

Genetic variants contribute to differences in response and toxicity to drugs used in autoimmune diseases: Rheumatoid arthritis and systemic lupus erythematosus

Dávila Fajardo, C.L.

Citation

Dávila Fajardo, C. L. (2020, September 29). *Genetic variants contribute to differences in response and toxicity to drugs used in autoimmune diseases: Rheumatoid arthritis and systemic lupus erythematosus*. Retrieved from https://hdl.handle.net/1887/136914

Version:	Publisher's Version
License:	<u>Licence agreement concerning inclusion of doctoral thesis in the</u> <u>Institutional Repository of the University of Leiden</u>
Downloaded from:	https://hdl.handle.net/1887/136914

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <u>http://hdl.handle.net/1887/136914</u> holds various files of this Leiden University dissertation.

Author: Dávila Fajardo, C.L.

Title: Genetic variants contribute to differences in response and toxicity to drugs used in autoimmune diseases: Rheumatoid arthritis and systemic lupus erythematosus **Issue date**: 2020-09-29

General introduction and outline of the thesis

RHEUMATOID ARTHRITIS AND OTHERS AUTOIMMUNE DISEASES

Rheumatoid arthritis (RA) is an autoimmune disease associated with progressive disability and systemic complications. RA is characterized by synovial inflammation and hyperplasia, autoantibody production (rheumatoid factor and anti-citrullinated protein antibody ACPA), cartilage and bone destruction, and systemic features, including cardiovascular, pulmonary, psychological and skeletal disorders (1). The etiology of this inflammatory disease remains unclear due to complexity of interacting factors including both genetic and environmental determinants. The long-established association with *HLA-DRB1* locus has been confirmed in patients who are positive for rheumatoid factor or ACPA (2). Smoking (3), infectious agents and female gender have been recognized as risk factors associated with RA (1). Moreover, gene-gene and gene-environment interactions increase the risk for RA. The environment-gene interactions promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification and detected in T-cell and B-cell compartments. Why the systemic loss of tolerance is linked to a localized onset of inflammation in the joint is still unclear (1).

Disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX) in RA have the capacity of reducing or preventing damage to the joints and preserving their integrity and function by modulating the immune response. However, the results of treatment with these drugs in patients diagnosed with RA are variable and unpredictable.

The anti-inflammatory mechanism of action of MTX is explained by its ability to inhibit cellular proliferation by reducing purine and pyrimidine synthesis, particularly in the cells most pertinent to synovial inflammation, such as T lymphocytes (4). MTX is well established as a competitive inhibitor of dihydrofolate reductase, and thereby prevents the regeneration from dihydrofolate of tetrahydrofolate, which is essential for the generation of folate cofactors required for de novo purine and pyrimidine synthesis (5).

The understanding of how MTX is effective at low doses in inflammatory diseases also provides some insights into how its well-known toxicities arise. The toxic effects have been suggested to result from a depletion of hepatic folate stores and the accumulation of MTX polyglutamates in the liver (6). When no complete response is obtained with MTX, other DMARDs can be used in sequential or combined therapy, or to add a biologic agent or with targeted therapy.

The introduction of biologic agents has notably altered the treatment of RA; these agents not only reduce symptoms and signs of the disease, but also delay its radiologic progression (7).

At present, five TNF inhibitors are available for the treatment of RA, three of which are full-length monoclonal antibodies: infliximab, adalimumab and golimumab. The fourth agent, etanercept, is a fusion protein of two TNFR2 receptor extracellular domains and the Fc fragment of human immunoglobulin 1 (IgG1). Certolizumab is a humanized Fab fragment conjugated to polyethylene glycol (PEG) without IgG1 region (8).

Biologic agents exert their pharmacological effects through their variable portion (designed to block the target molecule) and their constant portion (the Fc fragment of IgG1), which specifically binds the human FcG receptors (FcGRs) (9-12). FcGRs are expressed on the surface of most immune cells. Engagement of FcGRs by TNF antagonists could affect a number of cellular functions, including phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis, cytokine release and macrophage-mediated clearance of immune-complexes (12, 13).

However, these treatments are substantially more expensive than traditional DMARDs and, unfortunately not efficacious in all patients (14). Some studies point out that between 25% and 30% of subjects with RA do not respond to anti-TNF treatment (15). There are other biologic agents used in the treatment of RA: anti-IL-6 receptor (tocilizumab, sarilumab), anti-IL-1 receptor (anakinra), anti-CD20 (rituximab) and anti-CD80/86 (abatacept). Similarly, targeted synthetic DMARDs, as baricitinib and tofacitinib, were developed to interfere with a specific molecule, Janus kinases (JAKs), based on advances in molecular and structural biology. They interfere with JAKs— intracellular signal transduction molecules that translate the effects of some cytokines to cellular responses (16).

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of unknown cause that can affect virtually any organ of the body. Immunologic abnormalities, especially the production of a number of antinuclear antibodies (ANA), are a prominent feature of the disease. Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening renal, hematologic, or central nervous system involvement (17). The clinical heterogeneity of SLE and the lack of pathognomonic features or tests complicate the diagnostics (18).

The choice of therapy for SLE is highly individualized and depends on the predominant symptoms, organ involvement, response to previous therapy, and disease severity. A general approach to treating the predominant symptomatology include immunosuppressive agents: hydroxychloroquine or chloroquine, glucocorticoids, mycophenolate, cyclophosphamide and other agents targeting B-cell pathways as belimumab (19, 20) and rituximab (21). Belimumab has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in SLE patients, whereas use of rituximab is considered off-label use.

Rituximab is a chimeric monoclonal immunoglobulin G1 antibody against the CD20 protein of B-lymphocytes promoting B cell depletion (22, 23). It has become a crucial therapy against systemic autoimmune diseases, since an aberrant B cell regulation is among the common pathogenic mechanisms of these diseases (24). FDA and EMA have approved the use of rituximab in Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and RA in combination with MTX in adult patients with moderately to severely active RA who have an inadequate response to one or more tumor necrosis factor anti-TNF, Wegener's granulomatosis, and microscopic polyangiitis in adult patients in combination with glucocorticoids. Recent studies in other systemic autoimmune diseases show the importance of this therapy in refractory patients (25-30).

PHARMACOGENETICS OF DRUGS USED IN RA AND SLE

Pharmacogenetics is defined as the study of variability in drug responses attributed to genetic factors (31, 32). It has become one of the leading and potentially most actionable areas of the personalized medicine paradigm, as evidenced by the increased availability of clinical pharmacogenetic testing (33).

The consequences of treatment with DMARDs in patients diagnosed with RA or SLE are variable and largely unpredictable. A possible cause that explains the interindividual differences in both efficacy and adverse events can be the genetic variations in genes encoding drug metabolizing enzymes or drug transporters (34-43).

The treatment with biologic agents is substantially more expensive than use of traditional DMARDs and, moreover, are not effective and safe for everyone (14). Early identification of subjects who respond to these drugs may be helpful when establishing a (cost)effective and safe treatment with these drugs (44).

OUTLINE OF THIS THESIS

The primary objective of this thesis is to investigate the role of pharmacogenetics in predicting drug response in treatments for the autoimmune diseases: RA and SLE. For this reason, this thesis is divided in two parts: pharmacogenetics related with drugs used in RA and pharmacogenetics of rituximab used in SLE and other autoimmune diseases.

Part 1: Pharmacogenetics of drugs used in RA

MTX is the most common DMARD used in RA. However, its use is hampered by frequent adverse drug events among which gastrointestinal toxicity is most frequent. Hepatotoxicity is a relatively rare but serious adverse event related to the use of MTX and is largely unpredictable. In **chapter 2** an overview is presented of the previously performed studies concerning pharmacogenetic predictive biomarkers for MTX-induced hepatotoxicity.

Treatment with anti-TNF agents results in a reduction of disease activity in most RA patients. However, a substantial part of patients does not respond to this therapy for unknown reasons. It would be highly beneficial to be able to predict whether or not an individual patient responds to treatment. **Chapters 4** and **5** describe the investigations on the role of different candidate SNPs related to the efficacy of the treatment with different anti-TNFs in RA. In addition, in **chapter 3** a replication study is presented based on 4 polymorphisms that were found associated with anti-TNF response in RA in a previously published genomewide association study.

Part 2: Pharmacogenetics of rituximab used in SLE and other autoimmune diseases

In **chapters 6–8** the role of different genetic variants related to the pharmacodynamics of the drug or of the diseases are evaluated to study the contribution to differences in the response to rituximab in patients with SLE and other systemic autoimmune diseases.

In **chapter 6**, the possible involvement of the -174 IL-6 polymorphism in the clinical response to rituximab in different systemic autoimmune diseases is assessed. In **chapter 7**, the aim is to investigate the possible involvement of the *FCGR3A-158F/V* polymorphism in the clinical response to rituximab in Spanish patients with different systemic autoimmune diseases. In **chapter 8**, the role of G/T polymorphism at the *IL2–IL21* region in the rituximab response in a cohort of SLE patient and different autoimmune disorders is analyzed.

Chapter 9 provides a summary of this thesis, **chapter 10** the Dutch summary (Nederlandse samenvatting), and **chapter 11** the general discussion and future perspective of this thesis.

REFERENCES

- McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205-19.
- 2. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661-78.
- 3. Symmons DP, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DG, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum. 1997;40(11):1955-61.
- 4. Chan ES, Cronstein BN. Methotrexate--how does it really work? Nat Rev Rheumatol. 2010;6(3):175-8.
- 5. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev. 2005;57(2):163-72.
- Kremer JM, Galivan J, Streckfuss A, Kamen B. Methotrexate metabolism analysis in blood and liver of rheumatoid arthritis patients. Association with hepatic folate deficiency and formation of polyglutamates. Arthritis Rheum. 1986;29(7):832-5.
- Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum. 2002;46(6):1443-50.
- 8. Thalayasingam N, Isaacs JD. Anti-TNF therapy. Best Pract Res Clin Rheumatol. 2011;25(4):549-67.
- Bruhns P, Iannascoli B, England P, Mancardi DA, Fernandez N, Jorieux S, et al. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. Blood. 2009; 113(16):3716-25.
- 10. Julia M, Guilabert A, Lozano F, Suarez-Casasus B, Moreno N, Carrascosa JM, et al. The role of Fcgamma receptor polymorphisms in the response to anti-tumor necrosis factor therapy in psoriasis A pharmacogenetic study. JAMA Dermatol. 2013;149(9):1033-9.
- 11. O'Dell JR. Therapeutic strategies for rheumatoid arthritis. N Engl J Med. 2004;350(25):2591-602.
- 12. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117(2):244-79.
- 13. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol. 2008;8(1):34-47.
- 14. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400-11.
- 15. Greenberg JD, Ostrer H. Predicting response to TNF antagonists in rheumatoid arthritis: the promise of pharmacogenetics research using clinical registries. Bull NYU Hosp Jt Dis. 2007;65(2):139-42.
- 16. Aletaha D, Smolen JS. Diagnosis and Management of Rheumatoid Arthritis. A Review. JAMA. 2018; 320(13):1360-72.
- 17. Estes D, Christian CL. The natural history of systemic lupus erythematosus by prospective analysis. Medicine (Baltimore). 1971;50(2):85-95.
- Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore). 1993;72(2):113-24.
- 19. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-31.
- 20. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, et al. A phase III, randomized, placebocontrolled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63(12):3918-30.

- 21. Belmont HM. Treatment of systemic lupus erythematosus 2013 update. Bull Hosp Jt Dis (2013). 2013;71(3):208-13.
- 22. Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. Am J Transplant. 2006;6(5 Pt 1):859-66.
- 23. Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune diseasethe immune complex decoy hypothesis. Nat Clin Pract Rheumatol. 2007;3(2):86-95.
- 24. De Vita S, Zaja F, Sacco S, De Candia A, Fanin R, Ferraccioli G. Efficacy of selective B cell blockade in the treatment of rheumatoid arthritis: evidence for a pathogenetic role of B cells. Arthritis Rheum. 2002;46(8):2029-33.
- 25. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood. 2001;98(4):952-7.
- 26. Looney RJ, Anolik JH, Campbell D, Felgar RE, Young F, Arend LJ, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum. 2004;50(8):2580-9.
- 27. Ramos-Casals M, Garcia-Hernandez FJ, de Ramon E, Callejas JL, Martinez-Berriotxoa A, Pallares L, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol. 2010;28(4):468-76.
- 28. Ramos-Casals M, Soto MJ, Cuadrado MJ, Khamashta MA. Rituximab in systemic lupus erythematosus: A systematic review of off-label use in 188 cases. Lupus. 2009;18(9):767-76.
- 29. Diaz-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martinez-Berriotxoa A, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev. 2012;11(5):357-64.
- 30. Ezeonyeji AN, Isenberg DA. Early treatment with rituximab in newly diagnosed systemic lupus erythematosus patients: a steroid-sparing regimen. Rheumatology (Oxford). 2012;51(3):476-81.
- Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. Annu Rev Med. 2006;57:119-37.
- Evans WE, McLeod HL. Pharmacogenomics--drug disposition, drug targets, and side effects. N Engl J Med. 2003;348(6):538-49.
- 33. Scott SA. Personalizing medicine with clinical pharmacogenetics. Genet Med. 2011;13(12):987-95.
- 34. Kooloos WM, Huizinga TW, Guchelaar HJ, Wessels JA. Pharmacogenetics in treatment of rheumatoid arthritis. Curr Pharm Des. 2010;16(2):164-75.
- 35. Dervieux T, Wessels JA, van der Straaten T, Penrod N, Moore JH, Guchelaar HJ, et al. Gene-gene interactions in folate and adenosine biosynthesis pathways affect methotrexate efficacy and tolerability in rheumatoid arthritis. Pharmacogenet Genomics. 2009;19(12):935-44.
- 36. Kooloos WM, de Jong DJ, Huizinga TW, Guchelaar HJ. Potential role of pharmacogenetics in anti-TNF treatment of rheumatoid arthritis and Crohn's disease. Drug Discov Today. 2007;12(3-4):125-31.
- Kooloos WM, Guchelaar HJ, Huizinga TW, Wessels JA. Comment on: Investigation of candidate polymorphisms and disease activity in rheumatoid arthritis patients on methotrexate. Rheumatology (Oxford). 2009;48(9):1176-7; author reply 7.
- Kooloos WM, Wessels JA, van der Kooij SM, Allaart CF, Huizinga TW, Guchelaar HJ. Optimalization of the clinical pharmacogenetic model to predict methotrexate treatment response: the influence of the number of haplotypes of MTHFR 1298A-677C alleles on probability to respond. Ann Rheum Dis. 2009;68(8):1371.
- 39. Kooloos WM, Wessels JA, van der Straaten T, Allaart CF, Huizinga TW, Guchelaar HJ. Functional polymorphisms and methotrexate treatment outcome in recent-onset rheumatoid arthritis. Pharmacogenomics. 2010;11(2):163-75.
- 40. van der Kooij SM, Wessels JA, Huizinga TW, Guchelaar HJ. Comment on: The pharmacogenetics of methotrexate. Rheumatology (Oxford). 2008;47(4):557; author reply 5557-8.

- 41. van der Straaten RJ, Wessels JA, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Allaart CF, Bogaartz J, et al. Exploratory analysis of four polymorphisms in human GGH and FPGS genes and their effect in methotrexate-treated rheumatoid arthritis patients. Pharmacogenomics. 2007;8(2):141-50.
- 42. Wessels JA, Huizinga TW, Guchelaar HJ. Recent insights in the pharmacological actions of methotrexate in the treatment of rheumatoid arthritis. Rheumatology (Oxford). 2008;47(3):249-55.
- 43. Wessels JA, van der Kooij SM, le Cessie S, Kievit W, Barerra P, Allaart CF, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum. 2007;56(6):1765-75.
- 44. Ferraccioli G. The possible clinical application of pharmacogenetics in rheumatology. J Rheumatol. 2003;30(12):2517-20.