MERAL Publications and Solutions Pvt. Ltd.

Original Article

Impact of interleukin-10 gene polymorphisms on etanercept treatment response in Iraqi rheumatoid arthritis patients

Dhulfiqar Nidhal Alhilali[1]*, Samer Imad Mohammed[1], Faiq Isho Gorial[2]

[1]Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq. [2]College of Medicine, University of Baghdad, Baghdad, Iraq.

Correspondence: Dhulfiqar Nidhal Alhilali, Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq. thulfekarnkazam@copharm.uobaghdad.edu.iq

Received: 25 May 2025; **Revised:** 14 August2025; **Accepted:** 15 August 2025

ABSTRACT

The goal of the current study was to determine if interleukin-10 (IL-10) promoter polymorphisms may predict how well Iraqi patients with rheumatoid arthritis (RA) will respond to etanercept (ETN). The trial was conducted at the Baghdad Teaching Hospital's rheumatology unit in Medical City, Baghdad, Iraq. Three IL-10 promoter single-nucleotide polymorphisms (SNPs) were genotyped for a cohort of ninety RA patients: rs1800871 (-824), rs1800872 (-597), and rs1800896 (-1082). The patients were clinically evaluated for ETN response at baseline, three, and six months after ETN therapy. Based on the Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR). The results demonstrated that the mutant G allele of rs1800896 was significantly more frequent among responders (45.2%) compared to non-responders (25.0%) (OR=0.40, 95% CI 0.21–0.77, p=0.0055). Binary logistic regression further confirmed the G allele's strong association with a positive outcome (OR=0.217, p=0.001). Additionally, patients with the AG genotype exhibited a significantly greater improvement in DAS28-ESR than others after six months (p=0.009). In conclusion, the IL-10 rs1800896 G allele is a promising predictive biomarker for a favorable response to ETN therapy in Iraqi RA patients.

Keywords: Pharmacogenetics, Polymorphism, IL-10, Etanercept, Anti-TNF, Rheumatoid arthritis

Introduction

One of the chronic heterogeneous inflammatory autoimmune diseases, rheumatoid arthritis, is characterised by persistent synovitis, which is accompanied by stiffness, pain, swelling, and destruction of the joints. It significantly impairs the wrists as well as the proximal interphalangeal and metacarpophalangeal joints [1]. The prevalence is higher among women and older adults, and the occurrence of comorbidities correlates with higher disease activity scores [2-4]. The American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) criteria developed a scoring system to ensure accurate diagnosis and remission evaluation in RA [5]. Tumor necrosis factor (TNF) inhibitors, including ETN, are part of biologic disease-modifying antirheumatic drugs (bDMARDs), are widely used for RA management [4]. Etanercept is a soluble TNF receptor fusion protein that binds TNF-α and lymphotoxin, thereby diminishing the inflammatory responses [6, 7].

ETN has shown significant effectiveness in decreasing disease activity (DAS28-ESR) and enhancing clinical outcomes in RA patients [8]; yet, 30-40% of RA patients exhibit insufficient response and are classified as non-responders [9, 10].

The cytokine network plays a pivotal role in RA development and pathogenesis, where an imbalance between pro-inflammatory and anti-inflammatory mediators drives the disease process. Interleukin-10 is an essential immunoregulatory cytokine with double and often paradoxical functions in RA; it exerts an anti-inflammatory effect by suppressing pro-inflammatory cytokines synthesis like TNF-α and downregulating antigen-presenting cell function [11, 12].

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Alhilali DN, Mohammed SI, Gorial FI. Impact of interleukin-10 gene polymorphisms on etanercept treatment response in Iraqi rheumatoid arthritis patients. J Adv Pharm Educ Res. 2025;15(3):185-97. https://doi.org/10.51847/NU4a2X2vh4

Despite the presence of IL-10 in the rheumatoid synovium, its levels are often insufficient to counteract the overwhelming inflammatory response, and its deficiency is associated with exacerbated bone and cartilage damage in experimental models [13, 14]. Clinically, low serum levels of IL-10 have been frequently documented in RA patients in comparison to healthy controls [15, 16]. A recent study revealed that a higher blood IL-10 level was markedly related to a predicted greater clinical response and improvements in DAS28-CRP for RA patients treated with biological therapy [17].

Numerous studies have investigated the association between genetic polymorphisms of TNF-α and interleukins such as IL-6, IL-4, and IL-10, and RA susceptibility and therapeutic response to anti-TNF agents [13, 18-21]. Particular attention has focused on three promoter region polymorphisms (-1082A>G, -592C>A, and -819C>T), which appear to modulate IL-10 expression, influence RA susceptibility [13, 22], and also act as a clinical response predictor of RA patients to ETN [23]. Additionally, the IL-10 polymorphisms were also implicated in the susceptibility to type 2 diabetes mellitus and toxoplasmosis [24].

While the immunoregulatory cytokine IL-10 is known to inhibit TNF-α and its genetic polymorphisms influence RA susceptibility and IL-10 production, the specific role of these polymorphisms in determining ETN treatment outcomes remains inadequately investigated and poorly defined [23, 25], and the data regarding this aspect is scanty; therefore, the present study aimed to investigate the association between IL-10 gene promoter polymorphisms and potential influence on the clinical response to ETN therapy in Iraqi patients with RA.

Materials and Methods

Study population and design

A cohort (n=90) of RA patients (82 females and eight males, mean age 51.34 ± 10.51 years) was recruited from the Rheumatology unit at Baghdad Teaching Hospital in Medical City, Baghdad, Iraq. The study extended from March 2024 to March 2025. All patients were diagnosed depending on the RA-ACR/EULAR classification criteria (2010). The study was approved by the ethical committee of the College of Pharmacy, University of Baghdad, registration number (RECAUBCP123202406150H). Following treatment with ETN (Altebrel®; AryoGen Pharmed, Iran), study participants were categorized as either responders or non-responders based on ACR/EULAR criteria (2010).

Inclusion criteria

All RA patients were Iraqi adults (over 18 years), the severity of RA ranged from moderate to severe active RA (DAS28-ESR > 3.2), who had been receiving a consistent regimen of 50 mg of ETN weekly for at least six months.

Exclusion criteria

Patients who lost follow-up or were unable to comply with the study duration, Patients with missed doses (by measuring adherence through the medication possession ratio (MPR) of 85%), and patients with missing data.

Treatment protocol and response assessment

Altebrel® was administered subcutaneously to the RA patient (50 mg/mL) weekly for six months. Treatment response was measured at different stages, including baseline, three, and six months post-induction of treatment.

Depending on the response criteria of EULAR, patients were subdivided into two groups: Responders: Patients who achieved a reduction in DAS28 to < 5.1 with a change (ΔDAS28) of ≥ 0.6. The non-responders were defined as patients who failed to achieve the above criteria (DAS28 remained ≥ 5.1 with ΔDAS28 < 0.6).

Sample collection

Peripheral blood samples (10 mL) were collected from each patient; 6 mL was used for CBC and ESR assessments, and the other 4 mL was collected in K3 EDTA tubes for DNA extraction.

Laboratory analyses

Genotyping of IL-6 promoter polymorphisms

G-spin™ Total DNA Extraction Kit (Promega/USA) was used for genomic DNA extraction according to the manufacturer's protocol. The target promoter region was amplified by PCR (Thermal Cycler, BioRad, USA) using four specific primers, which were designed by the primer BLAST option in NCBI. The 20 µL PCR reaction mixture contained 1 µL of each primer (10 pmol/µL), 2 µL of DNA template, 10 µL of PCR Master Mix, and 6 µL of nuclease-free water. The primers used were:

IL10-F1: CAGGGAGGATGAGTGATTTG
IL10-R1: GTGTTCCAGGCTCCTTTAC
IL10-F2: GCCTCAGTTTGCTCACTATAA
IL10-R2 GTAGACCTTCACCTCTCTGT

The PCR cycling reaction conditions were used according to Abbas *et al*. (2023) [26]. The amplicons were visualized on a 2% agarose gel. Subsequently, PCR products were sent for Sanger sequencing (Macrogen, Korea) for definitive genotype identification.

Measurement of erythrocyte sedimentation rate (ESR)

ESR was determined using the modified Westergren method.

Statistical analysis

Genotype and allele frequencies will be compared between responders and non-responders using chi-square (χ^2) or Fisher's exact tests. Mean ± standard deviation was compared using a t-test and LSD depending on data distribution. The association between genotypes and treatment response was evaluated using logistic regression, adjusted for potential confounding variables. Paired t-tests and Welch's t-test for unequal variances were used to analyze the differences within and between groups, respectively, at different time points. Hardy–Weinberg expectations were used to ensure the random distribution of. The 95 % confidence intervals (CI) and odds ratios (OR) were utilized to calculate the minor allele. Welch's ANOVA (or Welch t-test for two-group comparisons) was used; otherwise, one-way ANOVA was also applied.

Results and Discussion

PCR amplification of the il-10 gene promoter region

Amplification of the promoter regions for IL-10 via PCR yielded specific and distinct amplicons corresponding to the expected sizes for each primer set. The first IL-10 primer pair (IL-10 Fragment 1) resulted in an 818-base pair (bp) product, and the second pair (IL-10 Fragment 2) generated a slightly smaller amplicon of 788 bp **(Figures 1, 2)**.

The genetic analysis of the amplified promoter sequences in RA revealed a total of three SNPs. The IL-10 gene harbored three variants: rs1800871 (-824C>T), rs1800872 (-597C>A), and rs1800896 (-1082A>G) **(Figure 3)**.

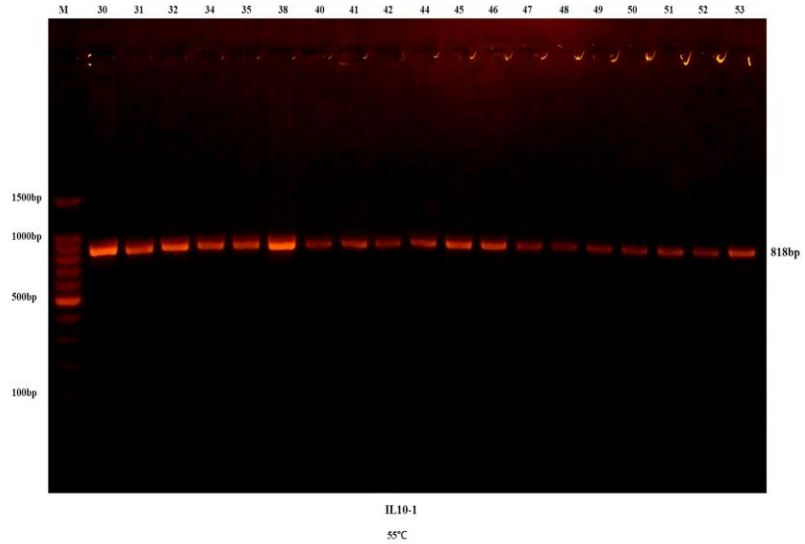


Figure 1. Electrophoretic analysis of the amplified IL-10 region was performed using a 1.5% agarose gel impregnated with ethidium bromide. A first amplicon fragment of 989 bp, corresponding to the target sequence, was successfully amplified and visualized in lanes 30 through 53.

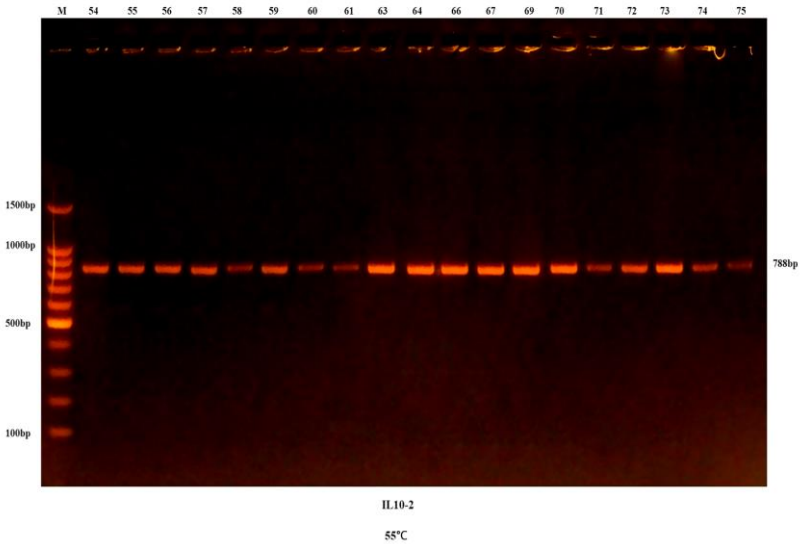


Figure 2. Electrophoretic analysis of the amplified IL-10 region was performed using a 1.5% agarose gel impregnated with ethidium bromide. A second amplicon fragment of 788 bp, corresponding to the target sequence, was successfully amplified and visualized in lanes 54 through 75.

Distribution of IL-10 genotype polymorphisms in the patient cohort

Three IL-10 promoter variants (rs1800871, rs1800872, and rs1800896) were identified in the full cohort of RA patients (n = 90), revealing clear patterns in their genotypic and allelic distribution. All analyzed loci conformed to Hardy–Weinberg equilibrium (HWE) ($p>0.05$), confirming the genetic stability and representativeness of the study population and the absence of selection bias within the sampled cohort [27]. The primary findings indicate that all three variants are located within the promoter/5′ flanking region of the IL-10 gene with a consistent pattern of major allele predominance across all three IL-10 loci.

For IL-10 rs1800871 (C>T), both CC and CT genotypes occurred at equal frequencies (42% each), while TT was less common (16%). The C allele thus constituted 63%, compared with 37% for T. In IL-10 rs1800872 (C>A), the CC genotype appeared in 47% of individuals, CA in 40%, and AA in 13%, giving a C-allele frequency of 67% and an A-allele frequency of 33%. Finally, for IL-10 rs1800896 (A>G), AG heterozygotes were the most prevalent (47%), followed by AA (40%) and GG (13%), corresponding to allele frequencies of 63% (A) and 37% (G).

This study has established the prevalence and equilibrium status of three IL-10 promoter polymorphisms (rs1800871, rs1800872, and rs1800896) in a well-characterized RA cohort. These variants have been widely studied, with multiple articles reporting an association between these variants and altered IL-10 expression patterns and RA susceptibility. Evidence from Chinese and East Asian populations reports an association of rs1800872 and rs1800871 with RA susceptibility, a finding postulated to be linked to lower IL-10 expression [22, 28]. A study by Hassanzadeh *et al.* [29] in a southwestern Iranian population identified the rs1800872 SNP as a significant susceptibility marker for RA. In contrast. However, findings from Iraq show no significant association between these variants and RA susceptibility in Iraqi Arab women [30], suggesting a population-specific pattern effect.

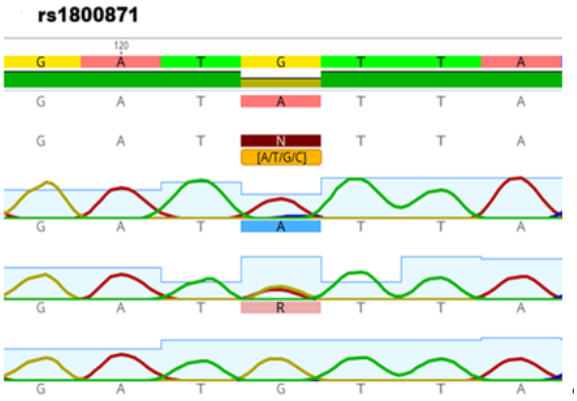
For IL-10 rs1800896, a recent meta-analysis by Stephen *et al.* [31] demonstrated a significant linkage between RA susceptibility and rs1800896 polymorphism driven by the G allele and the dominant genotypes model (GG and AG). Much evidence supported this genetic influence; Tayel *et al.* [32] directly correlated the -1082A allele and AA genotype with low IL-10 production. Earlier work by Hee *et al.* [33] in a Malaysian cohort demonstrated a significant association between the -1082 A>G and -824 C>T polymorphisms and increased RA susceptibility, linking specific genotypes to significantly lower IL-10 production. Similarly, studies in European populations, such as those by Pawlik *et al.* [34] and Paradowska-Gorycka *et al.* [35] in Poland, reported a higher correlation between the -1082 polymorphism and RA patients, suggesting a disease-predisposing role. While Yucel *et al.* [36] reported a possible protective role for the -1082 AA genotype against RA in the Turkish population.

IL-10 is a pivotal immunoregulatory cytokine with potent anti-inflammatory features; genetic variations that subtly influence its production could have profound implications for the chronic inflammatory processes that characterize RA [37, 38]. For instance, the -1082A/G (rs1800896) SNP has been extensively studied in various immune-mediated diseases, with certain alleles correlating with altered IL-10 production [39, 40]. Therefore, the variants identified here are strong candidates for functional studies to elucidate their precise impact on IL-10 expression in the context of RA.

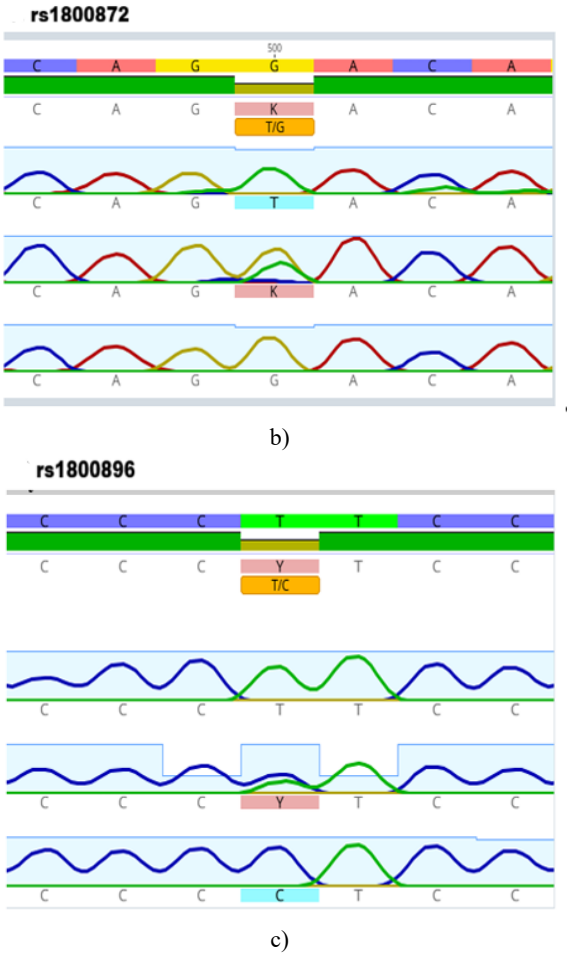
Changes in clinical and laboratory parameters after ETN treatment

Before treatment, no significant differences were detected between responders and non-responders in terms of disease activity indices, including Clinical Disease Activity Index (CDAI) and DAS28-ESR, or laboratory and clinical measures such as swollen joint count (SJ) and ESR, confirming pre-treatment comparability. Only tender joint counts (TJ) in non-responders were significantly higher than in responders ($P = 0.007$).

After 3 months, responders showed a statistically significant reduction in SJ and TJ, ESR, CDAI, or DAS28-ESR along with patient and physician assessments, including Assessment of Patient Global Disease Activity (PtGA) and Provider Global Assessment of Disease Activity (PrGA) (all $P<0.001$), while non-responders showed no or slight improvement.



a)



b)

c)

Figure 3. Genotyping of the IL10 rs1800871, rs1800872, and rs1800896 polymorphisms was performed via Sanger sequencing. Chromatogram analysis revealed wild homozygous genotypes characterized by a singular nucleotide peak in A, B, and C, while mutant heterozygous genotypes were identified by the concurrent presence of both peaks at the relevant position. Additionally, the mutant homozygous genotypes are also present in samples.

Improvement among responders persisted and deepened at 6 months, with the mean ΔDAS28-ESR decreasing from 5.16 ± 0.80 to 3.43 ± 0.76 (P<0.001), while non-responders showed stable or higher disease activity scores (5.14 ± 1.04).

At three and six months, there was a significant difference between the groups (P<0.001), indicating a distinct difference in clinical response patterns. Additionally, responders had a substantially higher mean ΔDAS28-ESR drop (1.73 ± 0.83 vs. -0.35 ± 0.65, P < 0.001).

These findings align with multiple studies like Nizar *et al.* [41, 42] and Aghdashi *et al.* [43], who reported that ESR, TJC, and DAS28 decreased significantly in RA patients several months post ETN induction. Matucci-Cerinic *et al.* [44] demonstrated that significant rates of good and moderate EULAR response were observed at six months post-treatment. Su *et al.* [45] Demonstrating significant improvement in all measured disease activity indices with durable remission.

On the other hand, after receiving ETN treatment, the non-responder group showed either a statistically significant deterioration in clinical measures or very little improvement. Reduced ETN levels [43, 46], genetic variability, increased inflammatory burden, and metabolic or concomitant disorders are some of the reasons why many RA patients did not respond to these medications as anticipated, and remission frequency is still less than 50% in RA patients [47].

Comparative baseline profiles and IL-10 genotype distributions between responders and non-responders

Table 1. Comparison of IL-10 genotypes and allele distributions between responders and non-responders after etanercept therapy.

SNP	Genotypes	Responders n=52 (%)	Non-Responders n=38 (%)	P-Value	OR (95% CI)
IL-10: rs1800871 C>T	CC	22 (42.3%)	16 (42.1%)	0.9986	1.01 (0.55–1.87)
	CT	22 (42.3%)	16 (42.1%)		
	TT	8 (15.4%)	6 (15.8%)		
	C	66 (63.5%)	48 (63.2%)	1	
	T	38 (36.5%)	28 (36.8%)		
IL-10: rs1800872 C>A	CC	24 (46.2%)	18 (47.4%)	0.7912	0.87 (0.46–1.64)
	CA	20 (38.5%)	16 (42.1%)		
	AA	8 (15.4%)	4 (10.5%)		
	C	68 (65.4%)	52 (68.4%)	0.67	
	A	36 (34.6%)	24 (31.6%)		
IL-10: rs1800896 A>G	AA	13 (25.0%)	23 (60.5%)	**0.0028****	0.40 (0.21–0.77)
	AG	31 (59.6%)	11 (28.9%)		
	GG	8 (15.4%)	4 (10.5%)		
	A	57 (54.8%)	57 (75.0%)	**0.0055****	
	G	47 (45.2%)	19 (25.0%)		

Chi-square test was applied for 2 × 3 genotype comparisons, whereas Fisher's exact test was used for 2 × 2 allele comparisons or whenever any expected cell count was < 5. When OR > 1 indicates increased odds of non-response; OR < 1 indicates a protective (response-favoring) effect. *P< 0.05, **P< 0.01

The baseline features of the study cohort showed a significantly higher mean age (P=0.0025) among non-responders compared to responders (54.8 ± 5.3 vs 48.8 ± 12.5 years), suggesting that younger patients were more likely to be better responders to ETN treatment.

Females predominated in both groups (94% of the non-responders group was female vs. 85% for the responders' group); however, the differences were not statistically significant, suggesting that sex-specific factors didn't predict response.

All other baseline parameters showed no significant differences, including the age of onset, disease duration, or baseline DAS28-ESR.

As shown in T**able 1**, comparison of genotypic and allelic distributions among responders and non-responders revealed significant differences in one SNP, IL-10 rs1800896 (A>G).

For the IL-10 rs1800896 (A>G), the G allele was more common among responders (45.2 %) than non-responders (25.0 %), conferring a protective effect against non-response (OR = 0.40, 95 % CI 0.21–0.77, P 0.0055). The other loci (rs1800871 C>T, rs1800872 C>A) showed no statistically significant variation in genotype or allele distributions between the two categories (P>0.05). IL-10 rs1800896 G allele appears beneficial and is associated with an improved response to ETN therapy.

The findings highlight the potential of specific IL10-SNPs as predictive biomarkers for treatment outcome. The allelic analysis suggests that G allele carriers possess 60% reduced odds of being non-responders. The genotypic analysis indicated that genotype distribution (AA, AG, GG) between responders and non-responders was highly significant (P=0.0028), suggesting a model of inheritance where the presence of the G allele alters the likelihood of response. Additionally, the inheritance patterns strongly implicate the rs1800896 G allele as a marker for improved response to ETN.

Table 2. Binary logistic regression analysis of IL-10 polymorphisms predicting non-response to etanercept under dominant, recessive, and additive genetic models.

SNP	Model	Minor allele	Major allele	β Coefficient	Std. Error	OR	95% CI	p- Value
IL-10: rs1800871 C>T	Dominant	T	C	0.008	0.432	1.008	0.43–2.35	0.985
	Recessive	T	C	0.031	0.588	1.031	0.33–3.26	0.958
	Additive	T	C	0.012	0.3	1.012	0.56–1.82	0.968
IL-10: rs1800872 C>A	Dominant	A	C	-0.049	0.428	0.952	0.41–2.20	0.909
	Recessive	A	C	-0.435	0.654	0.647	0.18–2.33	0.505
	Additive	A	C	-0.125	0.307	0.883	0.48–1.61	0.684
IL-10: rs1800896 A>G	Dominant	G	A	-1.526	0.461	0.217	0.09–0.54	**0.001 ****
	Recessive	G	A	-0.435	0.654	0.647	0.18–2.33	0.505
	Additive	G	A	-0.952	0.353	0.386	0.19–0.77	**0.007 ****

The dependent variable was treatment outcome (non-responder = 1, responder = 0). Independent variables were genotype categories coded according to dominant, recessive, or additive genetic models. Dominant (minor-allele carriers ≥ 1 vs non-carriers), recessive (minor-allele homozygotes vs others), and additive (per-allele increase in minor-allele count). The β coefficient represents the log odds of non-response, with the corresponding odds ratio (OR = e^β), 95% confidence interval (CI), and Wald p-value. Significance thresholds: * p < 0.05; ** p < 0.01

From a translational perspective, the identification of rs1800896 as a potential predictive marker holds promise for personalizing RA therapy. Genotyping this SNP could help clinicians stratify patients, identifying those more likely to respond favorably to ETN versus those for whom alternative biological therapies might be considered first [48, 49].

After ETN treatment, Schotte *et al.* [23] compared good responders versus moderate and non-responders in RA patients (as defined by the EULAR criteria). They indicated a significant difference in the allelic and haplotypic distribution pattern of the IL10 loci in patients with good response versus non-responders (46% vs. 22%).

Although the present findings support a favorable effect of certain IL-10 promoter variants, particularly rs1800896, on the clinical response to ETN, it is important to note that not all IL-10 loci exert the same influence on therapeutic outcomes. As reported by Schotte *et al.* [23]. This observation aligns with the model proposed by Padyukov *et al.* [50], who mentioned that the combined effect of multiple cytokine-related SNPs, including both pro-inflammatory (e.g., TNF-α, IL-6) and anti-inflammatory (e.g., IL-10), shapes the inflammatory environment in rheumatoid arthritis and also affects the clinical response to ETN. Padyukov *et al.* [50] reported that a combination of both IL-10 and TNF-α alleles correlated with diminished inflammatory reaction and improved response to ETN, and the –1087 G allele was associated significantly with good responsiveness to ETN.

Association between genotypes and the likelihood of being a non-responder

The binary logistic regression analysis offers a clinically intuitive perspective **(Table 2)** demonstrating a substantial protective effect of the G allele against non-response in the -1082 A>G locus. The significant associations under both the dominant (OR = 0.217, p = 0.0009) and additive (OR = 0.386, p = 0.007) models indicate a strong, dose-independent relationship. Carriage of even a single G allele nearly quintuples the odds of being a responder ($1/0.217 \approx 4.6$), an effect size that is considerable in the context of pharmacogenetic studies.

The remaining IL-10 (rs1800871 C>T and rs1800872 C>A) polymorphisms demonstrated no statistically significant correlation across any inheritance model ($P > 0.05$).

At the genotype level, two polymorphisms demonstrated significant associations with ETN treatment response after multiple-testing correction.

This result is further supported by the genotype-level analysis in **Table 3**, which shows that IL-10 rs1800896 (A>G) demonstrated a strong, inverse relationship between genotype and treatment outcome. The AA genotype (wild-type) was associated with the highest non-response rate ($\Delta \approx +0.22$; $\Phi = +0.36$; $p = 0.0007$), whereas carriers of the G allele (AG, GG) showed lower non-response rates ($\Delta \approx -0.16$ and -0.09, respectively). This pattern indicates a protective role of the G allele and implicates the A allele in ETN resistance.

Bartelds *et al*. [51] identified that RA patients' carriage of the (AA genotype) for IL10/-1082 showed a significant negative or unfavorable correlation with the anti-TNF agent (adalimumab) due to the rise of adalimumab antibodies in the serum of RA patients and subsequently with the response to anti-TNF.

Interleukin-10 is considered a potential anti-inflammatory agent that exerts a critical role in modulating cell-mediated immunity and maintaining immunological tolerance. It counteracts the pro-inflammatory effects of cytokines like TNF-α, the very target of ETN. It is well-established in the study that the rs1800896 (-1082A>G) polymorphism influences IL-10 gene transcription and subsequent cytokine production. The G allele has been previously related to higher levels of IL-10 secretion. Therefore, the observed pharmacogenetic association can be mechanistically explained: patients carrying the G allele likely have a genetically predetermined propensity for higher IL-10 production. This elevated anti-inflammatory background may act synergistically with TNF-α inhibition by ETN, leading to a more effective suppression of the inflammatory cascade and a superior clinical response [52-56].

The other IL-10 (rs1800871 C>T) and (rs1800872 C>A) variants exhibited no significant genotype-level associations [57-66].

This study reveals that IL-10 rs1800896 (A>G) is the key functional variant influencing inter-individual differences in ETN responsiveness among rheumatoid arthritis patients. In contrast, the lack of significant associations for the other tested IL-10 (rs1800871, rs1800872) highlights the specificity of the rs1800896 effect. This suggests that not all polymorphisms within these cytokine genes are functionally equivalent in influencing response to TNF-α inhibition [67-77].

Table 3. Genotype-specific association of IL-10 polymorphisms with non-response to ETN therapy in RA patients.

SNP	Genotypes	Effect size (Φ)	p-value	Δ non-response
	CC	-0.002	0.985	-0.001
IL-10: rs1800871 (C>T)	CT	-0.002	0.985	-0.001
	TT	0.006	0.958	0.006
	CC	0.012	0.909	0.006
IL-10: rs1800872 (C>A)	CA	0.037	0.727	0.022
	AA	-0.07	0.503	-0.089
	AA	0.358	**0.0007 ****	0.217
IL-10: rs1800896 (A>G)	AG	-0.304	**0.004 ****	-0.16
	GG	-0.071	0.503	-0.089

Data represent the correlation between each genotype and treatment non-response status (non-responder = 1, responder = 0). Φ-coefficient indicates the signed strength and direction of association (positive = higher likelihood of non-response). Δ non-response = P(non-response | genotype) − P(non-response overall), expressing the deviation in non-response rate for that genotype relative to the whole cohort. P-values were derived using the Chi-square test for valid expected counts or Fisher's exact test when assumptions were not met. Significance thresholds: * $p < 0.05$; ** $p < 0.01$

The de Lima *et al*. [78] study identified significant associations between only specific genetic polymorphisms and disease activity in RA. The IL10-1082 mutant genotype was associated with reduced disease activity (CDAI) and correlated with increasing IL-10 production; in other words, low severity of RA, measured by CDAI score. In contrast to other genotypes, which are linked to higher disease activity, including CDAI, DAS28, bone erosions, ESR, and IFN-γ. These findings suggest that the IL10-1082 polymorphisms have potential prognostic and monitoring value in RA.

The correlations between the genotypes and the difference in DAS28-ESR over 6 months

Table 4 summarizes the comparison of 6-month changes in disease activity (ΔDAS28-ESR) among RA patients stratified by IL-10 genotypes. Significant genotype-related differences in clinical response were observed for IL-10 rs1800896 (A>G), whereas the other polymorphisms showed no significant associations [58-66, 79-83].

Regarding IL-10 rs1800896 (A>G), the Welch ANOVA indicated a significant overall genotype effect (P 0.009, ω^2 = 0.09). Post-hoc Games–Howell comparison showed that individuals with the AG genotype achieved significantly greater improvement in DAS28-ESR compared with GG homozygotes (P 0.0016), whereas the AA genotype showed an intermediate response without a statistically significant association with the other groups. In contrast, IL-10 rs1800871 (C>T) and IL-10 rs1800872 (C>A) did not show significant differences in ΔDAS28-ESR among genotypes ($p > 0.05$).

Overall, these outcomes inferred that specific polymorphisms within IL-10, namely rs1800896 (A>G), were significantly related to the magnitude of clinical improvement (Disease activity indices) after six months of ETN therapy. The observed genotype–response associations for these loci were consistent with the corresponding logistic regression results, supporting their potential role as predictive genetic markers of therapeutic response in rheumatoid arthritis.

Collectively, these data highlight that while rs1800795 appears to be a functionally relevant predictor of IL-6-mediated treatment response, the rs1800796 and rs1800797 variants likely lack significant biological impact in the context of anti-TNF therapy.

These findings are consistent with Schotte *et al.* [23], who identified a statistically significant association between IL-10 promoter microsatellite polymorphisms and clinical response to ETN in RA. Their analysis of patient groups revealed distinct distributions of specific alleles and haplotypes; some alleles were associated with a favorable response, and others were predominant in patients with moderate or no response.

Table 4. Effect of IL-10 Gene Polymorphisms on 6-Month Change in Disease Activity (ΔDAS28-ESR) Among Rheumatoid Arthritis Patients Receiving Etanercept.

SNP	Genotype	n	ΔDAS28-ESR mean ± SD	p-value	Effect size (ω^2)	Post-hoc (Games–Howell)
IL-10: rs1800871 (C>T)	CC	38	0.64 ± 1.37	0.209		NS
	CT	38	1.13 ± 1.27			
	TT	14	0.66 ± 0.95			
IL-10: rs1800872 (C>A)	CC	42	0.71 ± 1.37	0.499		NS
	CA	36	0.90 ± 1.17			
	AA	12	1.19 ± 1.28			
IL-10: rs1800896 (A>G)	AA	36	0.41 ± 1.17 b	**0.009 ****	**0.09**	**AG vs GG p=0.0016**
	AG	42	1.37 ± 1.42 a			
	GG	12	1.07 ± 1.10 ab			

ΔDAS28-ESR represents the 6-month change in the Disease Activity Score based on erythrocyte sedimentation rate; higher positive values indicate greater clinical improvement after etanercept therapy. Statistical comparisons were performed between genotype groups. When genotype variances or sample sizes were unequal, Welch's ANOVA (or Welch t-test for two-group comparisons) was used; otherwise, one-way ANOVA was applied. Post-hoc pairwise comparisons were conducted using the Games-Howell test, which does not assume equal variances. Reported p-values correspond to the omnibus (overall) test of group mean differences. The effect size (ω^2) represents the proportion of total variance in ΔDAS28-ESR explained by the genotype, interpreted as small (≈0.01), medium (≈0.06), or large (≈0.14). Superscript letters (a, b) denote statistically distinct groups: means that share the same letter do not differ significantly ($p > 0.05$), while those with different letters differ significantly ($p < 0.05$). NS: not significant; * $p < 0.05$; **

The earlier results **(Table 4)** demonstrated that carriers of the AG genotype for IL-10 rs1800896 exhibited greater clinical improvement compared to the homozygote GG genotype following ETN therapy, which is an interesting observation. Although the G allele is known to be associated with higher IL-10 production compared to the A allele, the superior response of AG over GG suggests a non-additive, overdominant model of inheritance. This may be due to very high IL-10 (as expected in GG carriers), which may oversuppress antigen-presenting cell signaling and alter TNF-α/IL-6 feedback [84], potentially reducing the pharmacodynamic impact of TNF-α inhibition. Conversely, very low IL-10 expression (as expected with the AA genotype) may permit persistent inflammatory activity that decreases or limits ETN efficacy. The AG genotype may therefore create an optimum balance in the inflammatory environment [85] for ETN efficacy. Such a heterozygote advantage has been demonstrated in several studies, including for IL-10 promoter haplotypes [86].

It is important to mention that not all studies agreed with the above explanation. Some studies reported a better response in GG carriers, including de Lima *et al.* [78] and Li *et al.* [87], who linked the −1082 G allele to reduced disease activity. This reduction in disease activity is explained by the anti-inflammatory properties of IL-10 that block or suppress pivotal pro-inflammatory molecules in RA synovitis, such as TNF-α and IL-1β [88], and reduce their levels in synovial cultures [89]. Since these cytokines drive joint destruction by activating matrix metalloproteinases [90], the IL10-1082 AG and GG genotypes

may confer a genetic advantage. By upregulating IL-10 mRNA, this genotype could promote milder RA activity, as measured by the sensitive CDAI score, via the inhibition of pro-inflammatory cascades.

Conclusion

These results suggested that age might be a demographic predictor of ETN response. The study demonstrated the effectiveness of ETN in lowering RA disease activity in responders' patients by lowering TJC, SJC, CDAI, ESR, PtGA, PrGA, and DAS28-ESR at two intervals of three and six months after the start of treatment. Non-responders, however, showed little to no decrease in these metrics.

Evaluation of the IL-10 rs1800896 (−1082 A>G) polymorphism demonstrated that carriers of the A allele showed poor response to ETN at the six-month post-onset of therapy, whereas the presence of the G allele, particularly within the AG genotype, correlated with better therapeutic outcome. This emphasizes the functional relevance of −1082 A>G as the principal regulatory polymorphism within the IL-10 promoter. However, other IL-10 variants (rs1800871, rs1800872) did not show a predictive effect; rs1800896 appears to hold potential as a useful pharmacogenetic marker for stratifying patient response and optimizing ETN treatment strategies.

Acknowledgments: We are also thankful to the head of the clinical pharmacy department for the critical feedback and thoughtful insights, which have significantly improved the quality of this manuscript.

Conflict of interest: None

Financial support: None

Ethics statement: The study was approved by the ethical committee of the College of Pharmacy/University of Baghdad under the registration number (RECAUBCP123202406150H) on 12 March 2024.

References

1. Majithia V, Geraci SA. Rheumatoid arthritis: diagnosis and management. Am J Med. 2007;120(11):936-9.
2. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014;73(7):1316-22.
3. Wu Q, Wang H, Wu Y, Tao L, Wang W, Yin S, et al. The burden of rheumatoid arthritis in China from 1990-2021: an analysis based on the Global Burden of Disease Study 2021;1-23.
4. Faiq MK, Kadhim DJ, Gorial FI. The belief about medicines among a sample of Iraqi patients with rheumatoid arthritis. Iraqi J Pharm Sci. 2019;28(2):134-41.
5. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American college of rheumatology/european league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70(3):404-13.
6. Buhre JS, Pongracz T, Geisen UM, Schubert M, Wang W, Nouta J, et al. Anti-TNF therapy impairs both short-and long-term IgG responses after repeated vaccination. Allergy. 2024;00:1-17.
7. Zhao S, Mysler E, Moots RJ. Etanercept for the treatment of rheumatoid arthritis. Immunotherapy. 2018;10:433-45.
8. Hussain SA, Abood SJ, Gorial FI. The adjuvant use of calcium fructoborate and borax with etanercept in patients with rheumatoid arthritis: pilot study. J Intercult Ethnopharmacol. 2017;6(1):58.
9. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685-99.
10. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
11. Liu X, Xu J, Hu CD, Pan ZL, Zhang YC. The relationship between SNPs in the genes of the TLR signal transduction pathway downstream elements and rheumatoid arthritis susceptibility. Cytol Genet. 2014;48:155-9.
12. Carlini V, Noonan DM, Abdalalem E, Goletti D, Sansone C, Calabrone L, et al. The multifaceted nature of IL-10: regulation, role in immunological homeostasis, and its relevance to cancer, COVID-19, and post-COVID conditions. Front Immunol. 2023;14:1161067. doi:10.3389/fimmu.2023.1161067
13. Moller JC, Paul D, Ganser G, Range U, Gahr M, Kelsch R, et al. IL10 promoter polymorphisms are associated with systemic onset juvenile idiopathic arthritis (SoJIA). Clin Exp Rheumatol. 2010;28(6):912-8.
14. Greenhill C. Rheumatic disease: IL-10 deficiency exacerbates inflammatory joint disease. Nat Rev Rheumatol. 2014;10:502.
15. Qu CH, Hou Y, Bi YF, Han QR, Jiao CH, Zou QF. Diagnostic values of serum IL-10 and IL-17 in rheumatoid arthritis and their correlation with serum 14-3-3η protein. Eur Rev Med Pharmacol Sci. 2019;23(5):1899-906.
16. Rija FF, Hussein SZ, Abdalla MA. Physiological and immunological disturbance in rheumatoid arthritis patients. Baghdad Sci J. 2021;18(2):247-52. doi:10.21123/BSJ.2021.18.2.0247
17. Liu Y, Wang J, Zhang L, Li H, Chen Y, Li Z. Baseline serum IL-10 predicts clinical response to TNF inhibitors in rheumatoid arthritis. Clin Exp Rheumatol. 2024;42(2):265-72.

18. Mohammed SI, Zalzala MH, Gorial FI. The effect of TNF alpha gene polymorphisms at-376 G/A, -806 C/T, and 1031 T/C on the likelihood of becoming a non-responder to etanercept in a sample of Iraqi rheumatoid arthritis patients. Iraqi J Pharm Sci. 2022;31(2):113-28. doi:10.31351/vol31iss2pp113-128
19. Mohammed S, Zalzala M, Gorial F. Association of tumor necrosis factor-alpha promoter region gene polymorphism at positions -308G/A, -857C/T, and -863C/A with etanercept response in Iraqi rheumatoid arthritis patients. Arch Rheumatol. 2022;37(4):613-25. doi:10.46497/ArchRheumatol.2022.9272
20. Mohammed SI, Jasim AL, Jamal MY, Hussain SA. Factors influencing adalimumab treatment response in patients with rheumatoid arthritis: the future of clinical expertise. Al Rafidain J Med Sci. 2023;5:192-204. doi:10.54133/ajms.v5i.232
21. Mohammed SI, Jamal MY, Alshamari IO. The association of genetic polymorphisms in tumor necrosis factor-alpha and interleukins with disease severity or response to biological therapy in Iraqi rheumatoid arthritis patients: a narrative review. Al-Rafidain J Med Sci. 2023;4:24-33. doi:10.54133/ajms.v4i.100
22. Ying B, Shi Y, Pan X, Song X, Huang Z, Niu Q, et al. Association of polymorphisms in the human IL-10 and IL-18 genes with rheumatoid arthritis. Mol Biol Rep. 2011;38(1):379-85.
23. Schotte H, Schlüter B, Drynda S, Willeke P, Tidow N, Assmann G, et al. Interleukin 10 promoter microsatellite polymorphisms are associated with response to long-term treatment with etanercept in patients with rheumatoid arthritis. Ann Rheum Dis. 2005;64(4):575-81.
24. Salman O, Merdaw MA, Almaliky AA. A novel single-nucleotide polymorphism of the interleukin-10 gene is linked to type 2 diabetes mellitus in Iraqi patients with Toxoplasmosis (Conference Paper). Iraqi J Pharm Sci. 2022;31(Suppl):1-8.
25. Schotte H, Schlüter B, Schmidt H, Gaubitz M, Drynda S, Kekow J, et al. Putative IL-10 low producer genotypes are associated with a favourable etanercept response in patients with rheumatoid arthritis. PLoS One. 2015;10(6):e0130907. doi:10.1371/journal.pone.0130907
26. Abbas AH, Hatif ST, Gorial FI, Ali SB. The association of interleukin-10 single-nucleotide polymorphisms (rs1800871) and serum levels in Iraqi patients with celiac disease: a case-control study. Clin Epidemiol Glob Health. 2023;24:101437. doi:10.1016/j.cegh.2023.101437
27. Wittke-Thompson JK, Pluzhnikov A, Cox NJ. Rational inferences about departures from the Hardy-Weinberg equilibrium. Am J Hum Genet. 2005;76(6):967-86.
28. Ge L, Huang Y, Zhang H, Liu R, Xu N. Association between polymorphisms of interleukin 10 with inflammatory biomarkers in East Chinese Han patients with rheumatoid arthritis. Joint Bone Spine. 2015;82(3):182-6.
29. Hassanzadeh S, Hedayati F, Hosseini E, Malekzadeh J, Masnavi E, Keshtkari A. Association between IL-10 rs1800872 Polymorphism in the Promoter Region of Human IL-10 Gene and Susceptibility to Rheumatoid Arthritis in Patients in the Southwest of Iran. J Clin Care Skills. 2022;3(3):133-8.
30. AL-Hasnawi HR, Jalali A, Mousa RF. Association of Interleukin 10 gene promoter polymorphisms with Rheumatoid Arthritis susceptibility in Iraqi women population; A case control study. J Epigenetics. 2024;5(1).
31. Stephen SB, Wankhar D, Subbaraj GK. Genetic susceptibility to rheumatoid arthritis: a meta-analysis of interleukin-10 and protein tyrosine phosphatase non-receptor type 22 gene variants. Egypt Rheumatol Rehabil. 2025;52(1):1.
32. Tayel MY, Nazir A, Abdelhamid IM, Helmy ASM, Zaki NE, Elsharkawy NS, et al. TNF-α -308 G>A and IL10 -1082A>G polymorphisms as potential risk factors for lymphoproliferative disorders in autoimmune rheumatic diseases. Egypt J Med Hum Genet. 2020;21:2.
33. Hee CS, Gun SC, Naidu R, Gupta E, Somnath SD, Radhakrishnan AK. Comparison of single-nucleotide polymorphisms in the human interleukin-10 gene promoter between rheumatoid arthritis patients and normal subjects in Malaysia. Mod Rheumatol. 2007;17(5):429-35.
34. Pawlik A, Kurzawski M, Szklarz BG, Herczynska M, Drozdzik M. Interleukin-10 promoter polymorphism in patients with rheumatoid arthritis. Clin Rheumatol. 2005;24(5):480-4.
35. Paradowska-Gorycka A, Trefler J, Maciejewska-Stelmach J, Lacki JK. Interleukin-10 gene promoter polymorphism in Polish rheumatoid arthritis patients. Int J Immunogenet. 2010;37(4):225-31.
36. Yucel B, Sumer C, Gok I, Karkucak M, Alemdaroglu E, Ucar F. Associations between cytokine gene polymorphisms and rheumatoid arthritis in the Turkish population. North Clin Istanb. 2020;7(6):563-71.
37. Qadir FA, Pirdawid AO, Aali MH, Smail SW, Khudhur ZO, Shareef AA, et al. Association study of Interleukin 10 gene polymorphisms in Iraqi patients with multiple sclerosis. Gene Rep. 2020;21:100948.
38. Mishra B, Bachu M, Wingert C, Yuan R, Chaudhary V, Brauner C, et al. IL-10 Targets IRFs to Suppress IFN and Inflammatory Response Genes by Epigenetic Mechanisms. bioRxiv. 2024;2024-11.
39. Balakrishnan P, Shah J, Surmava S, Kvaratskhelia E, Abzianidze E, Vardiashvili N, et al. Association of polymorphism (RS1800896) of the IL-10 gene and IL-10 gene expression in ovarian cancer patients from Georgia. Scripta Medica. 2024;55(2):157-63.
40. Keegan AP, Savage K, Bousman CA, Nolidin K, Cribb L, Pipingas A, et al. Interleukin 10 (IL-10) promoter region polymorphism is associated with IL-10 serum concentrations and processing speed in healthy community-dwelling older adults. Behav Brain Res. 2024;458:114756.

41. Jassim NA. Predictors of Response to Etanercept in the Treatment of Iraqi Patients with Active Rheumatoid Arthritis. J Fac Med Baghdad. 2015;57(1):35-39. doi:10.32007/jfacmedbagdad.571304
42. Al-Ani N, Gorial F, Yasiry D, Al Derwibee F, Abbas Humadi Y, Sunna N, et al. Clinical outcomes in Iraqi patients with rheumatoid arthritis following earlier or later treatment with etanercept. Open Access Rheumatol. 2021;13:57-62. doi:10.2147/OARRR.S300838
43. Aghdashi M, Seyedmardani S, Forouzin M, Azari H. Comparison of efficacy of Infliximab and Etanercept on Rheumatoid Arthritis patients. Rheumatol Res. 2021;6(1):35-42.
44. Matucci-Cerinic M, Allanore Y, Kavanaugh A, Buch MH, Schulze-Koops H, Kucharz EJ, et al. Efficacy, safety, and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-to-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study. RMD Open. 2018;4(2):e000757.
45. Su KY, Lee HT, Chou CT, Tsai ST, Chen WS, Tsai CY. Improvement of active rheumatoid arthritis after etanercept injection: a single-center experience. J Chin Med Assoc. 2009;72(11):581-7.
46. Jamnitski A, Krieckaert CL, Nurmohamed MT, Hart MH, Dijkmans BA, Aarden L, et al. Patients non-responding to etanercept obtain lower etanercept concentrations compared with responding patients. Ann Rheum Dis. 2012;71(1):88-91.
47. Sebastiani M, Manfredi A, Iannone F, Gremese E, Bortoluzzi A, Favalli E, et al. Factors predicting early failure of etanercept in rheumatoid arthritis: an analysis from the gruppo Italiano di studio sulla early arthritis (Italian group for the study of early arthritis) registry. Arch Rheumatol. 2020;35(2):163-9. doi:10.46497/ArchRheumatol2020.7499
48. Prada AM, Cicalău GIP, Ciavoi G. Resin infiltration for white-spot lesion management after orthodontic treatment. Asian J Periodontics Orthod. 2024;4:19-23. doi:10.51847/ZTuGEanCSV
49. Poornachitra P, Maheswari U. Identifying non-specific symptoms in oral submucous fibrosis patients: a clinical perspective. Asian J Periodontics Orthod. 2023;3:18-24. doi:10.51847/xLpm4TfyCA
50. Padyukov L, Lampa J, Heimbürger M, Ernestam S, Cederholm T, Lundkvist I, et al. Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis. Ann Rheum Dis. 2003;62(6):526-9.
51. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Wolbink GJ, De Vries N, Tak PP, et al. Anti-adalimumab antibodies in rheumatoid arthritis patients are associated with interleukin-10 gene polymorphisms. Arthritis Rheum. 2009;60(8):2541-2.
52. Sugimori T, Yamaguchi M, Kikuta J, Shimizu M, Negishi S. The biomechanical and cellular response to micro-perforations in orthodontic therapy. Asian J Periodontics Orthod. 2022;2:1-15. doi:10.51847/Z9adSJ59rj
53. Spirito FD, Iacono VJ, Alfredo I, Alessandra A, Sbordone L, Lanza A. Impact of COVID-19 awareness on periodontal disease prevention and management. Asian J Periodontics Orthod. 2022;2:16-26. doi:10.51847/t8D9TJGOCU
54. Zhao D, Xue K, Meng J, Hu M, Tan X. Root canal treatment in posterior teeth: implications for orthodontic mechanics and stability. Asian J Periodontics Orthod. 2022;2:27-32. doi:10.51847/cTjogcutDJ
55. Dipalma G, Inchingolo AD, Fiore A, Balestriere L, Nardelli P, Casamassima L, et al. Comparative effects of fixed and clear aligner therapy on oral microbiome dynamics. Asian J Periodontics Orthod. 2022;2:33-41. doi:10.51847/mK28wdKCIX
56. Samaranayake L, Tuygunov N, Schwendicke F, Osathanon T, Khurshid Z, Boymuradov SA, et al. Artificial intelligence in prosthodontics: transforming diagnosis and treatment planning. Asian J Periodontics Orthod. 2024;4:9-18. doi:10.51847/nNyZ6VD1da
57. Alkhanova ZK, Abueva SL, Kadaeva FI, Dadaev KM, Esilaeva AV, Isaev EB. Exploring phytotherapy as a preventive approach for ischemic stroke recurrence. Spec J Pharmacogn Phytochem Biotechnol. 2023;3:10-4. doi:10.51847/UGwxDZUZdR
58. Manole F, Mekeres GM, Davidescu L. Genetic insights into allergic rhinitis: a comprehensive review. Interdiscip Res Med Sci Spec. 2023;3(1):39-44. doi:10.51847/GDXePBjkMJ
59. Danchin A, Ng TW, Turinici G. Transmission pathways and mitigation strategies for COVID-19. Interdiscip Res Med Sci Spec. 2024;4(1):1-10. doi:10.51847/p0YhQPxvkW
60. Muresan GC, Hedesiu M, Lucaciu O, Boca S, Petrescu N. Evaluation of bone turnover indicators before dental implant insertion in osteoporotic patients: a case-control investigation. J Curr Res Oral Surg. 2023;3:27-32. doi:10.51847/P4EfMAbJVb
61. Ku JK, Um IW, Jun MK, Kim IH. Clinical management of external apical root resorption using amnion membrane matrix and bio-dentine. J Curr Res Oral Surg. 2023;3:1-5. doi:10.51847/lOSwt6Qzpv
62. Uneno Y, Morita T, Watanabe Y, Okamoto S, Kawashima N, Muto M. Assessing the supportive care needs of elderly cancer patients at seirei mikatahara general hospital in 2023. Int J Soc Psychol Asp Healthc. 2024;4:13-9. doi:10.51847/o4njwxvRSF
63. Delcea C, Gyorgy M, Siserman C, Popa-Nedelcu R. Impact of maladaptive cognitive schemas on suicidal behavior in adolescents during the COVID-19 pandemic: a predictive study. Int J Soc Psychol Asp Healthc. 2024;4:42-6. doi:10.51847/EHCf9HzLEP
64. Alhossan A, Al Aloola N, Basoodan M, Alkathiri M, Alshahrani R, Mansy W, et al. Assessment of community pharmacy services and preparedness in saudi arabia during the COVID-19 pandemic: a cross-sectional study. Ann

Pharm Educ Saf Public Health Advocacy. 2024;4:43-9. doi:10.51847/C52qAb0bZW

65. Liu H, Xie X, Chen Q. Determinants of practice: exploring healthcare providers' beliefs and recommendations for cardiac rehabilitation in China. Ann Pharm Educ Saf Public Health Advocacy. 2024;4:63-74. doi:10.51847/UcQWoStr3h
66. Elamin SM, Redzuan AM, Aziz SAA, Hamdan S, Masmuzidin MZ, Shah NM. Educational impact on glycemic outcomes among children and adolescents diagnosed with type 1 diabetes. J Med Sci Interdiscip Res. 2023;3(1):41-64. doi:10.51847/s5KgRZ9e1O
67. Elshoubashy H, Elkader HA, Khalifa N. Exploring the impact of gamification on brand engagement: an empirical study. Asian J Indiv Organ Behav. 2023;3:59-71. doi:10.51847/v9Qc0ikIHr
68. Efremov A. Relieving psychosomatic pain and negative emotions through dehypnosis. Asian J Indiv Organ Behav. 2023;3:18-24. doi:10.51847/BPFsWgpeFd
69. Grant O, Wallace E. The influence of diversity-focused leadership on employee advocacy in selected indian fortune companies: the mediating roles of symmetrical internal communication and work engagement. Ann Organ Cult Leadersh Extern Engagem J. 2024;5:159-73. doi:10.51847/X2YHdX2Qz7
70. Oran IB, Azer OA. The evolution of Turkey's role in international development: a globalization perspective. Ann Organ Cult Leadersh Extern Engagem J. 2023;4:1-8. doi:10.51847/oNOPb4T9g1
71. Shrivastava Y, Yuwanati M, Ganesh N. Lack of combined effect of toluidine blue and cytomorphometry in differentiating dysplasia in oral exfoliative cytology. Asian J Curr Res Clin Cancer. 2023;3(2):25-31. doi:10.51847/sEjz14Y7qU
72. Al-Thani H, Al-Kuwari S, Abdulla M. Evaluating nurse-led interventions and symptom trajectories in head and neck cancer patients undergoing radiotherapy. Asian J Curr Res Clin Cancer. 2023;3(2):72-83. doi:10.51847/M9vTLVc9kC
73. Ferraz MP. Comparative evaluation of oral wound dressing materials: a comprehensive clinical review. Ann Pharm Pract Pharmacother. 2024;4:51-6. doi:10.51847/pEkEpZ0DjV
74. Khashashneh M, Ratnayake J, Choi JJE, Mei L, Lyons K, Brunton P. Comparative effectiveness and safety of low- vs high-concentration carbamide peroxide for dental bleaching: a systematic review. Ann Pharm Pract Pharmacother. 2023;3:21-7. doi:10.51847/hE26QqCyuQ
75. Iftode C, Iurciuc S, Marcovici I, Macasoi I, Coricovac D, Dehelean C, et al. Therapeutic potential of aspirin repurposing in colon cancer. Pharm Sci Drug Des. 2024;4:43-50. doi:10.51847/nyDxRaP7Au
76. Nkosi T, Dlamini A. Limited predictive performance of existing amisulpride poppk models: external validation and proposal of model-based remedial regimens for non-adherence. Pharm Sci Drug Des. 2023;3:53-66. doi:10.51847/iAz1QEBpk0
77. Awasthi A, Bigoniya P, Gupta B. Phytochemical characterization and pharmacological potential of moringa oleifera extract. Spec J Pharmacogn Phytochem Biotechnol. 2024;4:1-8. doi:10.51847/VEJJO91vAT
78. De Lima CA, Rushansky E, Adelino JE, de Oliveira Souza AP, Santos PD, de Araújo Mariano MH, et al. Are key cytokines genetic and serum levels variations related to rheumatoid arthritis clinical severity? Gene. 2020;722:144098.
79. Sonbol HS. Nutritional proteomics: a pathway to understanding and optimizing human health. J Med Sci Interdiscip Res. 2023;3(2):45-64. doi:10.51847/SnZlWLL5go
80. Tâlvan E, Budişan L, Mohor CI, Grecu V, Berindan-Neagoe I, Cristea V, et al. Interconnected dynamics among inflammation, immunity, and cancer–from tumor suppression to tumor onset, promotion, and progression. Arch Int J Cancer Allied Sci. 2023;3(1):25-8. doi:10.51847/nbSWsJHJMZ
81. Kim S, Bae H, Kim H. A diagnostic and therapeutic dilemma: giant multifocal retroperitoneal dedifferentiated liposarcoma with dual heterologous components. Arch Int J Cancer Allied Sci. 2024;4(2):1-5. doi:10.51847/5JnC3jAkZz
82. Su Z, Qin M, Hu D. Impact of lecture versus group discussion-based ethics training on nurses' moral reasoning, distress, and sensitivity: a randomized clinical trial. Asian J Ethics Health Med. 2024;4:81-96. doi:10.51847/iBvPMrJSLE
83. Welman A, Chima MD. Respecting autonomy in african communities: traditional beliefs and challenges for informed consent in South Africa. Asian J Ethics Health Med. 2023;3:1-16. doi:10.51847/KmUs6uzoc1
84. Guo Z, He Q, Zhang Y, Li Y, Zhang Z. Mechanisms of Interleukin-10-Mediated Immunosuppression in Viral Infections. Pathogens. 2025;14(10):989. doi:10.3390/pathogens14100989
85. Hoebee B, Rietveld E, Bont L, Oosten MV, Hodemaekers HM, Kimpen JL. Influence of promoter variants of interleukin-10, interleukin-9, and tumor necrosis factor-α-genes on respiratory syncytial virus bronchiolitis. J Infect Dis. 2004;189(2):239-47. doi:10.1086/380764
86. Hernández-Bello J, Oregón-Romero E, Vázquez-Villamar M, García-Arellano S, Valle Y, Padilla-Gutiérrez JR, et al. Aberrant expression of interleukin-10 in rheumatoid arthritis: Relationship with IL10 haplotypes and autoantibodies. Cytokine. 2017;95:88-96.
87. Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Associations between interleukin-10 polymorphisms and susceptibility to rheumatoid arthritis: a meta-analysis. Mol Biol Rep. 2012;39(1):81-7. doi:10.1007/s11033-011-0712-7
88. Lubberts E, van den Berg WB. Cytokines in the pathogenesis of rheumatoid arthritis and collagen-induced

arthritis. In: Durum SK, Muegge K, editors. Cytokine Knockouts. Totowa, NJ: Humana Press; 2013. p. 289-312.
89. Katsikis PD, Chu CQ, Brennan FM, Maini RN, Feldmann M. Immunoregulatory role of interleukin 10 in rheumatoid arthritis. J Exp Med. 1994;179(5):1517-27.
90. Burrage PS, Mix KS, Brinckerhoff CE. Matrix metalloproteinases: role in arthritis. Front Biosci. 2006;11:529-43.