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REVIEW

Systematic review and meta-analysis: pharmacogenetics of anti-TNF treatment response in rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects ~ 1% of the Caucasian population. Over the last decades, the availability of biological drugs targeting the proinflammatory cytokine tumour necrosis factor α, anti-TNF drugs, has improved the treatment of patients with RA. However, one-third of the patients do not respond to the treatment. We wanted to evaluate the status of pharmacogenomics of anti-TNF treatment. We performed a PubMed literature search and all studies reporting original data on associations between genetic variants and anti-TNF treatment response in RA patients were included and results evaluated by meta-analysis. In total, 25 single nucleotide polymorphisms were found to be associated with anti-TNF treatment response in RA (19 from genome-wide association studies and 6 from the meta-analyses), and these map to genes involved in T cell function, NFκB and TNF signalling pathways (including *CTCN5, TEC, PTPRC, FCGR2A*, *NFKBIB, FCGR2A, IRAK3)*. Explorative prediction analyses found that biomarkers for clinical treatment selection are not yet available.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects ~ 1% of the Caucasian population.[1] Disease onset typically manifests at age of 35–50 years, and females are affected 2.5 times more frequently than males. RA is characterised by synovial inflammation of joints most often affecting the joints of hands, wrist and feet, potentially leading to joint destruction, and functional disability. Furthermore, extra-articular manifestations may occur, for example, osteoporosis, vasculitis or interstitial lung disease. The manifestations are consequences of a chronically activated immune system. Both proinflammatory cytokines as tumour necrosis factor (TNF), interleukin (IL)-6, IL-8, GM-CSF, IL-1 and anti-inflammatory cytokines as IL-10 are involved. TNFα is a member of the TNF family of regulators of immune and inflammatory responses, which may also mediate cell death.[2]

In the 1980s, it was shown that TNFα has a prominent role in RA,[3–5] and over the past decades, the availability of drugs targeting tumour necrosis factor α (anti-TNF) has improved the treatment of RA patients. Nevertheless, only 60–70% of patients have a good to moderate response to the anti-TNF treatment, whereas 30–40% have no or insufficient response.[2,6] Apart from anti-TNF drugs, biological compounds targeting CD20, T-lymphocyte antigen 4 immunoglobulin, interleukin 6 receptor and B-cells have been developed.[7,8] Until now, the treatment paradigm has been 'one drug suits all'. Thereby, patients may remain in high disease activity, with irreversible joint damage as a possible consequence. Pharmacogenetics may identify the individual patient's signature that may help guide the treatment selection (reviewed in refs 9,10). Genetic variants may impact anti-TNF drug response.[9–16] They may therefore be utilised as biomarkers for treatment selection by stratifying patients according to the expected response following medical treatment. Furthermore, genetic biomarkers hold the advantage that they do not change over time.

Biomarkers able to predict treatment response will help optimising treatment, reduce adverse side-effects and avoid treatment with drugs without effect in the individual patients. In addition, such biomarkers will also help improving the use of health care resources. The expectations from patients, health care professionals and health authorities are high. 'Personalised medicine represents one of the most innovative new concepts in health care. It holds real promise for more effective early diagnosis and more effective and less toxic treatments for patients, for improved medical service to citizens, and for improving the overall health of the population' (http://permed2020.eu/., 2015). 'Personalised medicine refers to a medical model using characterisation of individual's phenotypes and genotypes (for example, molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention' (http://permed2020.eu/., 2015). Until now, most advances in applied pharmacogenetics have taken place in the field of anticancer therapy.[17]

Thus, we undertook to review case–control studies on genetic variants associated with anti-TNF treatment response in RA patients.

MATERIALS AND METHODS

A systematic review and meta-analysis were carried out according to the guidelines of 'Preferred Reporting Items for Systematic

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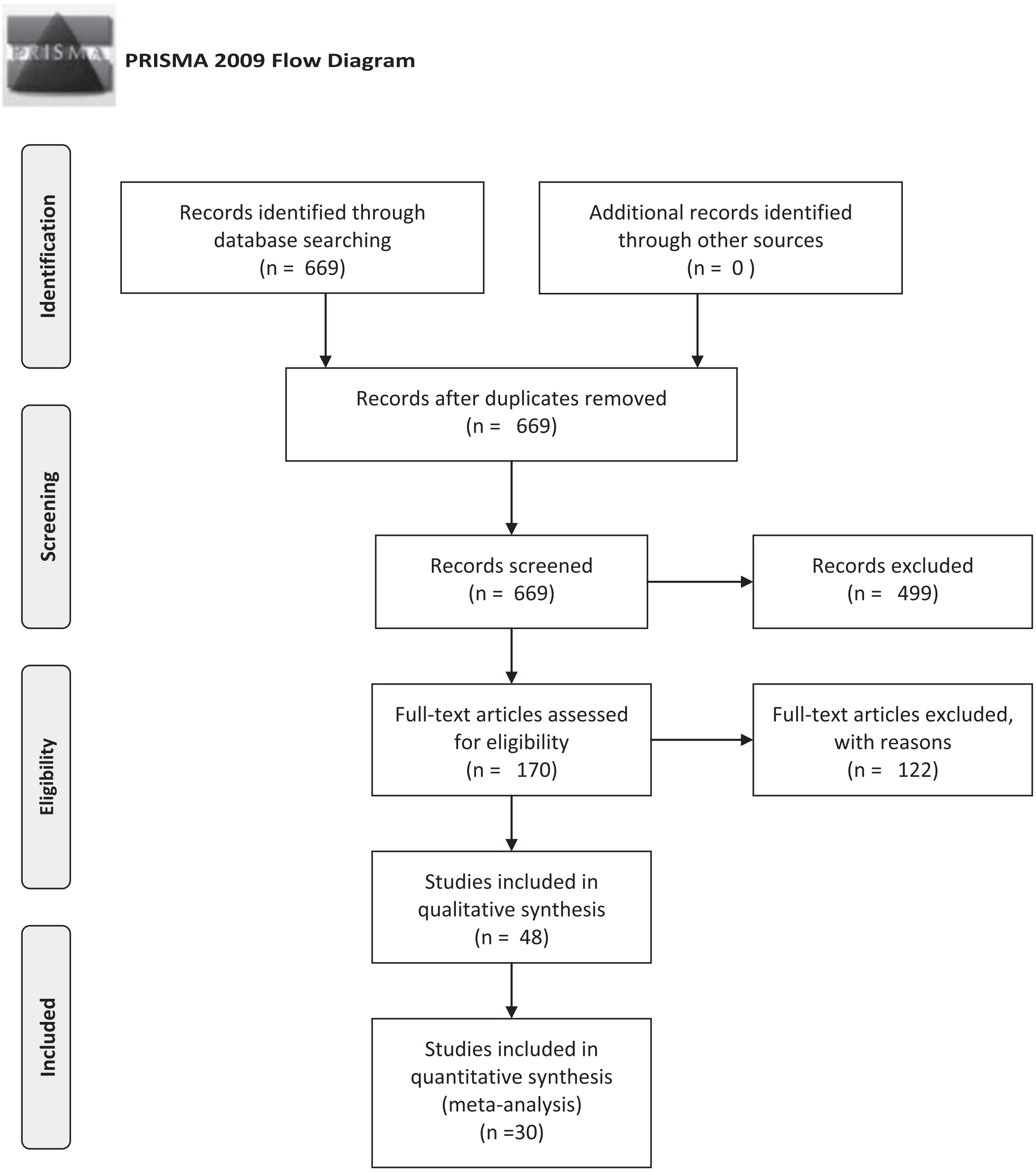

Figure 1. Flow diagram of included studies.

Reviews and Meta-Analyses' (PRISMA) statement.[18] Three individual searches were performed in PubMed combining various alternative search terms for (1) 'anti-TNF treatment', (2) 'genetic variation' and (3) 'autoimmune disease', respectively, resulting in 669 abstracts (latest search date: 29th of August 2016). A full list of search terms is found in Supplementary Table 1. Figure 1 shows the flow diagram of included studies. All studies suggesting that they presented original data on associations between polymorphisms and anti-TNF treatment response in autoimmune diseases were retrieved (170 articles) and reviewed by three independent authors (SiB, JVN, VA). Exclusion criteria were: <100 cases available for treatment evaluation, missing data on treatment response, not reporting original data and not reporting data on anti-TNF response in RA (122 studies). In total, 47 studies reported association between genetic markers and anti-TNF response in RA. No further studies were identified by searching the literature list of the retrieved articles. Data on study design, number of patients, response criteria, odds ratios (OR) and 95% confidence intervals (95% CI) or numbers of good responders, moderate and non-responders, and genotypes were included.

Statistics

Meta-analysis was performed on studies using EULAR response criteria.[19] All polymorphisms studied in at least two studies (with a minimum of one significant association with response), and where data on genotypes and treatment response could be retrieved, were included in a meta-analysis (30 studies). The meta-analysis was based on the total number of patients in the cohorts.

Table 1. Description of 43 candidate gene studies (candidate) and 5 GWAS on associations between polymorphisms and response to anti-TNF treatment in RA patients

Disease	*Ethnicity/country*	*Biological drug(s)*	*DMARDs*^{a} *(%)*	*MTX*^{a} *(%)*	*Response criteria bases on*	*Response evaluated after*	N *cases*	*Refs.*
Candidate								
RA	Caucasian, Spain	INX/ADM/ETC	100	57.7	ACR/EULAR		1239	Canet *et al.*[29]
RA	Caucasian, UK	INX/ADM/ETC	81.8	—	EULAR^{b}/ΔDAS28^{b}	3–6 months	1750	Smith *et al.*[23]
RA	Denmark	INX/ADM/ETC	84	73	EULAR^{c}	3–6 months	1007	Sode *et al.*[15]
RA	Denmark	INX/ADM/ETC	83	72	EULAR^{c}	3–6 months	469	Sode *et al.*[15]
RA	Caucasian, Poland	INX/ADM/ETC	—	93	EULAR^{c}/ΔDAS28^{d}	12 and 24 weeks	284	Iwaszko *et al.*[24]
RA	Denmark	INX/ADM/ETC	84	—	EULAR	2–6 months	538	Sode *et al.*[16]
RA	Caucasian, Poland	INX/ADM/ETC	—	92	EULAR^{c}/ΔDAS28^{d}	12 and 24 weeks	223	Iwaszko *et al.*[21]
RA	Spain and Greece	INX/ADM/ETC	95	—	EULAR^{c}/ΔDAS28	3 and 6 months	755	Ferreiro-Iglesias *et al.*[28]
RA	Multicenter^{e}	INX/ADM/ETC	—	86.2	EULAR^{c}	6 months	471	Canet *et al.*[22]
RA	Portugal	INX/ADM/ETC	91.8	82.2	EULAR^{f}/ΔDAS28	6 months	383	Canhão *et al.*[58]
RA	The Netherland	ADM	—	82.1	EULAR^{g}/ΔDAS28	14 weeks	302	Dávila-Fajardo *et al.*[32]
RA	Spain and Greece	INX/ADM/ETC	94.6	—	EULAR/ΔDAS28	3, 6 and 12 months	423	Montes *et al.*[33]
RA	Poland	INX/ADM/ETC	—	92.5	EULAR^{h}/ΔDAS28	6 months	280	Swierkot *et al.*[52]
RA	Denmark	INX/ADM/ETC	84.2	—	EULAR^{c}/ACR50	3–6 months	538	Sode *et al.*[14]
RA	Spain and Greece	INX/ADM/ETC	88.4	—	EULAR^{c}/ΔDAS28	3, 6 and 12 months	410	Montes *et al.*[56]
RA	Spanish	INX/ADM/ETC			EULAR/ΔDAS28	6 and 12 months	419	Márquez *et al.*[25]
RA	Spanish	INX/ADM/ETC			EULAR/ΔDAS28	6 and 12 months	134	Márquez *et al.*[25]
RA	Japan	INX/ADM/ETC	28.7	89.1	EULAR^{c}/ΔDAS28	24 weeks	101	Nishimoto *et al.*[31]
RA	Spain	INX/ADM/ETC	78.9		EULAR^{c}	6,12,18 and 24 months	199	Dávila-Fajardo *et al.*[31]
RA	Greece	INX/ADM/ETC	—	—	EULAR^{c}/ΔDAS28	6 months	183	Zervou *et al.*[55]
RA	United Kingdom	INX/ADM/ETC	—	—	EULAR$^{c,\ g}$/ΔDAS28	6 months	1278	Mathews *et al.*[44]
RA	Spain	INX/ADM/ETC	—	—	EULAR^{g}/ΔDAS28^{d}	12 weeks	315	Acosta-Colman *et al.*[59]
RA	Italy	ADM	—	—	EULAR	12 weeks	377	Ceccarelli *et al.*[30]
RA	United Kingdom	INX/ADM/ETC	73	—	EULAR^{g}/ΔDAS28^{d}	6 months	1115	Plant *et al.*[47]
RA	The Netherland	INX/ADM	—	61.0	EULAR^{i}	3 months	182	Coenen *et al.*[38]
RA	Sweden	ADM/ETC	—	68.8	EULAR^{i}	3 months	269	Coenen *et al.*[38]
RA	United Kingdom	INX/ADM/ETC	68	—	ΔDAS28 and EULAR^{c}	6 months	1102	Coulthard *et al.*[39]
RA	United Kingdom	INX/ADM/ETC	72	—	ΔDAS28 and EULAR^{c}	6 months	909	Potter *et al.*[48]
RA	United Kingdom	INX/ADM/ETC	72.7	—	ΔDAS28 and EULAR^{f}	6 months	1334	Tan *et al.*[53]
RA	Spain	INX/ADM/ETC	—	—	EULAR^{f}/ΔDAS28^{j}	3 months	151	Suarez-Gestal *et al.*[51]
RA	Multi-cohorts^{k}	INX/ADM/ETC	—	0–100	EULAR^{g}/ΔDAS28	3–12 months	1283	Cui *et al.*[40]
RA	United Kingdom	INX/ADM/ETC	—	—	ΔDAS28	6 months	602	Potter *et al.*[36]
RA	Caucasian	INX/ADM/ETC	—	—	EULAR^{i}/ΔDAS28	6 months	1050	Hassan *et al.*[41]
RA	United Kingdom	INX/ADM/ETC	73	—	ΔDAS28	6 months	624	Bowes *et al.*[26]
RA	United Kingdom	INX/ADM/ETC	68	—	ΔDAS28	6 months	411	Bowes *et al.*[26]
RA	United Kingdom	INX/ADM/ETC	69	—	EULAR^{g}/ΔDAS28	6 months	1050	Maxwell *et al.*[57]
RA	The Netherland	INX/ADM	—	—	ΔDAS28	3 and 6 months	234	Toonen *et al.*[54]
RA	United Kingdom	INX/ADM/ETC	73	—	ΔDAS28	6 months	642	Potter *et al.*[49]
RA	Italy	INX/ADM/ETC	—	—	ΔDAS28/ACR20/50/70^{l}	12 months	105	Ongaro *et al.*[45]
RA	Spain	INX	—	—	ΔDAS28^{d}	30 weeks	113	Pinto *et al.*[35]
RA	France	ADM	72	47	ACR50^{m}	12 weeks	388	Miceli-Richard *et al.*[27]
JIA	Caucasian	INX/ADM/ETC			ACR Pedi 30	3 months	107	Cimaz *et al.*[37]
RA	Sweden	INX/ ETC	—	—	EULAR/ACR20/50/70^{l}	3 months	282	Kastbom *et al.*[42]
JIA	Caucasian	ETC	—	—	ACR-JRA 30^{n}	3 months	137	Schmeling *et al.*[50]
RA	France	INX	—	—	ARC20^{o}	30 weeks	198	Marotte *et al.*[43]
RA	Sweden	ETC	—	—	ARC20^{o}/ΔDAS28	3 months	123	Padyukov *et al.*[46]
GWAS								
RA	Japanese	INX/ADM/ETC	—	—	ΔDAS28	3 and 6 months	444	Honne *et al.*[60]
RA	Spanish	INX/ADM/ETC	—	—	EULAR	12 weeks	361	Julià *et al.*[61]
RA	Dutch	INX/ADM/ETC	—	—	ΔDAS28	3 months	984	Umicevic et.al.[64]

Table 1. (Continued)

Disease	*Ethnicity/country*	*Biological drug(s)*	*DMARDs*[a] *(%)*	*MTX*[a] *(%)*	*Response criteria bases on*	*Response evaluated after*	N *cases*	*Refs.*
RA	Danish	INX/ADM/ETC	—	—	EULAR/ΔDAS28	14 weeks	196	Krintel *et al.*[62]
RA	Great Britain	INX/ADM/ETC	—	—	ΔDAS28[p]	6 months	566	Plant *et al.*[63]

Abbreviations: ACR, American College of Rheumatology outcome measure % improvement; ADM, adalimumab; DAS28, disease activity score for 28 joints; DMARDs, disease-modifying antirheumatic drugs; ETC, etanercept; EULAR, European League Against Rheumatism; INX, infliximab; JIA, juvenile idiopathic arthritis; MTX, methotrexate; RA, rheumatoid arthritis. [a]Treatment with additional drugs during biological treatment. [b]EULAR response was classified into. Good responders are those withΔDAS28 $\geqslant 1, 2$ and DAS28 $\leqslant 3, 2$. Non-responders are all the patients withΔDAS28 $< 0, 6$ and those withΔDAS28 $> 0, 6$ but $\leqslant 1, 2$ and DAS28 $> 5, 1$. All the remaining patients are moderate responders. [c]EULAR response were defined as good and moderate response. [d]Good responders are those withΔDAS28 $\geqslant 1, 2$ and DAS28 $\leqslant 3, 2$. Non-responders are all the patients withΔDAS28 $< 0, 6$ and those withΔDAS28 $> 0, 6$ but $\leqslant 1, 2$ and DAS28 $> 5, 1$. All the remaining patients are moderate responders. [e]Spain, Portugal and Romania. [f]EULAR defines anti-TNF response in three categories: good, moderate and non-response—moderate response were removed and good versus non-response were analysed. [g]EULAR response were defined as good response. [h]EULAR response were defined as remission and low disease activity. [i]EULAR response were not specific defined as seen in refs 6 and 7. [j]Anti-TNF response was evaluated by absolute (ΔDAS28) and relative (ΔDAS28/DAS28$_{\text{baseline}}$) DAS28 score change. [k]ABCoN ($n = 116$), AMC ($n = 157$), BeSt ($n = 126$), BRAGGSS ($n = 81$) BRASS ($n = 55$) EIRA ($n = 291$), ERA ($n = 218$), KI ($n = 163$), JBI ($n = 76$). [l]ARC20, 50 and 70 responses is defined if the patients have 20, 50 or 70% improvement in tender and swollen joints, respectively. Patients with ACR20, 50 or 70 response were considered low-, medium and high responders, respectively. [m]ARC50 is defined as responder if 20% improvement in tender and swollen joints were achieved as well as a 50% improvement in at least three of the five criteria: Patients assessment, physician assessment, pain scale, disability/functional questionnaire and acute phase reactant (erythrocyte sedimentation rate or C-reactive protein (CRP)). [n]ARC-JRA 30 is defined as responder if 30% improvement in tender and swollen joints were achieved as well as a 30% improvement in at least three of the five criteria: Patients assessment, physician assessment, pain scale, disability/functional questionnaire and acute phase reactant (erythrocyte sedimentation rate or CRP). [o]ARC20 is defined as responder if 20% improvement in tender and swollen joints were achieved as well as a 20% improvement in at least three of the five criteria: Patients assessment, physician assessment, pain scale, disability/functional questionnaire and acute phase reactant (erythrocyte sedimentation rate or CRP). [p]Anti-TNF response was evaluated by absolute (ΔDAS28) and relative (ΔDAS28/DAS28$_{\text{baseline}}$) DAS28 score change.

Statistical analyses were performed in Stata version 14 (StataCorp, Collage Station, TX, USA) using the meta-analysis plugin, metan. Random effects models were specified as the studies included were based on samples from heterogeneous populations. Heterogeneity is reported as I^2.[20]

We also evaluated the potential for predicting treatment response based on genotyping using a data set (15–17) with information on a cohort of RA patients treated with anti-TNF. We first estimated associations between single nucleotide polymorphisms (SNPs) and non-response using logistic (EULAR) and linear regression (ΔDAS28) to identify significant associations and to determine dominance of alleles. After dichotomising SNPs based on allelic dominance, five genotypes were significantly associated with non-response. We finally tested the association between the number of risk genotypes and treatment non-response using logistic regression, and positive and negative predictive values of each level.

RESULTS

In total, 47 studies were included in the analysis; 42 candidate gene studies[14–16,21,22–59] and 5 genome-wide association studies (GWAS)[60–64] analysing responders versus non-responders from anti-TNF therapy in RA (Table 1). Two studies reported associations between polymorphisms and treatment response in juvenile idiopathic arthritis (JIA)[37,50] and the others on adult RA. The studies differed according to the studied population, response criteria and elapsed time before evaluation of response (Table 1).

Table 2 shows polymorphisms associated with response to anti-TNF treatment in RA identified by GWS. Response criteria as well as study design differed among the studies as described in Table 2. In total 19 polymorphisms, including polymorphisms in

Table 2. Identified genetic markers associated with response after anti-TNF treatment of RA patients in GWS

SNPs	*Statistical criteria*	*Refs.*
rs284515		
rs75908454	$P < 10^{-6}$	Honne *et al.*[60]
rs1679568		
rs113878252[a]	$P < 10^{-7}$, for replication $P < 0.05$	Julià *et al.*[61]
rs4411591		
rs7767069		
rs4651370		
rs1813443		
rs1447722	$P < 10^{-3}$, $P < 0.05$ in two replication steps	Umicevic *et al.*[64]
rs1568885		
rs12142623		
rs2378945		
None	$P < 5 \times 10^{-8}$	Krintel *et al.*[62]
rs12081765		
rs1532269		
rs17301249		
rs7305646	$P < 10^{-3}$, the statistical signal remained the same or diminished in significance in the second meta-analyses	Plant *et al.*[63]
rs4694890		
rs1350948		
rs7962316		

[a]rs113878252 was statistically significant in a subgroup of etanercept-treated patients in discovery cohort of 372 participants genotyped with Illumina Quad610 ($P < 1e{-}7$). Replication genotyping was performed in 245 patients (115 etanercept-treated) using Illumina GoldenGate (San Diego, CA) using the closest most significant non-imputed SNP for replication (rs4821915).

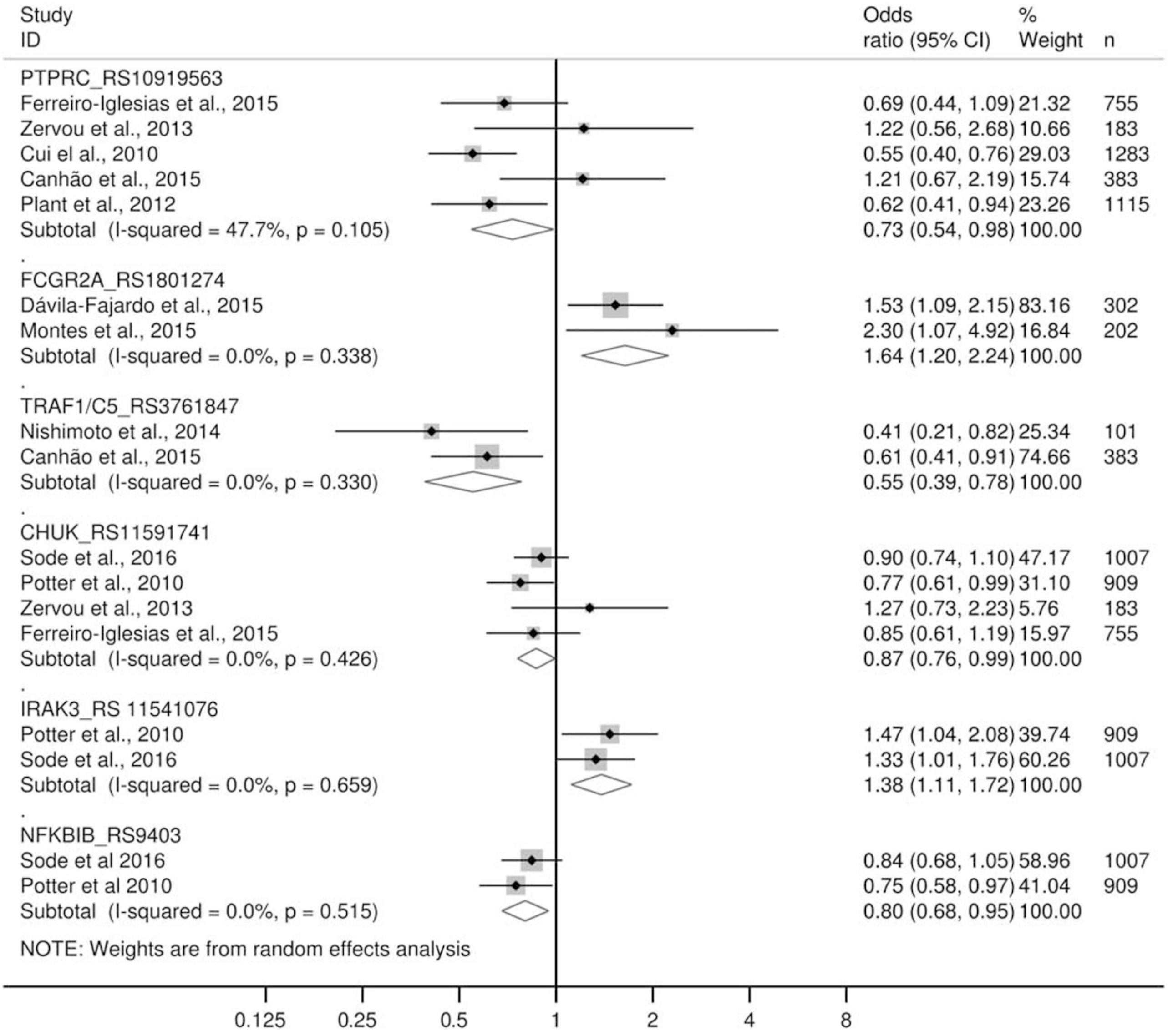

Figure 2. Meta-analyses of 6 polymorphisms in 6 genes, which were associated with treatment response in rheumatoid arthritis (RA).

Table 3. Positive and negative prediction values for selected genotypes in an exploratory analyses based on data from Sode *et al.*[14–16]

No. of risk genotypoes	*Response* (n)	*Non-response* (n)	*Logistic regression predicting non-response*			*Predictive values*	
			Crude OR	*Adj.OR*	*Adj. 95% CI*	*Pos.*	*Neg.*
0	18	3	(Ref. odds = 0.17)	—	—	0.86	0.14
1	70	30	2.57	3.08	(0.83, 11.49)	0.7	0.3
2	113	55	2.92	3.36	(0.93, 12.13)	0.67	0.33
3	59	52	5.29*	6.03**	(1.65, 22.06)	0.53	0.47
4	9	9	6.00*	6.35*	(1.32, 30.48)	0.5	0.5

N = 418. Non-response versus full or partial response. Adjusted for: gender, DAS28, HAQ and DMARD status at baseline. Risk genotypes: CHUK rs11591741 (CC), IKBKB rs11986055 (CC), IFNGR2 rs17882748 (CT/TT), IL6 rs10499563 (CT/TT), NLRP3 rs4612666 (CT/TT). $^*P < 0.05$, $^{**}P < 0.01$. Data from Sode *et al.*[14–16]

WDR27, GFRA1, MED15, LINC01387, LOC102723883, CNTN5, NUBPL, PDZD2, EYA4, TEC and *C12orf79* were identified.

The polymorphisms investigated in candidate gene studies in relation to the outcome from anti-TNF treatment of patients with RA and JIA are shown in Supplementary Table 2. Hundreds of polymorphisms in various pathways have been selected for evaluation as candidate genes. Many of the assessed polymorphisms were found to be associated with response after anti-TNF treatment in one study. However, only few of these polymorphisms have been sought replicated in other candidate gene studies.

Supplementary Table 3 shows the ORs and 95% CI for the associations between polymorphism and treatment response for

Table 4. Proposed functions of selected polymorphisms that are identified in GWS or meta-analysis as associated with treatment response in RA

SNPs	*Gene*	*MAF*	*Allele*	*Proposed function of genes/proteins and SNPs associated with treatment response in RA*
rs3761847	*TRAF1*	0.46	G	Gene/protein function: This protein and TRAF2 form a heterodimeric complex, which is required for TNF-alpha-mediated activation of MAPK8/JNK and NF-kappaB SNP function: rs3761847 is associated with changes in mRNA levels. However, the direction of the effect differs between tissue types (GTEx, http://www.gtexportal.org.). Furthermore, rs3761847GG homozygotes have higher Gp210 autoantibody as compared with AA homozygotes. In contrast, rs3761847AA homozygotes have higher antichromatin as compared to GG homozygotes.[66] In addition, rs3761847GG homozygotes increases the risk of death in RA and appears to be independent of RA activity and severity as well as comorbidities relevant to cardiovascular disease[67]
rs4612666	*NLRP3*	0.41	T	Gene/protein function: A member of the NALP3 inflammasome complex. This complex functions as an upstream activator of NF-kappaB signalling, and it has a role in the regulation of inflammation, the immune response and apoptosis SNP function: rs4612666T decreases expression[68]
rs9403	*NFKBIB*	0.45	C	Gene/protein function: Inhibit NF-kappa-B by complexing with, and trapping it in the cytoplasm SNP function: rs9403 is associated with changes in mRNA levels. However, the direction of the effect differs between tissue types (GTEx, http://www.gtexportal.org.)
rs1061622	*TNFRSF1B*	0.19	G	Gene/protein function: The protein encoded by this gene is thought to potentiate TNF-induced apoptosis by the ubiquitination and degradation of TNF-receptor-associated factor 2, which mediates anti-apoptotic signals SNP function: Unknown
rs1801274	*FCGR2A*	0.44	G	Gene/protein function: Member of a family of immunoglobulin Fc receptor genes found on the surface of many immune response cells that is involved in the process of phagocytosis and clearing of immune complexes. Autoimmune diseases with elevated circulating autoantibodies drive tissue damage and the onset of disease. The Fcγ receptors bind IgG subtypes modulating the clearance of circulating immune complexes. SNP function: rs1801274 at nucleotide 519 is involved in its ligand binding domain, causing an arginine (G-allele) to histidine (A-allele) amino acid substitution at position 131. The FcγRIIa-H131 shows higher binding efficiency for CRP[65] and human IgG2 and IgG3 isoforms, compared to FcγRIIa-R131[69]

Abbreviation: CRP, C-reactive protein.

polymorphisms that were significantly associated with response in more than one cohort. In total, 23 polymorphisms in 21 genes were identified. These polymorphisms were selected for meta-analyses. Figure 2 shows the results for 6 polymorphisms in 6 genes (*CHUK, PTPRC, TRAF1/C5, NFKBIB, FCGR2A* and *IRAK3)* that were associated with treatment response in our meta-analyses. Supplementary Figure 1 shows the results for 17 polymorphisms in 16 genes (including *FCGR3A, TNF, CD226, MAPKAPKA, RPS6KA5, MAP2K6, TLR5, TLR1, IFNG, IKBKB* and *TLR10*) that were not associated with treatment response.

Next, to evaluate the current status of clinical use of the biomarkers we perform an explorative analysis of one cohort with available genotyping data.[14–16] First, we used logistic regression to identify genotypes associated with non-response (risk genotypes) (*CHUK* rs11591741 (CC), *IKBKB* rs11986055 (CC), *IFNGR2* rs17882748 (CT/TT), *IL6* rs10499563 (CT/TT), *NLRP3* rs4612666 (CT/TT)). Next, we calculated the OR and 95% CI based on the number of risk genotypes (Table 3; Supplementary Table 4). OR for non-response increased dose-dependently with the number of risk genotypes carried by the patients. For example, individuals with 4 out of 5 non-response-associated genotypes had an OR of 6.35 (95% CI: 1.32–30.48) and a negative predictive value of 0.5. The reference group of individuals with none of the five risk genotypes had the lowest odds (0.17) for non-response and a positive predictive value of 0.86 (indicating a somewhat higher chance of effective treatment than the first-best average (60–70%)).

DISCUSSION

We identified polymorphisms associated with treatment outcome from anti-TNF treatment in RA patients from 47 studies with available data (Table 1). Among the 25 polymorphisms that were identified, 19 polymorphisms were found in GWS (Table 2). Our meta-analyses further identified 6 polymorphisms in 6 genes (Figure 2). Furthermore, we analysed the potential predictive power in an exploratory analysis of an available cohort.[14–16] We found increasing OR for carrying increasing numbers of non-response associated polymorphisms (Table 3; Supplementary Table 4). However, the positive and negative predictive values were moderate.

Knowledge on the biological pathways involved in the treatment response in RA may allow for development of new treatment strategies. The results suggest that genetic variants in *CTCN5, NUBPL, PD2D2, EYA4* and *TEC* (from the GWS), and *CHUK, PTPRC, TRAF1/C5, NFKBIB, FCGR2A* and *IRAK3* (from our meta-analysis) may be implicated in treatment response to anti-TNF drugs in RA (Tables 2 and 4, Figure 2 and Supplementary Table 5). Some of the polymorphisms may indeed be functional or be linked to functional polymorphisms. Rs3761847 in *TRAF1/C5* is associated with changes in mRNA levels. However, the direction of the effect differs between tissue types (GTEx, http://www.gtexportal.org.). Likewise, rs9403 in *NFKBIB* has been associated with allele-specific mRNA levels with the variant alleles having the highest expression in liver (GTEx, http://www.gtexportal.org.). *FCGR2A* rs1801274 is also a missense polymorphism resulting in a non-conservative amino acid substitution (His to Arg). The variant receptor has lowered affinity towards CRP.[65] The lack of associations may suggest that the assessed genes are not of major importance for treatment response provided that the studies had sufficient power and the investigated polymorphisms are functional themselves or linked to functional polymorphisms. Our meta-analyses suggested that *FCGR3A, TNF, CD226, MAPKAPKA, RPS6KA5, MAP2K6, TLR5, TLR1, IFNG, IKBKB* and *TLR10* were not associated with response after anti-TNF treatment in RA (Supplementary Figure 1).

Recently, we performed a review and meta-analysis of genes involved in response to anti-TNF treatment in patients with inflammatory bowel disease (IBD).[12] SNPs involved in the TLR signalling pathway were found to be associated with anti-TNF treatment response in IBD, thus suggesting a significant role for the host–microbial interaction. Thus, different genes have been identified to be involved in RA and IBD treatment response to anti-TNF therapy. This may suggest that genes involved in the adaptive immune response may have a larger role in RA than in IBD treatment response to anti-TNF therapy. However, the role of host–microbial interactions in RA is not clear. Patients with active RA were found to have dysbiosis in the gut microbiota that partly resolved after medical treatment.[70] The reason for this observation and how it may relate to treatment mechanism(s) is not known.

RA is a highly heterogeneous disease in terms of clinical presentation, prognosis and response to treatment.[71] It is likely that this also applies to the pathogenesis of RA, in fact, studies have shown pronounced heterogeneity in RA synovial tissue of inflammatory cell types and gene expression.[72] Through an improved discrimination of different RA subsets, SNP associations may prove to be more clinically useful, as they could at least in theory be very important for a certain subgroup while irrelevant for others.

An explorative approach was used when identifying potential candidate biomarkers in order not to overlook relevant candidates. Response criteria varied between the reviewed studies and more than one criterion were used in most studies. Our findings may furthermore be subject to bias from, for example, publication bias and selective reporting within studies. Replication of findings in other cohorts is of major importance in studies of genetic epidemiology. Therefore, replication of the findings in another cohort was chosen as criterion for association in the present review. Furthermore, environmental factors such as nutrition, smoking, lifestyle and other medication may impact genetic susceptibility and treatment outcome. These factors may not have been captured in the present studies.

Further evaluation of pharmacogenetics of anti-TNF treatment response in rheumatoid arthritis including gene–environmental interactions will require large cohorts of well-characterised patients and replication of positive findings in other cohorts. This work necessitates collaboration between researchers, for example, via International Consortia. Investigations of genomics combined with microbiome and mucosa expression profiles in each patient may thus allow us to understand which pathways and cytokines are deregulated in each case. Such knowledge may be utilised to select the best treatment for each patient.

However, at present, the pharmacogenomic basis for stratifying patients according to the expected response to anti-TNF treatment is not yet available.

CONFLICT OF INTEREST

VA receives compensation as a consultant and an advisory board member for Merck (MSD) and Janssen. The remaining authors declare no conflict of interest.

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