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Review Article

Factors Influencing Adalimumab Treatment Response in Patients with Rheumatoid Arthritis: The Future of Clinical Expertise

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ABSTRACT

Rheumatoid arthritis (RA) is characterized by persistent joint inflammation, a defining feature of this chronic inflammatory condition. Considerable advancements have been made in the field of disease-modifying anti-rheumatic medicines (DMARDs), which effectively mitigate inflammation and forestall further joint deterioration. Anti-tumor necrosis factor-alpha (TNF-α) drugs, which are a class of biological DMARDs (bDMARDs), have been efficaciously employed in the treatment of RA in recent times Adalimumab, a TNF inhibitor, has demonstrated significant efficacy in reducing disease symptoms and halting disease progression in patients with RA. However, its usage is associated with major side effects and high costs. In addition, ongoing advancements in therapeutic development have resulted in the production of medications that exhibit enhanced efficacy and safety characteristics. However, further investigation is required before RA can be deemed a manageable pathology. This review presents an analysis of the utilization of adalimumab for the treatment of RA by synthesizing information from relevant literature and emphasizing its effectiveness and safety to improve the overall outcomes along with potential cost reductions for patients with RA.

Keywords: Adalimumab, Rheumatoid arthritis, Effectiveness and safety, TNF-α receptors.

العوامل المؤثرة على الاستجابة لعلاج أداليموماب في مرضى التهاب المفاصل الرثوي: مستقبل الخبرة السريرية

الخلاصة

يتميز التهاب المفاصل الرثوي بالتهاب المفاصل المستمر، وهي سمة مميزة لهذه الحالة الالتهابية المزمنة. تم إحراز تقدم كبير في مجال الأدوية المضادة للروماتيزم المعدلة للأمراض، والتي تخفف بشكل فعال من الالتهاب وتمنع المزيد من تدهور المفاصل. تم استخدام ألأدوية المضادة لعامل لنخر الورم ألفا، وهي فئة من العلاجات البيولوجية الفعالة في علاج التهاب المفاصل الرثوي في الآونة الأخيرة وقد أظهر أداليموماب، وهو مثبط لعامل نخر الورم، فعالية كبيرة في الحد من أعراض المرض ووقف تطور المرض لدى المرضى الذين يعانون من التهاب المفاصل الرثوي. ومع ذلك، يرتبط استخدامه بآثار جانبية كبيرة وتكاليف عالية. بالإضافة إلى ذلك، أدت التطورات المستمرة في التطوير العلاجي إلى إنتاج الأدوية التي تظهر خصائص فعالية وسلامة معززة. ومع ذلك، هناك حاجة إلى مزيد من التحقيق قبل اعتبار التهاب المفاصل الرثوي مرضا يمكن التحكم فيه. تقدم هذه المراجعة تحليلا لاستخدام أداليموماب لعلاج التهاب المفاصل الرثوي من خلال تجميع المعلومات من الأدبيات ذات الصلة والتأكيد على فعاليتها وسلامتها لتحسين النتائج الإجمالية جنبا إلى جنب مع تخفيضات التكاليف المحتملة للمرضى الذين يعانون من التهاب المفاصل الرثوي.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is highly prevalent. It has the potential to cause damage to cartilage and bones, resulting in disability that can impose a considerable burden on both the individual and society [1]. TNF-α, a proinflammatory cytokine, has been identified as a major contributor to the pathogenesis of chronic immune-mediated disorders [2]. At present, anti-tumor necrosis factor (anti-TNF) medications are recognized as an efficacious therapeutic option for RA [3]. TNF-α, a proinflammatory cytokine, has been identified as a major contributor to the pathogenesis of chronic immune-mediated disorders. Apart from adalimumab, various other TNF-α inhibitors have obtained regulatory endorsement for their clinical application in rheumatology, such as etanercept, golimumab, infliximab, and certolizumab [2]. The management of rheumatoid arthritis usually entails the utilization of these agents. Several studies [5-8] suggest that TNF-α inhibitors may have adverse effects on patients with RA, despite their therapeutic benefits. The preponderance of the trials primarily concentrated on the general adverse effects (AEs) or a solitary type of AE, and certain meta-analyses conducted initially were subsequently refuted by subsequent research. Although several pair-wise and network meta-analyses have assessed the safety of different TNF-α inhibitor therapies for patients with RA, Bongartz *et al*. found that those receiving anti-TNF therapy had a higher likelihood of experiencing serious infections and malignancies. Conversely, another study investigating the risk of malignancy in RA patients concluded that there was insufficient evidence to suggest an elevated risk of malignancy associated with TNF-α inhibitors. The efficacy and tolerability of anti-TNF therapy in patients with RA have been demonstrated in various studies [11,12]. However, it should be noted that not all patients exhibit an immediate response to this treatment, and in some cases, the effectiveness of these medications may diminish over time. Currently, a comprehensive investigation into the specific mechanism underlying the inadequate response to anti-TNF therapy has yet to be undertaken [13]. Currently, there is a lack of established methodologies for prognosticating a patient's reaction to TNF-α inhibition. The early detection of individuals who are likely to respond poorly to therapy would necessitate the implementation of alternative treatment approaches, which would result in a delay in disease progression and a reduction in unnecessary expenses [14]. The efficacy of TNF inhibitors may be hindered in certain individuals due to factors such as variances in patient pathophysiological responses and the primary cytokine involved in each patient's disease progression [15]. The original compound of adalimumab was granted approval by the FDA for the treatment of rheumatoid arthritis. Following the approval of etanercept and infliximab, the third TNF-α inhibitor was granted FDA approval, as reported in reference 16. Extensive clinical testing has been conducted on adalimumab. The monoclonal anti-TNF antibody is composed solely of human amino acid sequences. Clinical trials have demonstrated that adalimumab is both safe and effective when administered alone or in conjunction with other antirheumatic medications [17,18]. The comparative efficacy of adalimumab and other targeted drugs was evaluated through direct and indirect comparisons. The findings revealed notable variations in effectiveness, which could potentially impact the management of RA [19]. Adalimumab has been associated with severe infections and various adverse effects, including but not limited to cancer, significant cardiac events, venous thromboembolism, and mortality. The administration of Adalimumab has been associated with various adverse effects such as herpes zoster, lymphopenia, hepatic impairment, and an increase in CPK levels [20]. While anti-TNF therapy has demonstrated efficacy and tolerability in the treatment of RA patients [21], not all patients exhibit an immediate response, and some individuals may experience a reduction in drug efficacy over time [22]. The exact mechanism responsible for the insufficient response to anti-TNF therapy has not been comprehensively studied, as indicated by previous research [23]. Currently, there is a lack of established techniques for predicting the response of patients to TNF-α blockade [24]. The identification of poor responders prior to commencing therapy would necessitate the implementation of alternative treatment methods, resulting in delayed disease progression and reduced wastage of expenses [24]. Due to variations in the pathophysiological response of each patient and the primary cytokine involved in their specific illness process, a subset of individuals may not experience the desired therapeutic effects of TNF inhibitors [25]. The efficacy and safety of adalimumab over an extended period of more than three years in treated patients remains largely uncertain [20]. The aim of this review is to examine the long term clinical effectiveness and safety, as well as the clinical and pharmacogenetic factors that impact the response to adalimumab therapy in patients with RA.

METHOD

A systematic and comprehensive search using specific keywords "adalimumab", "rheumatoid arthritis," "safety," "effectiveness," "genetic polymorphism," clinical," "epidemiological," and "response" from PubMed, Google Scholar, and ResearchGate databases will be conducted. All the papers were thoroughly investigated and presented in the text. Since the approval of adalimumab in 2002, all studies that meet the inclusion criteria and have been published were included. Authors conducted full-text verification if they cannot classify research based on their titles and abstracts. During the study selection process, any

disagreements will be declared and resolved by consensus.

Inclusion criteria

The primary search results were imported into Mendeley, and the publications discovered there will be examined using the criteria listed therein: 1) any and all research that investigated the link between the effectiveness, safety, clinical, epidemiological, and pharmacogenetic factors impacting response to adalimumab in RA patients; 2) papers containing adequate data to extract.

Exclusion criteria

The duplicates, meta-analyses, case reports, book chapters, letters to the editor, and conference abstracts will be omitted.

RESULTS

Effectiveness and Safety of Adalimumab in RA

TNF-α is a crucial cytokine that regulates the immune response and plays a vital role in the inflammatory cascade. Elevated levels of TNF-α have been reported in both the synovial tissue and synovial fluid of individuals diagnosed with RA, as documented in a previous study [26]. The erosion of bone and breakdown of cartilage can lead to functional impairment and loss of function. Additionally, it has the potential to induce inflammation in a specific area and result in the formation of pannus. According to previous studies [27], it is recommended to use TNF-α inhibitors for managing conditions with moderate to high levels of activity. Numerous studies have demonstrated the safety and efficacy of adalimumab, a TNF-alpha inhibitor, in the treatment of RA, either as a monotherapy or in conjunction with methotrexate (MTX) [28–30]. According to Weisman *et al*., adalimumab is deemed to be safe and devoid of significant adverse reactions. In this study, intravenous administration of adalimumab was performed at variable dosages. The trial demonstrated that adalimumab was generally well-tolerated and did not exhibit any adverse effects related to dosage. This study reported that a considerable proportion of patients who received adalimumab in conjunction with MTX exhibited noteworthy and persistent improvements. During the 4-week double-blind and placebo-controlled period, 64.4% (29/45) and 24.4% (11/45) of individuals exhibited American College of Rheumatology improvement by 20% and 50% (ACR20 and ACR50) responses, respectively, upon receiving a single dose of adalimumab with MTX [31]. In the United States, the selection of a biological agent for specific clinical applications is often based on factors such as the ease of administration and the level of self-injection anxiety experienced by patients. Although adalimumab is considered to be more pragmatic, it resulted in a higher incidence of injection/infusion-site burning and stinging (ISBS) compared to etanercept. Furthermore, the severity of this unfavorable outcome surpassed that observed in previous clinical trials [32]. The utilization of three TNF-α inhibitors in conjunction with MTX has been shown to elicit favorable self-reported outcomes in the management of active RA among patients. [33]. In a study conducted by Weinblatt *et al*. to evaluate the safety and efficacy of adalimumab in comparison to MTX plus placebo, it was demonstrated that the inclusion of subcutaneously administered adalimumab at doses of 20 mg, 40 mg, or 80 mg every other week to long-term MTX treatment resulted in a significant, rapid, and enduring reduction in disease activity over a 24-week period [17]. In a clinical trial conducted by Huang *et al*., participants were administered adalimumab or a placebo at varying dosage levels. The objective of the study was to assess the efficacy and safety of adalimumab in conjunction with MTX, specifically at doses of 40 mg or 80 mg, for the management of RA. Prior to participating in the trial, each participant had undergone MTX therapy. The study findings indicate that the combination of adalimumab and MTX demonstrated superior efficacy in managing RA compared to the use of MTX monotherapy. The combination of adalimumab and MTX is generally considered to be safe and well-tolerated. This treatment approach has been shown to result in a notable increase in response rates, a gradual reduction in rheumatic symptoms and inflammatory markers, and benefits in terms of reducing disability levels and enhancing the overall quality of life for patients [18]. In another study, Heiberg *et al*. made a discovery indicating that the administration of adalimumab in combination with MTX was more effective than the administration of adalimumab alone in patients who had pre-existing RA. The group that received the combined treatment exhibited a significantly higher proportion of patients who were cured (p=0.07) compared to the other groups. Additionally, there was a significant change observed in all parameters when compared to the baseline [34]. The study known as "STAR" was designed to investigate the efficacy and safety of adalimumab in individuals with chronic RA who exhibited an inadequate response to conventional anti-rheumatic therapies. The objective of the study was to assess the effectiveness of adalimumab as a therapeutic intervention for the aforementioned medical condition. The primary outcomes of the study were the incidence rates of side effects, major side effects, severe or life-threatening side effects, withdrawal-inducing side effects, infections, and serious infections. The addition of adalimumab to the conventional treatment for RA over a period of 24 weeks demonstrated a high level of tolerability and a significant reduction in the clinical manifestations of RA. A dose of 40 mg of adalimumab was subcutaneously administered biweekly. The efficacy and safety of adalimumab as a therapeutic option were

established through the analysis of outcomes in patients with active RA who exhibited an inadequate response to conventional anti-rheumatic treatment [35]. Post-marketing surveillance has revealed that the safety profile of adalimumab is comparable to that of other anti-rheumatic biologics. Additionally, there were no unanticipated adverse drug reactions (ADRs) observed that could have compromised the safety of adalimumab. The research revealed a noteworthy association between diabetes mellitus and heightened susceptibility to various infections, ranging from mild to severe, along with a possible reduction in the efficacy of adalimumab treatment. As per the literature, it is recommended that individuals diagnosed with both RA and diabetes mellitus should receive adalimumab treatment while maintaining strict adherence to infection control protocols [36]. The incidence of adverse drug reactions (ADRs) and the progression rate of the disease subsequent to adalimumab therapy was found to be comparable irrespective of whether the administration of MTX was concomitant or the biological treatment had been administered previously. However, a notable disparity was observed in glucocorticoid-treated patients when juxtaposed with those who had not undergone such treatment, as evidenced by studies [36,37]. An open prospective cohort study was conducted by Brazilian researchers to investigate the effectiveness and safety of adalimumab and etanercept in treating patients with rheumatoid arthritis over a period of six and twelve months. The Disease Activity Clinical Index, Health Assessment Questionnaire, and EuroQol-5D were utilized as assessment tools. The findings of the present investigation indicate that adalimumab and etanercept exhibit comparable levels of safety and efficacy in the management of patients with RA [38]. The study conducted by Burmester *et al*. aimed to investigate the efficacy and safety of adalimumab in patients with active RA who had previously received at least one DMARD treatment but did not achieve the intended therapeutic outcome. The present study conducted a comprehensive observational analysis to evaluate the effectiveness and safety of adalimumab in routine clinical practice. The findings revealed that the efficacy and safety outcomes of adalimumab were consistent with those reported in controlled trials. Moreover, the safety profile of adalimumab remained unchanged during the follow-up period of over five years. Notably, adalimumab demonstrated sustained effectiveness throughout the prolonged observation period, which is a favorable outcome [39]. A multicenter, open-label, prospective single-cohort study was conducted in Canada to evaluate the safety and efficacy of adalimumab for treating patients with RA in a clinical context that reflected the Canadian standard of care. The aim of the study was to determine the comparative effectiveness of adalimumab and the conventional treatment regimen in managing RA symptoms. The study recruited a cohort of 879 participants, whose average disease duration exceeded 12 years. Out of the total sample, 772 individuals (constituting 87.9% of the sample) successfully fulfilled the requisite 12-week participation period as mandated by the study. The study's results indicate that the administration of adalimumab therapy was associated with notable enhancements in the clinical presentation of RA. These improvements were observed as early as the fourth week of treatment and endured for a substantial duration. According to the incidence rates of unfavorable effects, the categories of unfavorable effects that transpired, and the results of laboratory assessments, it was demonstrated that adalimumab exhibited a general profile of safety and tolerability [40]. The findings of a real-world study investigating the long-term persistency and effectiveness of adalimumab in the treatment of RA patients led researchers to conclude that the medication demonstrated sustained effectiveness and long-term control in patients who adhered to the treatment regimen for the entire 10-year treatment period [41]. Flouri *et al*. conducted an evaluation of the efficacy, drug survival, and safety profiles of three anti-TNF medications (namely, infliximab, adalimumab, and etanercept) in a sizable cohort of RA patients from various regions of the world. The comparability of response rates among the drugs was observed in this study. Nevertheless, the drug survival rates for infliximab, adalimumab, and etanercept after a period of five years were 31%, 43%, and 49%, respectively. The results indicate that Adalimumab (odds ratio 0.62; range: 0.38–1.00) and etanercept (odds ratio 0.39; range: 0.21-0.72) exhibited a reduced occurrence of severe infections in comparison to infliximab. [42]. Prospective clinical research has demonstrated the efficacy and safety of fully human recombinant adalimumab in treating patients with RA, particularly those who have not responded to conventional anti-TNF drugs [43]. Horneff *et al*. conducted a multinational open-label study spanning 12 weeks to investigate the achievement of remission and/or low disease activity in RA patients who were administered adalimumab. The study findings revealed that clinical remission was observed in around 33% of patients with active RA who were receiving adalimumab therapy. The aforementioned discovery suggests that individuals who suffer from active RA exhibit a favorable response to adalimumab treatment [44]. The recommended dose of adalimumab for adults is 40 mg to be administered biweekly. In the event of a requirement, the aforementioned dose may be escalated to 40 mg on a weekly basis. Alternatively, it may be increased to 80 mg biweekly. In cases where there is no observed improvement following a 12-week treatment regimen, it is recommended that dosage adjustments be limited to individuals receiving adalimumab monotherapy [45].

Immunogenicity of Adalimumab

It is nonetheless extremely concerning that people with RA are unable to respond to TNF inhibitors regularly. Although some patients report a primary response failure in lowering their symptoms, other patients experience medication resistance and are exposed to secondary loss of response. In this regard, another TNF inhibitor can routinely administered to patients who are not responding to one treatment, however, there is little evidence from clinical trials to support this practice. Switching to a different class of medicine may be the best line of action if the currently used TNF inhibitor does not yield enough results or if there are equivalent tolerability issues [46]. Adalimumab (Humira®; Abbott Laboratories) was manufactured genetically by mimicking naturally occurring human immunoglobulin G1 (IgG1) utilizing phage display technology. It is physically and functionally identical to normal human IgG1 in the human body since it only comprises amino acid sequences from the human germline [20]. Additionally, adalimumab has a terminal half-life of around two weeks, the same as that of human IgG1. It acts by inhibiting TNF-α from interacting with the p55 and p75 TNF cell surface receptors, among others [47]. Accordingly, adalimumab is thought to have a lesser immunogenic potential than chimeric proteins due to being a totally human immunoglobulin [48]. There has been speculation in the past that human anti-human antibodies may also develop in response to adalimumab, despite the scant information that is currently available. Adalimumab monotherapy at a dose of 40 mg every other week was reported to be effective in 12% of RA patients who had anti-adalimumab antibodies [49]. Radioimmunoassay was performed by many researchers to identify anti-drug antibodies in RA patients receiving adalimumab therapy [50,34,51]. A prospective cohort trial lasting 28 weeks found that 17% of RA patients produced anti-adalimumab antibodies, and a decrease in disease activity was linked to the existence of these antibodies. In contrast to the use of concurrent MTX, which was linked to a lower rate of antibody generation (12%), adalimumab monotherapy was related to a higher rate of antibody development (38%) [34]. Adalimumab was used as the treatment when infliximab failed to provide any results, which increased the drug's immunogenicity [51]. Anti-adalimumab antibodies were more likely to form in patients (33/52) who had previously produced anti-infliximab antibodies than they were in patients (63%) who were anti-TNF naive. Therefore, compared to patients who did not produce anti-adalimumab antibodies, these patients were less likely to respond to adalimumab. However, 89% of individuals who did not have adalimumab anti-drug antibodies also used MTX concurrently. Compared to the 54% of patients who did develop anti-adalimumab antibodies, this figure was noticeably greater. The same team also assessed how immunogenicity affected 272 RA patients on long-term adalimumab treatment. Over the course of three years, they discovered that 28% of patients acquired anti-drug antibodies, with the majority doing so during the first six months of therapy. Anti-drug antibodies were discovered to be strongly related to greater rates of drug withdrawal as a result of ineffective therapy, poorer rates of remission, and a lower likelihood of minimal disease activity [50]. At baseline, there was a significantly lower risk of concurrent MTX use and a significantly lower mean dose in patients who developed anti-adalimumab antibodies over the course of the study. Other DMARDs were not related to this impact when used concurrently, but their usage was significantly less common. Additionally, there was no appreciable distinction between individuals who acquired anti-drug antibodies and those who did not in terms of prednisolone dosage or amount administered. In a group of patients who showed a definite dose-dependent association with MTX as well as a decrease in the production of anti-drug antibodies, Krieckaert *et al*. looked deeper into the relationship between immunogenicity and the effectiveness of drugs [52]. The baseline MTX dose was used to stratify the RA patients (n = 272) in the adalimumab cohort. The number of patients who received no concurrent MTX (n = 70), a low dose of MTX between 5 and 10 mg/week (n = 40), an intermediate dose of MTX between 12.5 and 20 mg/week (n = 54), or a high dose of MTX beyond 22.5 mg/week (n = 108) was provided to these patients. Compared to patients who weren't treated, those who received MTX had a decreased incidence of generating anti-drug antibodies. The percentage of patients who produced anti-drug antibodies was shown to be inversely correlated with the dose of MTX administered; the group receiving a dose of less than 22.5 mg/week had the lowest percentage of patients who became immunogenic. Additionally, it is probable that a sizable percentage of RA patients receiving adalimumab treatment would lose their initial response. When a person generates anti-adalimumab autoantibodies, this might lead to insufficient therapeutic benefits or increased adverse effects [34]. The link between antidrug antibodies and the therapeutic response to adalimumab and etanercept, as well as the blood trough levels of these drugs, was examined in a study conducted by Chen and colleagues. It was discovered that antidrug antibodies were associated with decreased EULAR (European League Against Rheumatism) responses. The researchers came to the conclusion that tracking drug levels is a useful way to assess how anti-TNF drugs are influencing the patient's response to therapy [38]. The most likely explanations for these observations in individuals who were not responding well to the medication were immunological complexation between adalimumab and anti-adalimumab and increased clearance [48].

Genetic Polymorphisms and the Response to Adalimumab

The introduction of biological anti-TNF medication has drastically changed how RA is managed. Anti-TNF medication therapy has been shown to be helpful in reducing the degree of tissue and joint long-term damage as well as in reducing inflammation [53]. Nevertheless, despite the fact that TNF-α medications have been shown to have therapeutic efficacy, about 25% of patients exhibit either an insufficient response or none at all [54]. The constant portion of biological agents, the Fc fragment of IgG1, which precisely binds to the human FcG receptors (FcGRs), and their variable portion, which is designed to block the target molecule, are what give biological agents their pharmacological effects [55,56]. FcGRs are present on the surface of the majority of immune cells. A number of cellular processes, including phagocytosis, antibody-dependent cellular cytotoxicity, activation of apoptosis, cytokine production, and macrophage-mediated clearance of immune complexes, may be impacted by TNF antagonists' engagement of FcGRs [57]. Numerous candidate gene investigations have convinced scientists that the heterogeneity of the FcGR is a necessary condition for the anti-TNF therapeutic response [58,59]. In fact, it is well known that the FcGR2A and FcGR3A subclasses are also subject to genetic variations that can result in varying degrees of ligand binding. The extracellular Fc-binding region of the FcGR contains each of these polymorphisms, and as a result, they each affect the affinity with which the FcGR interacts with the different IgG subclasses [60], which may have an impact on the clearance of immune complexes [61].

Polymorphism of human Fc fragment of IgG1 receptors (FcGR)

The pharmacological effects of biological medication are a result of both the variable portion of this medication, which is intended to inhibit the target molecule, and the constant portion of biological agents, which is the Fc fragment of IgG1 that binds specifically to human Fc fragments of IgG receptors [62]. FcGRs are present on the surface of the vast majority of immune cells. A number of diverse cellular processes, including phagocytosis, antibody-dependent cellular cytotoxicity, the induction of apoptosis, the production of cytokines, and macrophage-mediated clearance of immune complexes, may be impacted by the interaction of FcGRs with TNF -inhibitors [63]. In order to determine whether FcGR genetic variations might be a predictor of adalimumab effectiveness in RA patients, Fajardo and associates conducted a study that compared the allelic frequencies of responders with those of non-responders. They found that the presence of the FcGR2A*R allele was associated with an EULAR excellent response at 14 weeks. Additionally, there was no discernible link between FcGR3A and a favorable response or remission of the illness. There is some proof that FcGR polymorphisms can be employed to forecast the efficacy of adalimumab in RA patients [64]. A functional polymorphism in FCGR2A H131R and a patient's response to treatment with Fc-containing inhibitors of TNF-α (infliximab, etanercept, and adalimumab) were the subjects of a separate study by Montes *et al*. The results show that there is no relationship between the FCGR2A H131R polymorphism and how well a patient reacts to adalimumab therapy [65]. In a separate study, Tutuncu *et al*. investigated the relationship between polymorphisms in the FcGR3A-158 and clinical efficacy in RA and PsA patients receiving adalimumab, etanercept, and infliximab therapy. The distribution of the alleles among people who are exceptional responders is as follows, according to the study's findings: F/F: 48, V/F: 13, and V/F: 38 percent. The distribution of the alleles among people who did not take part in the study was as follows: 0% for F/F, 8% for V/V, and 92% for V/F. The homozygous low-affinity F/F genotype was found to be strongly associated with responses to TNF inhibitor therapy. These results suggest that FcGR3A-158 polymorphisms may influence the efficacy of TNF-blocking medications [66].

Transcriptional biomarker (CD11c) polymorphism

There was a substantial association between the levels of disease activity and the expression of monocyte-related genes prior to patients starting therapy with a new DMARD (either MTX or an anti-TNF drug). IFN and TNF, in turn, significantly influence the various gene expression profiles that monocytes in RA produce [67]. The emergence of RA is caused by these gene expression profiles. According to research, even a single biomarker on monocytes may be adequate to measure disease activity and forecast responsiveness to anti-TNF biologics, such as CD11c in RA [68]. Additionally, it was found that patients with RA had differing frequencies of classical, intermediate, and non-classical blood monocytes compared to healthy donors [69]. Given their significant involvement in the RA pathological processes that are especially susceptible to anti-TNF, it appeared advantageous to look into enriched monocytes in this regard [70]. This is due to the significant role that monocytes play in these processes. In general, this hypothesis offers proof-of-concept for the possibility that stringent purification combined with genome-wide analysis of important cell types in the easily accessible blood compartment (i.e., monocytes) may be a successful method for discovering functionally relevant biomarkers so that exposure to biologicals can be restricted to therapy responders. This is significant because it enables the selective targeting of biological exposure to patients who will benefit from the treatment. To prove that future responders to adalimumab monotherapy will experience it, larger studies involving other anti-TNF biologics and treatment methods targeting other targets must confirm the predictive usefulness of CD11c [68]. Data collected revealed that CD11c is expressed on the surface of

human monocytes as well as other myelomonocytic lineage cells (such dendritic cells), and that the amount of this protein is markedly increased in RA monocytes. The presence of CD11c on the surface of these cells served as confirmation, because the complement component 3 receptor 4 subunit and the CD11c form of the Integrin-X protein both have expertise in inflammation and cell attachment [71]. Since monocytes are crucial to the pathophysiology of RA, to the best of our knowledge, Stuhlmüller *et al*. has looked into the increased monocyte transcriptional biomarker (CD11c). The results (100% sensitivity; 91.7% specificity; 99.6% power; P=0.01) demonstrated an increase in CD11c expression in patients who reacted to adalimumab. Pretherapy CD11c levels and the ACR response criteria showed a substantial association (r=0.656, P=0.0001) [68].

Protein tyrosine phosphatase non–receptor–22 (PTPN22) genetic polymorphism

Numerous biological predisposing variables, including genetic elements, have been identified to contribute to RA susceptibility [72]. In this context, 30–50% and 23%, respectively, of the genetic load of RA are attributed to the human leukocyte antigen (HLA) locus and non-HLA genes, such as the *PTPN22* gene [73]. The *PTPN22* gene is one example of a non-HLA gene. In order to stop T cells from spontaneously activating, a family of enzymes known as protein tyrosine phosphatases dephosphorylate and inactivate T cell antigen receptor-associated kinases and other substrates. A member of this family of enzymes is PTPN22. Therefore, any alteration to the *PTPN22* gene may have an impact on its products and functions [74]. One of the many single nucleotide polymorphisms (SNPs) in the *PTPN22* gene is the C-to-T mutation at position 1858 (1858C/T), which has been associated with a higher chance of developing RA [75]. The *PTPN22* gene is currently thought to be one of the most important inherited risk factors that can result in the emergence of autoimmune illness. There is proof that inheriting the *PTPN22* gene raises your risk of contracting a variety of autoimmune illnesses [76]. The early functional influence of *PTPN22* in autoimmune diseases was investigated by genetic association studies. C1858T, rs2476601, a missense SNP, were discovered to be substantially correlated with RA [77]. In a sizable, multicenter cohort study conducted in the UK, the relationship between the *PTPN22* 620W (C1858T) polymorphism and clinical response to anti-TNF medications (infliximab and adalimumab) was examined. Participants with RA who were using the anti-TNF medications infliximab and adalimumab were included in this trial. According to the results, there is no link between the presence of the *PTPN22* gene variation, which raises the chance of developing RA, and the response to adalimumab treatment [78].

TNF-α-308 G/A (rs1800629) promoter polymorphism

More and more emphasis is being paid to the single nucleotide polymorphisms (SNPs) discovered in the TNF-α promoter. The most extensive study has focused on the G-to-A transition at position 308 (rs1800629) [79]. The precise mechanism by which the SNP at TNF-α-308G/A is related to autoimmune illnesses like RA, however, has not been satisfactorily demonstrated. One of the biggest challenges to treating RA is the emergence of drug resistance to traditional treatments [80]. A number of TNF-α-targeting therapies (like adalimumab) have been launched in the treatment of RA and have demonstrated efficacy on the basis of the notion that excessive TNF-α buildup may have harmful effects [81]. Despite the possibility of severe side effects, 40–60% of patients did not respond to TNF-alpha inhibitors [82]. These severe negative effects include the possibility of life-threatening infections and perhaps cancer. The effectiveness of anti-TNF-α medication should be assessed using biomarkers that take into account the particular traits of each patient. Other studies [83,84] have demonstrated that TNF-α-308G/A is a highly accurate predictor of responsiveness to TNF-α inhibitors. The G/A polymorphism at position 308 of the TNF-α promoter gene has been reported to be the most strongly associated with both the risk of developing RA and the severity of the disease [85], and polymorphisms in the TNF-α promoter region have been linked to individual variations in TNF production [86]. The first study to examine the effect of the -308 G/A polymorphism in the TNF-alpha promoter on the clinical response of RA patients receiving adalimumab medication was conducted by Cuchacovich and colleagues. To ascertain if 81 RA patients possessed the polymorphism 308 G/A, they underwent genotyping. The proportion of individuals in the GG genotype group who reacted favorably to adalimumab at 24 weeks was substantially greater than the proportion of individuals in the GA genotype group (68%). Additionally, the GG genotype group improved their average DAS28 score more than the GA genotype group [87]. Seitz *et al*. looked into whether the -308 G/A polymorphism of the TNF-alpha promoter affects the therapeutic response to anti-TNF-α medication that includes adalimumab in the treatment of 54 RA patients, in keeping with the results of the prior study. The GG genotype showed a larger average improvement in DAS28 score than the GA genotype after receiving anti-TNF-α medication for 24 weeks. These results showed that RA patients with GG TNF-α-308 genotype responded better to anti-TNF-α medication than RA patients with AA or GA genotype [88]. In addition, O'Rielly *et al*. performed a meta-analysis of the TNF-α 308 G/A polymorphism, which indicated that individuals with RA on adalimumab would not respond well to TNF-α inhibitors. The odds ratio for possessing the A allele status was found to be

considerably lower in survey respondents (OR: 0.43; CI 95%: 0.28-0.65; *P* = 0.000245) [89].

TNF-α Receptor 2 (TNFR2) Polymorphism

A pleiotropic cytokine called TNF-α is crucial for modulating a number of immunological processes, such as inflammation, the control of apoptosis and necrosis, and the generation of cytotoxicity [90]. It can communicate through either type I (CD120a, TNFRSF1A) or type II (CD120b, TNFRSF1B) membrane-bound receptors, which are both capable of inducing a number of distinct immune responses [91]. Compared to type 2 TNF-α receptors (TNFR2), which are mostly found on immune system cells, type 1 TNF-α receptors (TNFR1) are more common and expressed on all cell types [92]. Proliferation induction and apoptosis induction via a death domain-independent mechanism are the primary functions of TNFR2, which is primarily activated by membrane-bound TNF-α [93]. Numerous polymorphisms have been discovered in the TNFR2 and TNF genes, and it has been researched whether there is a connection between these variants and RA [94]. Ongaro *et al*. studied 105 RA patients who had received anti-TNF therapy with adalimumab for a duration of one year in accordance with ACR criteria to see if polymorphisms in the TNFR2 gene at position 676 T/G could affect their clinical response. After receiving adalimumab therapy for three to six months, individuals with the TG genotype had roughly a threefold higher likelihood of developing into good responders than patients with the TT genotype. Additionally, the presence of a single G allele, as in the GT genotype, is linked to a less responsive phenotype during adalimumab treatment. Comparatively speaking, the GG genotype is linked to a more responsive phenotype [95]. TNF-α receptors can exist as soluble proteins in addition to their membrane-bound forms, which are produced from the membrane-bound form by the proteolytic operations of the disintegrin metalloproteinase TNF-α converting enzyme [96]. Many different types of cells include soluble TNF-α receptors. The soluble variations retain their ability to bind to ligands after cleavage [97], and by engulfing soluble forms of the protein, they may function as natural inhibitors of TNF-α. Therefore, it is plausible that reduced amounts of soluble TNFRs in individuals with the G allele may encourage the binding of TNF-α to its membrane receptor, decreasing the effectiveness of anti-TNF-α therapy. This is due to the fact that TNF-α prefers to bind to its membrane receptor at lower concentrations of soluble TNFRs [98]. From this perspective, the genetic mutation known as TNFR2 676T>G has the ability to influence the disease's eventual prognosis as well as the body's response to anti-TNF-α therapy. A poorer response to anti-TNF-α therapy and TNFR2 676T>G are associated, but it is impossible to rule out the possibility that there are other ramifications [99]. Moreover, the identification of gene mutation might be a valuable addition to the regional databases on rare genetic variant, although a functional analysis should be performed to explain its pathological consequences [100]. An overview of some research that evaluate the effectiveness, safety, and factors influencing the clinical response to adalimumab is included in Table 1.

CONCLUSION

This study presented an overview of how effectively adalimumab works and how safe it is for patients with RA, compiling the majority of the evidence that is currently accessible. Finding methods to manage RA has drawn more attention in recent years. This prompted a number of studies in which patients with RA were exposed to various therapies. The quality of life for those who have the disease has significantly improved, despite the fact that there is no cure. Understanding the parameters that define the safe and effective use of adalimumab in RA as well as the causes of response variability would help to considerably increase the clinical efficacy of adalimumab in the treatment of RA. To assess appropriate dose protocols and make sure that the advantages of the extra medication outweigh the hazards of further long-term immunosuppression, more longitudinal data are required. Future adalimumab dose optimization in future RA patients who may have a genetic predisposition that makes them prone to immunogenicity could lead to anti-TNF dose reductions in those who achieve remission. Adalimumab treatment has the potential to prolong drug survival and prevent secondary non-response, which could have a significant financial impact and benefit patients by extending the time they are free from their disease for those who initially responded well to monoclonal-based therapies.

Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023-2038. doi: 10.1016/S0140-6736(16)30173-8.

2. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, Nam J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76:960-977. doi: 10.1136/annrheumdis-2016-210715.

3. Koga T, Kawakami A, Tsokos GC. Current insights and future prospects for the pathogenesis and treatment for rheumatoid arthritis. *Clin Immunol*. 2021;225:108680. doi: 10.1016/j.clim.2021.108680.

Table 1: Studies that assess the efficacy, safety, and variables affecting the clinical response to adalimumab.

Author and year	Design and treatment	Main outcomes	Factors influencing response
Navarro-Millán *et al*., 2016 [32]	A cross-sectional study was conducted in California, USA. From October 2010 to August 2022, 267 RA patients were given etanercept and adalimumab.	After 6 months, there was no difference in patient-reported outcomes between etanercept and adalimumab users.	Adalimumab users reported 3.2 times more infusion-site burning and stinging than etanercept users.
Curtis *et al.*, 2011 [101]	A retrospective and prospective data analysis of 504 and 3326 patients using etanercept and adalimumab in the USA was performed to determine the prevalence of infusion-site burning and stinging.	Many rheumatology practices underestimate the prevalence of ISBS.	ISBS was common in patients receiving etanercept or adalimumab (56% and 61%, respectively), and the prevalence of ISBS is likely to be underestimated in many rheumatology practices.
Dávila-Fajardo *et al*., 2015 [64]	In 2014, a prospective study of 302 Dutch RA patients was conducted to investigate the potential of *FcGR* genetic polymorphisms as a predictor of adalimumab efficacy.	At 14 weeks, the presence of the *FcGR2A*R* allele was associated with a good response to EULAR. FcGR3A had no significant association with good response or remission.	*FcGR2A* (R131>H; rs1801274) and FcGR3A (F158>V; rs396991) genetic variants, as well as FcGR polymorphisms, may influence adalimumab efficacy in RA patients.
Tutuncu *et al*., 2005 [66]	A prospective study of 30 RA patients in California was conducted to determine whether Fc RIIIA polymorphisms correlate with anti-TNF agent efficacy (infliximab, etanercept, and adalimumab).	TNF-blocking agent treatment outcomes may be influenced by Fc RIIIA-158 polymorphisms.	Homozygous (F/F) accounts for 31.5%, V/V accounts for 11.5%, and V/F heterozygous (V/F) accounts for 57%. The following allele distributions were found in extremely good responders: 48% for F/F, 13% for V/V, and 39% for V/F. The following alleles were distributed among non-responders: 0% for F/F, 8% for V/V, and 92% for V/F.
Chen *et al*., 2015 [38]	A prospective study in Taiwan examined the relationships between ADAb and therapeutic response, ADAb and serum drug nadir levels, and serum levels and therapeutic responses in 36 RA patients receiving adalimumab or etanercept.	The positive correlation between drug levels and DAS28 suggests that monitoring would be beneficial for assessing the therapeutic efficacy of TNF-α inhibitors.	Response and drug levels were inversely proportional to ADAb levels (more likely to have a poor EULAR response); 22.2% and 27.8% of 36 adalimumab-treated patients were positive for ADAb. To assess the efficacy of TNF- inhibitors, drug monitoring would be helpful.
Bartelds *et al*., 2007 [34]	In the Netherlands, a prospective case-control study of 212 RA patients was conducted to assess the incidence of ADAb formation against adalimumab and its relationship with serum adalimumab levels and response.	Patients with ADAb improved less in DAS28. During follow-up, patients with ADAb had lower serum adalimumab levels.	Serum adalimumab levels were higher in good responders than in moderate and non-responders. Concomitant MTX use was lower in the ADAb group (52% vs. 84%) than in the non-ADAb group.
Miceli-Richard *et al*., 2008 [102]	In 2007, prospective study on 388 French RA patients to determine whether TNF gene polymorphisms and/or the shared epitope are genetic predictors of response to adalimumab.	TNF locus revealed that the GGC haplotype (–238G/Á308G/–857C) in a homozygous form was significantly associated with a lower ACR50 response to adalimumab at 12 weeks.	single TNF locus haplotype (–238G/–308G/–857C), present on both chromosomes is associated with a lower response to adalimumab in combination with MTX.
Seitz *et al.*, 2007 [88]	A prospective study of 54 RA patients in Switzerland using adalimumab to see if a G-to-A polymorphism at position Á308 in the TNF gene promoter influences the therapeutic response to TNF-blockers.	TNF Á308 G/G genotypes respond better to anti-TNF treatment than A/A or A/G genotypes.	Anti-TNF treatment was ineffective in all patients with the A/A genotype. Good response was only seen in patients with the Á308 G/G diplotype, whereas moderate response was seen in 14/14 patients with the Á308 A/G genotype and unresponsiveness in 3/3 patients with the Á308 AA diplotype. DAS28 score improvement: A/A genotype 0.83; A/G genotype 1.50; G/G genotype 2.72.
Canhão *et al*., 2015 [103]	A Spanish prospective study (2010–2011) on 265 RA patients assessed the association of the *PTPRC* locus with response to anti-TNF treatment.	In the southern European population, there is no link between PTPRC and anti-TNF response.	*TRAF1/C5* RA risk variants may have an impact on anti-TNF treatment response.
Ochi *et al.*, 2020 [104]	A retrospective cohort study compared the outcomes of 1613 Japanese RA patients (2003-2019) who responded differently to initial TNF inhibitor treatment.	A higher DAS28-CRP before treatment was a risk factor for a poor response but not for a good response.	To fully understand the etiology and risk factors for bDMARDs refractoriness, response to bDMARDs should be assessed separately.
Weinblatt *et al*., 2003 [17]	A randomized, double-blind, placebo-controlled study was conducted in 271 Canadian and US RA patients to assess the efficacy and safety of adalimumab in combination with MTX.	Responses were rapid in the vast majority of adalimumab-treated patients after 1 week. Adalimumab was safe and well tolerated.	Adding 20, 40, and 80 mg of adalimumab every other week to long-term MTX therapy in patients with active RA provided significant, rapid, and sustained improvement in disease activity over 24 weeks when compared to MTX plus placebo.
Potter *et al*., 2010 [105]	A prospective study was conducted on 909 RA patients in the United Kingdom (2010) to determine the effect of genetic variation within TLR and NFκB genes on response to anti-TNF treatment.	In the anti-TNF-treated subgroups, a total of 187 SNPs were linked to response. Twelve SNPs spread across nine genes were linked to treatment response (DAS28 and/or EULAR).	A total of 187 SNPs were linked to response in the anti-TNF-treated subgroups. Twelve SNPs in nine genes were found to be associated with treatment response (DAS28 and/or EULAR).
Pouw *et al*., 2015 [18]	A multi-center, randomized, double-blind, placebo-controlled clinical trial on 302 Chinese RA patients was conducted in 2009 to investigate the efficacy and safety of adalimumab plus MTX.	Adalimumab plus MTX is effective and has increased the response rate.	Adalimumab improves the response rates for ACR20, ACR50, and ACR70 in the two treatment groups (40 and 80 mg adalimumab) from week 12 to week 24.
Furst *et al*., 2003 [106]	A double-blind, randomized trial involving 636 RA patients from the United States and Canada was conducted in 2003 to assess the safety and efficacy of 40mg adalimumab.	The use of 40 mg of adalimumab every other week with standard anti-rheumatic therapy is well tolerated and improves RA symptoms.	After 24 weeks, there were no significant differences in the rates of serious adverse events between the adalimumab and placebo groups.
Popescu *et al*., 2022 [107]	A prospective observational study compared the efficacy and safety of biosimilar and brand adalimumab in 441 Romanian RA patients (2019-2022).	After the first six months of treatment, the biosimilar adalimumab showed similar efficacy and safety to the brand-name drug.	According to Boolean results, there were no significant differences between the brand and biosimilar adalimumab after six months of treatment (15.0% *vs.* 12.3%, p = 0.401).
Genovese *et al*., 2007 [108]	Adalimumab's safety and efficacy were assessed in a placebo-controlled, double-blind, randomized, multicenter study of 100 Canadian and US patients with active psoriatic arthritis in 2003-2004.	Adalimumab is well tolerated and, after 12 weeks, significantly improved the signs, symptoms, and disability.	Response was achieved by 39% of adalimumab-treated patients versus 16% in the placebo group (p =0.012).
Weisman *et al*., 2003 [31]	Adalimumab efficacy, pharmacokinetics, and safety profile were evaluated in 60 RA patients from the United States and Canada in a phase I randomized dose-titration study.	Adalimumab has linear pharmacokinetic properties. The mean apparent terminal half-life of adalimumab after a single IV dose ranged from 15 to 19 days across the five dose groups.	Adalimumab produces a rapid response, with 22.2% of patients responding within 24 hours of dosing. When compared to placebo plus MTX, the addition of adalimumab produced a significantly longer-term improvement in patients with active RA who did not respond adequately to MTX.

4. Bradley JR. TNF-mediated inflammatory disease. *J Pathol*. 2008;214:149-160. doi: 10.1002/path.2287.

5. Gottenberg JE, Morel J, Perrodeau E, Bardin T, Combe B, Dougados M, et al. Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: Prospective cohort study. *BMJ*. 2019;364:l7. doi: 10.1136/bmj.l67.

6. Genovese MC, Fleischmann R, Kivitz A, Lee EB, Hoogstraten HV, Kimura T, et al. Efficacy and safety of sarilumab in combination with csDMARDs or as monotherapy in subpopulations of patients with moderately to severely active rheumatoid arthritis

in three phase III randomized, controlled studies. *Arthritis Res Ther*. 2020;22:139. doi: 10.1186/s13075-020-02194-z.

7. Dantes E, Tofolean DE, Fildan AP, Craciun L, Dumea E, Tofolean I, et al. Lethal disseminated tuberculosis in patients under biological treatment - Two clinical cases and a short review. *J Int Med Res*. 2018;46:2961-2969. doi: 10.1177/0300060518771273.

8. Papadopoulos CG, Gartzonikas IK, Pappa TK, Markatseli TE, Migkos MP, Voulgari PV, et al. Eight-year survival study of first-line tumour necrosis factor alpha inhibitors in rheumatoid arthritis: Real-world data from a university centre registry. *Rheumatol Adv Pract*. 2019;3:rkz007. doi: 10.1093/rap/rkz007.

9. Bongartz T, Sutton AJ, Sweeting MJ. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA*. 2006;295:2275-2285. doi: 10.1001/jama.295.19.2275.

10. Maneiro JR, Souto A, Gomez-Reino JJ. Risks of malignancies related to tofacitinib and biological drugs in rheumatoid arthritis: Systematic review, meta-analysis, and network meta-analysis. *Semin Arthritis Rheum*. 2017;47:149-156. doi: 10.1016/j.semarthrit.2017.02.007.

11. Machado MA, Moura CS, Ferré F, Bernatsky S, Rahme E, Acurcio Fde A. Treatment persistence in patients with rheumatoid arthritis and ankylosing spondylitis. *Rev Saude Publica*. 2016;50:50. doi: 10.1590/S1518-8787.2016050006265.

12. Yokoyama S, Ishii Y, Masuda J. Persistence and safety of golimumab in elderly patients with rheumatoid arthritis and renal dysfunction in a real-world setting. *Drugs Real World Outcomes*. 2023;10(1):51-60. doi: 10.1007/s40801-022-00338-y.

13. Atreya R, Neurath MF. IL-23 blockade in anti-TNF refractory IBD: From mechanisms to clinical reality. *J Crohns Colitis*. 2022;16(Suppl. 2):ii54-ii63. doi: 10.1093/ecco-jcc/jjac007.

14. Michielsens CAJ, Boers N, den Broeder N, Wenink MH, van der Maas A, Mahler EAM, et al. Dose reduction and withdrawal strategy for TNF-inhibitors in psoriatic arthritis and axial spondyloarthritis: design of a pragmatic open-label, randomized, non-inferiority trial. *Trials*. 2020;21(1):90. doi: 10.1186/s13063-019-4000-5.

15. Evangelatos G, Bamias G, Kitas GD, Kollias G, Sfikakis PP. The second decade of anti-TNF-alpha therapy in clinical practice: new lessons and future directions in the COVID-19 era. *Rheumatol Int*. 2022;42(9):1493-1511. doi: 10.1007/s00296-022-05136-x.

16. Brankov N, Jacob SE. Adalimumab. *J Dermatol Nurses Assoc*. 2016;8(3):216-220. doi: 10.1097/JDN.0000000000000229.

17. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003;48(1):35-45. doi.: 10.1002/art.10697.

18. Pouw MF, Krieckaert CL, Nurmohamed MT, van der Kleij D, Aarden L, Rispens T, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis*. 2015;74(3):513-518. doi: 10.1136/annrheumdis-2013-204172.

19. Cacciapaglia F, Venerito V, Stano S, Fornaro M, Lopalco G, Iannone F. Comparison of adalimumab to other targeted therapies in rheumatoid arthritis: Results from systematic literature review and meta-analysis. *J Pers Med*. 2022;12(3):353. doi: 10.3390/jpm12030353.

20. Fleischmann R, Mysler E, Bessette L, Peterfy CG, Durez P, Tanaka Y, et al. Long-term safety and efficacy of upadacitinib or adalimumab in patients with rheumatoid arthritis: results through 3 years from the SELECT-COMPARE study. *RMD Open*. 2022;8(1):e002012. doi: 10.1136/rmdopen-2021-002012.

21. Kievit W, Fransen J, Adang EM, den Broeder AA, Bernelot Moens HJ, Visser H, et al. Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. *Rheumatology (Oxford)*. 2011;50(1):196-203. doi: 10.1093/rheumatology/keq325.

22. Rubbert-Roth A, Finckh A. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Res Ther*. 2009;11(Suppl 1):S1. doi: 10.1186/ar2666.

23. van Schouwenburg PA, van de Stadt LA, de Jong RN, van Buren EE, Kruithof S, de Groot E, et al. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. Ann Rheum Dis. 2013;72(1):104-109. doi: 10.1136/annrheumdis-2012-201445.

24. Catrina AI, af Klint E, Ernestam S, Catrina SB, Makrygiannakis D, Botusan IR, et al. Anti-tumor necrosis factor therapy increases synovial osteoprotegerin expression in rheumatoid arthritis. *Arthritis Rheum*. 2006;54(1):76-81. doi: 10.1002/art.21528.

25. Fletcher A, Lassere M, March L, Hill C, Barrett C, Carroll G, et al. Patterns of biologic and targeted-synthetic disease-modifying antirheumatic drug use in rheumatoid arthritis in Australia. *Rheumatology (Oxford)*. 2022;61(10):3939-3951. doi: 10.1093/rheumatology/keac048.

26. Blüml S, Scheinecker C, Smolen JS, Redlich K. Targeting TNF receptors in rheumatoid arthritis. *Int. Immunol*. 2012;24:275-281. doi: 10.1093/intimm/dxs047.

27. Chen Y, Yuan J, Cai Z, Ma Y. Efficacy of tumor necrosis factor inhibitor combined with intra-articular injection of triamcinolone acetonide in the treatment of refractory rheumatoid arthritis synovitis: a retrospective study. *Clin Rheumatol*. 2023. doi: 10.1007/s10067-023-06530-x.

28. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(5):625-639. doi: 10.1002/acr.21641.

29. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014;73(3):492-509. doi: 10.1136/annrheumdis-2013-204573.

30. Keystone EC, Breedveld FC, van der Heijde D, Landewé R, Florentinus S, Arulmani U, et al. Long-term effect of delaying combination therapy with tumor necrosis factor inhibitor in patients with aggressive early rheumatoid arthritis: 10-year efficacy and safety of adalimumab from the randomized controlled PREMIER trial with open-label extension. *J Rheumatol*. 2014;41(1):5-14. doi: 10.3899/jrheum.130543.

31. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid

arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther*. 2003;25(6):1700-1721. doi: 10.1016/s0149-2918(03)80164-9.

32. Navarro-Millán I, Herrinton LJ, Chen L, Harrold L, Liu L, Curtis JR. Comparative effectiveness of etanercept and adalimumab in patient reported outcomes and injection-related tolerability. *PLoS One*. 2016;11(3):e0149781. doi: 10.1371/journal.pone.0149781.

33. Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Annals of the rheumatic diseases. 2006;65(6):753-759. doi: 10.1136/ard.2005.044404.

34. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis*. 2007;66(7):921-926. doi: 10.1136/ard.2006.065615.

35. Emery P. Optimizing outcomes in patients with rheumatoid arthritis and an inadequate response to anti-TNF treatment. *Rheumatology (Oxford)*. 2012;51(Suppl 5):v22-30. doi: 10.1093/rheumatology/kes115.

36. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of 7740 patients. *Mod Rheumatol*. 2014;24(3):390-398. doi: 10.3109/14397595.2013.843760.

37. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. *Mod Rheumatol*. 2012;22(4):498-508. doi: 10.1007/s10165-011-0541-5.

38. Chen DY, Chen YM, Tsai WC, Tseng JC, Chen YH, Hsieh CW, et al. Significant associations of antidrug antibody levels with serum drug trough levels and therapeutic response of adalimumab and etanercept treatment in rheumatoid arthritis. *Ann Rheum Dis*. 2015;74(3):e16. doi: 10.1136/annrheumdis-2013-203893.

39. Burmester GR, Matucci-Cerinic M, Mariette X, Navarro-Blasco F, Kary S, Unnebrink K, et al. Safety and effectiveness of adalimumab in patients with rheumatoid arthritis over 5 years of therapy in a phase 3b and subsequent postmarketing observational study. *Arthritis Res Ther*. 2014;16(1):R24. doi: 10.1186/ar4452.

40. Haraoui B, Cividino A, Stewart J, Guérette B, Keystone EC. Safety and effectiveness of adalimumab in a clinical setting that reflects Canadian standard of care for the treatment of rheumatoid arthritis (RA): results from the CanACT study. *BMC Musculoskelet Disord*. 2011;12:261. doi: 10.1186/1471-2474-12-261.

41. 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):3716-3725. doi: 10.1182/blood-2008-09-179754.

42. Flouri I, Markatseli TE, Voulgari PV, Boki KA, Papadopoulos I, Settas L, et al. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: Low rates of remission and 5-year drug survival. *Semin Arthritis Rheum*. 2014;43(4):447-457. doi: 10.1016/j.semarthrit.2013.07.011.

43. Wang Z, Huang J, Xie D, He D, Lu A, Liang C. Toward overcoming treatment failure in rheumatoid arthritis. *Front Immunol*. 2021;12:755844. doi: 10.3389/fimmu.2021.755844.

44. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. *Arthritis Res Ther*. 2016;18(1):272. doi: 10.1186/s13075-016-1170-3.

45. Huang JY, Leong PY, Ker A, Chen HH, Wei JC. The long-term persistence of tumor necrosis factor inhibitors in patients with moderate to severe immune-mediated rheumatic diseases: A nation-wide, population-based real-world study. *Int J Rheum Dis*. 2022;25(11):1295-1305. doi: 10.1111/1756-185X.14423.

46. Taylor PC, Matucci Cerinic M, Alten R, Avouac J, Westhovens R. Managing inadequate response to initial anti-TNF therapy in rheumatoid arthritis: optimizing treatment outcomes. *Ther Adv Musculoskelet Dis*. 2022;14:1759720X221114101. doi: 10.1177/1759720X221114101.

47. Fischer R, Kontermann RE, Pfizenmaier K. Selective targeting of TNF receptors as a novel therapeutic approach. *Front Cell Dev Biol*. 2020;8:401. doi: 10.3389/fcell.2020.00401.

48. Atiqi S, Hooijberg F, Loeff FC, Rispens T, Wolbink GJ. Immunogenicity of TNF-inhibitors. *Front Immunol*. 2020;11:312. doi: 10.3389/fimmu.2020.00312.

49. Jani M, Barton A, Warren RB, Griffiths CE, Chinoy H. The role of DMARDs in reducing the immunogenicity of TNF inhibitors in chronic inflammatory diseases. *Rheumatology (Oxford)*. 2014;53(2):213-222. doi: 10.1093/rheumatology/ket260.

50. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA*. 2011;305(14):1460-1468. doi: 10.1001/jama.2011.406.

51. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. *Ann Rheum Dis*. 2010;69(5):817-821. doi: 10.1136/ard.2009.112847.

52. Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann Rheum Dis*. 2012;71(11):1914-1915. doi: 10.1136/annrheumdis-2012-201544.

53. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med*. 2000;343(22):1594-1602. doi: 10.1056/NEJM200011303432202.

54. Ebell M, Kripke C. Adalimumab for rheumatoid arthritis? *Am Fam Physician*. 2006;73(3):435-436.

55. Yu J, Song Y, Tian W. How to select IgG subclasses in developing anti-tumor therapeutic antibodies. *J Hematol Oncol*. 2020;13(1):45. doi: 10.1186/s13045-020-00876-4.

56. Julià M, Guilabert A, Lozano F, Suarez-Casasús B, Moreno N, Carrascosa JM, et al. The role of Fcγ receptor polymorphisms in the response to anti–tumor necrosis factor therapy in psoriasis A pharmacogenetic study. *JAMA Dermatol*. 2013;149(9):1033-1039. doi: 10.1001/jamadermatol.2013.4632.

57. Lu J, Spencer M, Zou Z, Traver M, Brzostowski J, Sun PD. FcγRI FG-loop functions as a pH sensitive switch for IgG binding and release. *Front Immunol*. 2023;14:1100499. doi: 10.3389/fimmu.2023.1100499.

58. Morales-Lara MJ, Conesa-Zamora P, García-Simón MS, Pedrero F, Santaclara V, Perez-Guillermo M, et al. Association between the FCGR3A V158F polymorphism and the clinical response to infliximab in rheumatoid arthritis and spondyloarthritis patients. *Scand J Rheumatol*. 2010;39(6):518-520. doi: 10.3109/03009741003781969.

59. Jezernik G, Gorenjak M, Potočnik U. Gene ontology analysis highlights biological processes influencing non-response to anti-TNF therapy in rheumatoid arthritis. *Biomedicines*. 2022;10(8):1808. doi: 10.3390/biomedicines10081808.

60. Kim J, Lee JY, Kim HG, Kwak MW, Kang TH. Fc receptor variants and disease: A crucial factor to consider in the antibody therapeutics in clinic. *Int J Mol Sci*. 2021;22(17):9489. doi: 10.3390/ijms22179489.

61. Márquez Pete N, Maldonado Montoro MDM, Pérez Ramírez C, Martínez Martínez F, Martínez de la Plata JE, Daddaoua A, et al. Influence of the *FCGR2A* rs1801274 and *FCGR3A* rs396991 polymorphisms on response to abatacept in patients with rheumatoid arthritis. *J Pers Med*. 2021;11(6):573. doi: 10.3390/jpm11060573.

62. Li X, Kimberly RP. Targeting the Fc receptor in autoimmune disease. *Expert Opin Ther Targets*. 2014;18(3):335-350. doi: 10.1517/14728222.2014.877891.

63. Ravaei A, Pulsatelli L, Assirelli E, Ciaffi J, Meliconi R, Salvarani C, et al. *MTHFR* c.665C>T and c.1298A>C polymorphisms in tailoring personalized anti-TNF-α therapy for rheumatoid arthritis. *Int J Mol Sci*. 2023;24(4):4110. doi: 10.3390/ijms24044110.

64. Dávila-Fajardo CL, van der Straaten T, Baak-Pablo R, Medarde Caballero C, Cabeza Barrera J, Huizinga TW, et al. FcGR genetic polymorphisms and the response to adalimumab in patients with rheumatoid arthritis. *Pharmacogenomics*. 2015;16(4):373-381. doi: 10.2217/pgs.14.178.

65. Montes A, Perez-Pampin E, Narváez J, Cañete JD, Navarro-Sarabia F, Moreira V, et al. Association of FCGR2A with the response to infliximab treatment of patients with rheumatoid arthritis. *Pharmacogenet Genomics*. 2014;24(5):238-245. doi: 10.1097/FPC.0000000000000042.

66. Tutuncu Z, Kavanaugh A, Zvaifler N, Corr M, Deutsch R, Boyle D. Fcgamma receptor type IIIA polymorphisms influence treatment outcomes in patients with inflammatory arthritis treated with tumor necrosis factor alpha-blocking agents. *Arthritis Rheum*. 2005;52(9):2693-2696. doi: 10.1002/art.21266.

67. Smiljanovic B, Grün JR, Biesen R, Schulte-Wrede U, Baumgrass R, Stuhlmüller B, et al. The multifaceted balance of TNF-α and type I/II interferon responses in SLE and RA: how monocytes manage the impact of cytokines. *J Mol Med (Berl)*. 2012;90(11):1295-1309. doi: 10.1007/s00109-012-0907-y.

68. Stuhlmüller B, Häupl T, Hernandez MM, Grützkau A, Kuban RJ, Tandon N, et al. CD11c as a transcriptional biomarker to predict response to anti-TNF monotherapy with adalimumab in patients with rheumatoid arthritis. *Clin Pharmacol Ther*. 2010;87(3):311-321. doi: 10.1038/clpt.2009.244.

69. Yoon BR, Yoo SJ, Choi Yh, Chung YH, Kim J, Yoo IS, Kang SW, et al. Functional phenotype of synovial monocytes modulating inflammatory T-cell responses in rheumatoid arthritis (RA). *PLoS One*. 2014;9(10):e109775. doi: 10.1371/journal.pone.0109775.

70. Sugimoto C, Hasegawa A, Saito Y, Fukuyo Y, Chiu KB, Cai Y, Breed MW, et al. Differentiation kinetics of blood monocytes and dendritic cells in Macaques: Insights to understanding human myeloid cell development. *J Immunol*. 2015;195(4):1774-1781. doi: 10.4049/jimmunol.1500522.

71. Loke P, Niewold TB. By CyTOF: Heterogeneity of human monocytes. *Arterioscler Thromb Vasc Biol*. 2017;37(8):1423-1424. doi: 10.1161/ATVBAHA.117.309645.

72. Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*. 2014;506(7488):376-381. doi: 10.1038/nature12873.

73. Kallberg H, Padyukov L, Plenge RM, Ronnelid J, Gregersen PK, van der Helm-van Mil AH, et al. Gene-gene and gene-environment interactions involving HLA-DRB1, PTPN22, and smoking in two subsets of rheumatoid arthritis. *Am J Hum Genet*. 2007;80(5):867-875. doi: 10.1086/516736.

74. Kyogoku C, Langefeld CD, Ortmann WA, Lee A, Selby S, Carlton VE, et al. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *Am J Hum Genet*. 2004;75(3):504-507. doi: 10.1086/423790.

75. Abbasifard M, Imani D, Bagheri-Hosseinabadi Z. PTPN22 gene polymorphism and susceptibility to rheumatoid arthritis (RA): Updated systematic review and meta-analysis. *J Gene Med*. 2020;22(9):e3204. doi: 10.1002/jgm.3204.

76. Diaz-Gallo LM, Martin J. *PTPN22* splice forms: a new role in rheumatoid arthritis. *Genome Med*. 2012;4:13. doi: 10.1186/gm312.

77. Tizaoui K, Terrazzino S, Cargnin S, Lee KH, Gauckler P, Li H, et al. The role of PTPN22 in the pathogenesis of autoimmune diseases: A comprehensive review. *Semin Arthritis Rheum*. 2021;51(3):513-522. doi: 10.1016/j.semarthrit.2021.03.004.

78. Potter C, Hyrich KL, Tracey A, Lunt M, Plant D, Symmons DP, et al. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. *Ann Rheum Dis*. 2009;68(1):69-74. doi: 10.1136/ard.2007.084715.

79. Gao S, Liang W, Xu T, Xun C, Cao R, Deng Q, et al. Associations of tumor necrosis factor alpha gene polymorphisms and ankylosing spondylitis susceptibility: A meta-analysis based on 35 case-control studies. *Immunological Invest*. 2021;51(4):859-882. doi: 10.1080/08820139.2021.1882485.

80. Bergman MJ, Kivitz AJ, Pappas DA, Kremer JM, Zhang L, Jeter A, et al. Clinical utility and cost savings in predicting inadequate response to anti-TNF therapies in rheumatoid arthritis. *Rheumatol Ther*. 2020;7(4):775-792. doi: 10.1007/s40744-020-00226-3.

81. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Curr Dir Autoimmun*. 2010;11:180-210. doi: 10.1159/000289205.

82. Strand V, Kimberly R, Isaacs JD. Biologic therapies in rheumatology: lessons learned, future directions. *Nat Rev Drug Discov*. 2007;6(1):75-92. doi: 10.1038/nrd2196.

83. Lim SH, Kim K, Choi CI. Pharmacogenomics of monoclonal antibodies for the treatment of rheumatoid arthritis. *J Pers Med*. 2022;12(8):1265. doi: 10.3390/jpm12081265.

84. Miler M, Nikolac Gabaj N, Ćelap I, Grazio S, Tomašić V, Bišćanin A, et al. Association of polymorphisms in promoter region of TNF-α -238 and -308 with clinical outcomes in patients

with immune-mediated inflammatory diseases on anti-TNF therapy. *Rheumatol Int*. 2021;41(12):2195-2203. doi: 10.1007/s00296-021-05016-w.

85. Hadinedoushan H, Noorbakhsh P, Soleymani-Salehabadi H. Tumor necrosis factor alpha gene polymorphism and association with its serum level in Iranian population with rheumatoid arthritis. *Arch Rheumatol*. 2016;31(4):306-313. doi: 10.5606/ArchRheumatol.2016.5907.

86. Membrive Jiménez C, Pérez Ramírez C, Sánchez Martín A, Vieira Maroun S, Arias Santiago S, Ramírez Tortosa MC, et al. Clinical application of pharmacogenetic markers in the treatment of dermatologic pathologies. *Pharmaceuticals (Basel)*. 2021;14(9):905. doi: 10.3390/ph14090905.

87. Cuchacovich M, Soto L, Edwardes M, Gutierrez M, Llanos C, Pacheco D, et al. Tumour necrosis factor (TNF)alpha -308 G/G promoter polymorphism and TNFalpha levels correlate with a better response to adalimumab in patients with rheumatoid arthritis. *Scand J Rheumatol*. 2006;35(6):435-440. doi: 10.1080/03009740600904284.

88. Seitz M, Wirthmüller U, Möller B, Villiger PM. The -308 tumour necrosis factor-alpha gene polymorphism predicts therapeutic response to TNFalpha-blockers in rheumatoid arthritis and spondyloarthritis patients. *Rheumatology (Oxford)*. 2007;46(1):93-96. doi: 10.1093/rheumatology/kel175.

89. O'Rielly DD, Roslin NM, Beyene J, Pope A, Rahman P. TNF-alpha-308 G/A polymorphism and responsiveness to TNF-alpha blockade therapy in moderate to severe rheumatoid arthritis: a systematic review and meta-analysis. *Pharmacogenomics J*. 2009;9(3):161-167. doi: 10.1038/tpj.2009.7.

90. Saddala MS, Huang H. Identification of novel inhibitors for TNFα, TNFR1 and TNFα-TNFR1 complex using pharmacophore-based approaches. *J Transl Med*. 2019;17(1):215. doi: 10.1186/s12967-019-1965-5.

91. Chen W, Xu H, Wang X, Gu J, Xiong H, Shi Y. The tumor necrosis factor receptor superfamily member 1B polymorphisms predict response to anti-TNF therapy in patients with autoimmune disease: A meta-analysis. *Int Immunopharmacol*. 2015;28(1):146-153. doi: 10.1016/j.intimp.2015.05.049.

92. Prieto-Pérez R, Cabaleiro T, Daudén E, Abad-Santos F. Gene polymorphisms that can predict response to anti-TNF therapy in patients with psoriasis and related autoimmune diseases. *Pharmacogenomics J*. 2013;13(4):297-305. doi: 10.1038/tpj.2012.53.

93. Ruiz A, Palacios Y, Garcia I, Chavez-Galan L. Transmembrane TNF and its receptors TNFR1 and TNFR2 in mycobacterial infections. *Int J Mol Sci*. 2021;22(11):5461. doi: 10.3390/ijms22115461.

94. El-Tahan RR, Ghoneim AM, El-Mashad N. TNF-α gene polymorphisms and expression. *Springerplus*. 2016;5(1):1508. doi: 10.1186/s40064-016-3197-y.

95. Ongaro A, De Mattei M, Pellati A, Caruso A, Ferretti S, Masieri FF, et al. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading to anti-TNFalpha therapy in rheumatoid arthritis? *Rheumatol Int*. 2008;28(9):901-908. doi: 10.1007/s00296-008-0552-5.

96. Canault M, Leroyer AS, Peiretti F, Lesèche G, Tedgui A, Bonardo B, et al. Microparticles of human atherosclerotic plaques enhance the shedding of the tumor necrosis factor-alpha converting enzyme/ADAM17 substrates, tumor necrosis factor and tumor necrosis factor receptor-1. *Am J Pathol*. 2007;171(5):1713-1723. doi: 10.2353/ajpath.2007.070021.

97. Sethi JK, Hotamisligil GS. Metabolic messengers: tumour necrosis factor. *Nat Metab*. 2021;3(10):1302-1312. doi: 10.1038/s42255-021-00470-z.

98. Ben-Baruch A. Tumor necrosis factor α: Taking a personalized road in cancer therapy. *Front Immunol*. 2022;13:903679. doi: 10.3389/fimmu.2022.903679.

99. Steeland S, Libert C, Vandenbroucke RE. A new venue of TNF targeting. *Int J Mol Sci*. 2018;19(5):1442. doi: 10.3390/ijms19051442.

100. Pojskic L, Gavrankapetanovic I, Lojo-Kadric N, Hadziselimovic R, Bajrovic K. A genotyping assay for missense mutation in WISP3 gene associated with childhood onset pseudorheumatoid arthropathy. *J Health Sci*. 2015;5(2):59-64. doi: 10.17532/jhsci.2015.241.

101. Curtis JR, Hobar C, Hansbrough K. Injection-site burning and stinging in patients with rheumatoid arthritis using injectable biologics. *Curr Med Res Opin*. 2011;27(1):71-78. doi: 10.1185/03007995.2010.534959.

102. Miceli-Richard C, Comets E, Verstuyft C, Tamouza R, Loiseau P, Ravaud P, et al. A single tumour necrosis factor haplotype influences the response to adalimumab in rheumatoid arthritis. *Ann Rheum Dis*. 2008;67(4):478-484. doi: 10.1136/ard.2007.074104.

103. Canhão H, Rodrigues AM, Santos MJ, Carmona-Fernandes D, Bettencourt BF, Cui J, et al. TRAF1/C5 but not PTPRC variants are potential predictors of rheumatoid arthritis response to anti-tumor necrosis factor therapy. *Biomed Res Int*. 2015;2015:490295. doi: 10.1155/2015/490295.

104. Ochi S, Saito K, Mizoguchi F, Kato S, Tanaka Y. Insensitivity versus poor response to tumour necrosis factor inhibitors in rheumatoid arthritis: a retrospective cohort study. *Arthritis Res Ther*. 2020;22(1):41. doi: 10.1186/s13075-020-2122-5.

105. Potter C, Cordell HJ, Barton A, Daly AK, Hyrich KL, Mann DA, et al. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signaling pathways. *Ann Rheum Dis*. 2010;69(7):1315-1320. doi: 10.1136/ard.2009.117309.

106. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human antitumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol*. 2003;30(12):2563-2571.

107. Popescu CC, Mogoșan CD, Enache L, Codreanu C. Comparison of efficacy and safety of original and biosimilar adalimumab in active rheumatoid arthritis in a real-world national cohort. *Medicina (Kaunas)*. 2022;58(12):1851. doi: 10.3390/medicina58121851.

108. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol*. 2007;34(5):1040-1050.