of clinical and genetic variables on the treatment response according to each TNF-alpha inhibitor could not be revealed. The limited number of patients included and the absence of replicative cohort warrants future investigation with larger sample size in longer study period.

Conclusion

There is an evidence that ADAM17 affects clinical phenotype. However, as most SNP frequencies are relatively low and clinical variations associated with these SNPs are not severe, the impact of a single SNP on TNFi response may be limited. Further studies of the mechanisms underlying the observed association of SNPs with clinical outcomes could provide additional understandings that may assist the results of this study leading to new possibilities for drug treatment.

Abbreviations

RA, rheumatoid arthritis; TNFi, tumor necrosis factor- α inhibitor; TACE, TNF- α converting enzyme; ADAM17, A disintegrin and metalloproteinase 17; SNPs, single-nucleotide polymorphisms; DAS, disease activity score; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; LD, linkage disequilibrium.

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Disclosure

The authors report no conflicts of interest in this work.

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