Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

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To cite this article: Santos Castañeda MD, PhD, Raquel López-Mejías PhD & Miguel A. González-Gay MD, PhD (2016): Gene polymorphisms and therapy in rheumatoid arthritis, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1517/17425255.2016.1141405

To link to this article: http://dx.doi.org/10.1517/17425255.2016.1141405

Accepted author version posted online: 12 Jan 2016.

Publisher: Taylor & Francis

Journal: *Expert Opinion on Drug Metabolism & Toxicology*

DOI: 10.1517/17425255.2016.1141405

EDITORIAL

Gene polymorphisms and therapy in rheumatoid arthritis

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Running title: *Gene polymorphisms and therapy in rheumatoid arthritis*

Abbreviations:

ABCB1: ATP-binding cassette, sub-family B, member 1

ACR: American College of Rheumatology

5-ASA: 5-aminosalicylic acid

ATIC: 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclo-hydrolase

BAFF: B-cell activating factor

CARD8: caspase recruitment domain-containing protein 8

CDAI: clinical disease activity index

CHUK: conserved helix-loop-helix ubiquitous kinase

CYP1A2: cytochrome P450 1A2

CYP2C19: cytochrome P450 2C19

CYP3A4: cytochrome P450 3A4

DAS28: 28 joint count disease activity score

DHODH: dihydroorotate dehydrogenase

DMARD: disease-modifying antirheumatic drugs

ESR1: estrogen receptor 1

EULAR: European League Against Rheumatism

FCG3A: Fc region receptor III-A

GWAS: genome-wide association study

HAQ: health assessment questionnaire

HLA: human leukocyte antigen

HLA-DRB1: major histocompatibility complex, class II, DR beta 1

IL: interleukin

JAK: Janus kinase pathway

MTHFR: methylene tetrahydrofolate reductase

NAT: N-acetyltransferase

NF-kB: nuclear factor-kappa B

NLRP3: NOD-like receptor family, pyrin domain 3

PADI4: peptidyl arginine deiminase, type IV

PDE3A: phosphodiesterase 3A

PTPN22: protein tyrosine phosphatase, non-receptor type 22

PTPRC: protein tyrosine phosphatase, receptor type C

RFC-1: reduced folate carrier 1

SLC19A1: solute carrier family 19 (folate transporter), member 1

SNP: single nucleotide polymorphism

TGFb: transforming growth factor β

TNF: tumor necrosis factor

TNFi: TNF inhibitors

TYMS: thymidylate synthetase

TSER: thymidylate synthase enhancer region

UTR: in molecular genetics, untranslated region

Keywords: biologic therapy, disease-modifying antirheumatic drugs (DMARDs), pharmacogenetics, pharmacogenomics, rheumatoid arthritis

1. Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory and autoimmune disease characterized by the progressive destruction of the joints. RA is associated with increased morbidity and mortality. The disease is more frequent in women (3:1) and shows prevalence around of 0.5-1% in developed countries [1]. RA is a complex, polygenic and heterogeneous disease characterized by intricate interactions between genetic and environmental factors. The main genes related to susceptibility and severity of the disease are located in the major histocompatibility complex- HLA- region. Specifically, the *HLA-DRB1* alleles, encoding the so-called shared epitope (SE), can explain around 40% of the genetic burden of disease [2]. Other important genes related to susceptibility and/or severity of the disease are *PTPN22*, *PADI4* and some loci related with the TNFα pathway [3,4].

The course and prognosis of RA has changed considerably since the advent of biologic treatments. An early diagnosis and treatment along with tight control of the disease have improved the outcome of the disease. The mainstay of treatment for RA is currently based on two different therapeutic groups: conventional or synthetic disease-modifying antirheumatic drugs (DMARDs) and biological DMARDs, including TNF inhibitors (TNFi), monoclonal antibody directed against CD20 receptor of B cells (rituximab), IL-6 receptor antagonist (tocilizumab) and a specific neutralizer of the union between CD80/CD86 at antigen presenting cell and CD28 at T lymphocyte surface (abatacept). In last years, a new generation of “targeted” DMARDs, i. e. JAK inhibitors, are available in several countries and recommended by some clinical guidelines for the management of RA. Nevertheless, these agents have not yet been well studied in terms of predictors of response beyond the usual disease characteristics.

2. Pharmacogenomics steps toward personalized medicine

Regrettably, the response to the therapy in RA is not uniform; rather, there is wide interindividual variability ~~in the response~~. On the other hand, the possibility of side effect due to the therapy is not negligible. Furthermore, the high costs of these new therapies place a heavy burden on governments. Because of that, the search for tools that can help select the patients who are more appropriate for each specific therapeutic target is of major importance. In this regard, an objective to be reached in the near future is the personalized medicine by using biomarkers that can predict the response to treatment and avoid the possible occurrence of adverse effects (AEs) individually. This is especially true since at present 40-60% of patients with RA fail to achieve a satisfactory response to DMARDs, and around 15-30% can develop adverse drug events [5].

Pharmacogenetics and pharmacogenomics hold a special interest in the search for ~~possible~~ accurate genetic markers that can predict ~~the target and~~ the response to a specific therapeutic target. Pharmacogenetics focuses on the study of genetic variations that determine the differential response to drugs as well as the prediction about the efficacy and occurrence of AEs with a specific drug in ~~a particular~~ an individual patient. In this issue of the Journal, Tarnowski et al performed an exhaustive review of the literature on the most important genetic variants involved in the metabolism of synthetic and biological DMARDs [6].

Despite the fact that genetic factor are of major importance in the response to the therapy, it is important to keep in mind that “non-genetic” factors, such as demographic and environmental factor as well as clinical or serologic markers can influence or predict the efficacy or toxicity of a drug in patients with RA, sometimes even better than the genetic biomarkers [7]. This is the case for the age, sex or smoking. For

example, younger patients with RA tend to respond better to therapies and active smokers worse, possibly because they have higher levels of pro-inflammatory cytokines. Also, some parameters related to the disease itself, such as duration or activity and health assessment questionnaire (HAQ) at baseline may influence the response to therapy. In general, the higher basal activity or worse HAQ are the poorer is the response [7].

3. Pharmacogenetics on conventional (synthetic) DMARDs

In their manuscript, Tarnowski et al review the main gene polymorphisms related to the efficacy or toxicity of methotrexate (MTX), leflunomide and sulfasalazine [6]. With respect to MTX, many genes are involved in its transportation into cells and out of them, its polyglutamation and the inhibition of the synthesis of purines, pyrimidines or DNA repair. Nevertheless, few are the genes in which polymorphisms show interest from a point of view of efficacy and toxicity [8,9]. Firstly, it has been shown that the 80AA genotype of RFC-1 (also called SLC19A1) gene that carries MTX into the cell interior has been associated with a better response. Also, carriers of the 3435(C>T) T allele located in the exon 26 of the *ABCB1* gene, which returns MTX outside of the cells, appear to have better response to MTX.

In contrast, RA patients carrying a triple repeat sequence in the homozygous form at the 5´-UTR end of the *TYMS* (thymidylate synthetase) gene (TSER*3/*3) need higher doses of drug to obtain the same effects, whereas six-base pair deletion in the 3´-UTR region individuals have a good response to conventional doses of MTX [10]. In the case of polymorphisms 677C/T and 1298A/C of the *MTHFR* gene, results related to efficacy or toxicity are not conclusive. Finally, the C>G polymorphism at the 347 position in the *ATIC* gene is associated with increased efficacy and toxicity [10].

Regarding leflunomide, the most relevant enzymatic ways studied are the DHODH, a key enzyme of de novo pyrimidine synthesis, and the cytochrome pathway. As Tarnowski et al pointed in their review [6], it seems that individuals with RA carrying the 19AA genotype in the coding region of *DHODH* have lower rate of remission compared with those C allele carriers [10,11].

Results regarding several SNPs in the cytochrome pathway, especially in the *CYP1A2*, *CYP2C19* and *CYP3A4* genes, are inconclusive and appear to be more related to drug toxicity. An interesting aspect related to the efficacy of leflunomide is the possible association between some polymorphisms at the estrogen receptor 1 (*ESR1*) and a better response to this drug in women [11].

Sulfasalazine (SASP) is another drug commonly used in low-grade RA. SASP is converted into 5-ASA and sulfapyridine, and later it is metabolized in the liver through acetylation by N-acetyltransferases (NAT1, NAT2). Slow acetylators due to polymorphisms in these genes, especially in *NAT2*, are at increased risk of developing toxicity. The prevalence of slow acetylators varies greatly between races; 20% in Asiatic individuals and 60% in Africans or Caucasian. Yet, common doses of SASP seem to be more effective in patients with RA who are slow acetylators [10].

Overall, the study of SNPs in genes involved in the metabolism of conventional (synthetic) DMARDs seems to be more useful in detecting patients susceptible to develop toxicity, since these drugs induce a high rate of AEs. Table 1 summarizes the candidate genes and SNPs implicated in the efficacy and/or toxicity of conventional DMARDs.

Finally, in last years, a new generation of promising “targeted” DMARDs (JAK inhibitors) has been developed. Nevertheless, these agents have not yet been extensively studied in terms of pharmacogenetics and prediction of response in patients with RA.

4. Pharmacogenetics of biologic DMARDs

Unlike conventional DMARDS, biologic DMARDS are high-cost drugs and, due to this, studies on these new agents are focused on the search of good responders. Unfortunately, although this is an exciting issue, there are few polymorphisms that so far have shown a significant participation in the prediction of the efficacy or safety of these drugs in clinical practice.

4.1 TNF inhibitors (TNFi)

Regarding TNFα antagonists, most studies were conducted on small numbers of patients with controversial results. The most interesting data seem to be related to some SNPs located at -238, -308 and -857 positions in *TNF* promoter region with questionable results. In this regard, although some studies found that -308GG genotype was associated with a good response to TNFi, especially to etanercept; two recent meta-analyses concluded that the -308G/A polymorphism of *TNF* is not a good predictor of clinical response to TNFi [12,13]. By contrast, a sensitivity analysis revealed a possible association between response to infliximab and the *TNF* -238A/G polymorphism [12]. Other studies have demonstrated association between clinical response and some polymorphisms in TNFα receptor genes.

A meta-analysis involving more than 2 million common variants in 2706 RA patients disclosed a positive association between CD84 expression and response to etanercept. Other genes that have been associated with satisfactory and consistent results in terms of response to various anti-TNF agents are *NLRP3/CARD8* (encoding NLRP3-inflammasome), *PTPRC*, *PDE3A*, *NF-kB* and *CHUK* [14,15]. In contrast, no association has been detected with other important genes involved in RA pathogenesis such as the *IL-6 receptor* gene, *HLA-DRB1* shared epitope, *PTPN22* or *TGFb* [7]. A summary of

the main genes and polymorphisms implicated in the efficacy and safety of biologic DMARDs is shown in Table 2.

4.2 Other biologic DMARDs

Experience with the use of other biologics is more limited. In the case of tocilizumab, it appears that some variants in the gene of IL-6 receptor, located in exon 9 and introns 1 and 9, could be associated with a poorer clinical response when the AAC haplotype is expressed.

Regarding rituximab, the available information is quite poor. Nevertheless, some polymorphisms located in the *IL-6* (174G/C), *TGFB1*, *FCG3A* and promoter region of *BAFF* genes suggest promising results. Table 2 shows a more detailed information on the main genes related to response to biologic DMARDs.

5. Conclusions

Pharmacogenetics is a discipline that can provide important solutions to the problems related to the management of chronic and complex diseases such as RA. This is especially true for drugs that have a high rate of AEs (conventional DMARDs) or a high cost (biological DMARDs), where besides safety and efficacy criteria, cost-effectiveness criteria should also be kept in mind. Pharmacogenetics and related disciplines can yield answer to many of these issues, although there are still many questions to be elucidated.

6. Expert Opinion

At present, we are still far from being able to apply the concepts known on the pharmacogenetics of DMARDs into clinical practice. This can be due to several reasons. First, RA is a polygenic, heterogeneous and complex disease, in which many of

the pathogenic mechanisms are not well known. Furthermore, much of the research conducted have been focused on candidate genes related to susceptibility or severity of the disease that are not necessarily the same as those involved in the response to treatment. Likewise, in many cases results of different studies show contradictory or inconclusive conclusions.

Low statistical power due to small sample size is another important factor that reduces the potential relevance of most studies. Selection bias, heterogeneity of the populations studied and lack of replication are also important limitations.

Other factors such as race and sex, duration of the disease, smoking as well as other environmental and epigenetic factors account for the disparity of the results obtained in different pharmacogenetic studies. The presence or absence of antibodies to citrullinated peptide antigens, which in many studies is not especified, may greatly influence in the results. More importantly, there is no uniformity in the criteria used for the evaluation of the responses or remission between studies (i.e. DAS28, CDAI, EULAR or ACR responses).

Taken together, we conclude that the use of pharmacogenetics in clinical practice in patients with RA is currently limited. Results derived from genome-wide association studies (GWAS) conducted in homogeneous and well characterized populations will allow us to obtain more reliable information. Also, the introduction of more powerful and complementary techniques based on pharmacogenomics, proteomics and transcriptomics will provide useful information to design individual therapeutic management. This is probably the only way towards personalized health care, focused on the search for greater efficiency and safety, with fewer side effects and a more cost effective approach for each patient.

Currently, with the available data, an approach for the treatment of a patient with RA is based on clinical aspects and tight control of the disease along with cost-effectiveness data, the experience of the physician and the available scientific evidence. In most cases the use of information related to gene polymorphisms associated with disease susceptibility and severity is not available. Nevertheless, we hope that in the near future the use of composite indexes mixing of genetic markers and clinical tools may improve the management of patients with RA.

Declaration of Interest

The authors were supported by a grant from “Fondo de Investigaciones Sanitarias” PI12/01578, FEDER, (Spain), issued to S Castañeda; R López-Mejías is a recipient of a Sara Borrell postdoctoral fellowship from the “Instituto Carlos III de Salud” at the Spanish Ministry of Health (Spain) (CD12/00425). MA González-Gay is supported by grants from Fondo de Investigaciones Sanitarias, FEDER, Spain (PI06/0024, PS09/00748 and PI12/00060), and also partially supported by RETICS Program, RD08/0075 and RD12/0009/0013 (RIER) from Instituto de Salud Carlos III, Spain. MA González-Gay has received grants/research support and consultation/ participation fees in company-sponsored speaker’s bureaus from Abbvie, MSD, Pfizer and Roche. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Bibliography

Papers of special note have been highlighted as:

*** of interest**

**** of considerable interest**

1. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005;4:130-6.

* **Updated review of the epidemiology of RA**

2. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30:1205-13.

3. Hajeer AH, Dababneh A, Makki RF, et al. Different gene loci within the HLA-DR and TNF regions are independently associated with susceptibility and severity in Spanish rheumatoid arthritis patients. Tissue Antigens 2000;55:319-25.

4. Rodriguez-Rodriguez L, López-Mejias R, Fernández-Gutiérrez B, et al. Rheumatoid arthritis: genetic variants as biomarkers of cardiovascular disease. Curr Pharm Des 2015;21:182-201.

* **Comprehensive review about genetics biomarkers of cardiovascular disease in patients with rheumatoid arthritis.**

5. Kooloos WM, Huizinga TW, Guchelaar HJ, Wessels JA. Pharmacogenetics in treatment of rheumatoid arthritis. Curr Pharm Des 2010;16:164-75.

* **Comprehensive review about the Pharmacogenetics in rheumatoid arthritis.**

6. Tarnowski M, Paradowska-Gorycka A, Dabrowska-Zamojcin E, et al. The effect of gene polymorphisms on patient responses to rheumatoid arthritis therapy. Expert Opin Drug Metab Toxicol 2016 (in press).

7. Salgado E, Maneiro JR, Gomez-Reino JJ. Predictors of response to TNF antagonists. Curr Pharm Des 2015;21:221-32.

** **Excellent & comprehensive review of predictors of response to anti-TNF in RA.**

8. Zhu H, Deng FY, Mo XB, et al. Pharmacogenetics and pharmacogenomics for rheumatoid arthritis responsiveness to methotrexate treatment: the 2013 update. Pharmacogenomics 2014;15:551-66.

9. Zhang LL, Yang S, Wei W, Zhang XJ. Genetic polymorphisms affect efficacy and adverse drug reactions of DMARDs in rheumatoid arthritis. Pharmacogenet Genomics 2014;24:531-8.

** **Comprehensive mini review of genetic polymorphisms of DMARDs in RA treatment.**

10. Szekanecz Z, Meskó B, Poliska S, et al. Pharmacogenetics and pharmacogenomics in rheumatology. Immunol Res 2013;56:325-33.

11. Davila L, Ranganathan P. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol 2011;7:537-50.

* **Excellent review on the Pharmacogenetics in rheumatic diseases.**

12. Lee YH, Ji JD, Bae SC, Song GG. Associations between tumor necrosis factor-alpha (TNF-alpha) -308 and -238 G/A polymorphisms and shared epitope status and

responsiveness to TNF-alpha blockers in rheumatoid arthritis: a meta-analysis update. J Rheumatol 2010;37:740-6.

13. Pavy S, Toonen EJ, Miceli-Richard C, et al. Tumour necrosis factor alpha -308G->A polymorphism is not associated with response to TNF alpha blockers in Caucasian patients with rheumatoid arthritis: systematic review and meta-analysis. Ann Rheum Dis 2010;69:1022-8.

14. Potter C, Cordell HJ, Barton A, et al. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signalling pathways. Ann Rheum Dis 2010;69:1315-20.

15. Mathews RJ, Robinson JI, Battellino M, et al. Evidence of NLRP3-inflammasome activation in rheumatoid arthritis (RA); genetic variants within the NLRP3-inflammasome complex in relation to susceptibility to RA and response to anti-TNF treatment. Ann Rheum Dis 2014;73:1202-10.

* **First evidence of implication of NLRP3-inflammasome and response to anti-TNF treatment in RA.**

Table 1. Pharmacogenetics of conventional (synthetic) DMARDs[§].

Drug	Gene	Genetic variants	Clinical effects
Methotrexate	*RFC-1 (SLC19A1)*	80G>A (AA genotype)	Increased efficacy
	ABCB1 (MDR1)	3435C>T (T allele)	Increased or unaffected efficacy
	MTHFR	677C>T	Controversial results
	MTHFR	1298A>C	Controversial results
	TYMS	5´-UTR repeat element	Decreased efficacy; probably increased toxicity
	TYMS	3´-UTR, 6 bp deletion	Increased efficacy
	ATIC	347C>G (GG genotype)	Increased toxicity and probably efficacy
	SHMT1	1420C>T	Increased toxicity
Leflunomide	*DHODH*	19C>A (AA genotype)	Decreased efficacy
	CYP1A2	CYP1A2*1F (CC genotype)	Increased toxicity; efficacy ?
	ESR1	SNF	Increased efficacy in women
Sulfasalazine	*NAT2*	NAT2*4	Increased toxicity in slow acetylators
Azathioprine	*TPMT*	TPMT*2, *3[a], *3C	Increased toxicity

Abbreviations: ABCB1: ATP-binding cassette, sub-family B, member 1; ATIC: 5 aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclo-hydrolase; bp: base pair; CYP1A2: cytochrome P450 1A2; DHODH: dihydroorotate dehydrogenase; DMARDs: disease-modifying antirheumatic drugs; ESR1: estrogen receptor 1; MDR1: multidrug resistance 1; MTHFR: methylene tetrahydrofolate reductase; RFC-1: reduced folate carrier 1; SLC19A1: solute carrier family 19 (folate transporter), member 1; TYMS: thymidylate synthetase; SHMT1: serine hydroxymethyltransferase; TPMT: thiopurine methyltransferase; UTR: untranslated region. [§]Table modified from reference 10.

Table 2. Pharmacogenetics of biological DMARDs[§].

Drug family	Gene	Genetic variants	Clinical effects
Anti-TNF agents	*TNF*	-238A>G (AA genotype)	Increased efficacy
	TNF	-308G>A (GG genotype)	Increased efficacy, especially to ETN
	TNF	-857C>T	Controversial results
	TNFRSF1A	Several SNPs	Inconclusive results
	TNFRSF1B	196T>G	Decreased efficacy or no effect
	CD84	SNPs	Positive response to ETN
	FCGR2A	H131R (RR genotype)	Increased efficacy?
	FCGR3A	158V>F (FF genotype)	Increased efficacy?
	NLRP3/CARD8	SNPs	Increased efficacy
	PTPRC	rs10919563	Increased efficacy
Rituximab	*IL-6*	-174G>C (CC genotype)	Predictor of no response
	FCG3A	158V>F (V allele carriers)	Discordant results, influenced by sex?
	TGFβ1	SNPs	Small positive effect
	BAFF	-871C>T (C allele carriers)	Increased efficacy
Tocilizumab	*IL-6 receptor*	AAC haplotype	Decreased efficacy

Abbreviations: Anti-TNF agents: TNF neutralizing agents/TNF inhibitors; BAFF: B-cell activating factor; CARD8: caspase recruitment domain-containing protein 8; CD84: cluster differentiation number 84; DMARDs: disease-modifying antirheumatic drugs; ETN: etanercept; FCG3A: Fc gamma region type IIIA; FCGR2A: Fc region receptor II-A; NLRP3: NOD-like receptor family, pyrin domain 3; PTPRC: protein tyrosine phosphatase, receptor type C; SNP: single nucleotide polymorphism; TGFb: transforming growth factor β; TNF: tumor necrosis factor; TNFRSF1A (or 1B): tumor necrosis factor receptor superfamily, member 1. [§]Table modified from reference 10.