Khafagi *et al.*
Egyptian Rheumatology and Rehabilitation (2024) 51:26
https://doi.org/10.1186/s43166-024-00260-x

Egyptian Rheumatology and Rehabilitation

RESEARCH Open Access

Predictors of tumor necrosis factor inhibitors primary failure in rheumatoid arthritis patients

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Abstract

Background Tumor necrosis factor inhibitors (TNFi) have emerged as an efficient therapeutic modality for rheumatoid arthritis (RA). A ratio of patients does not give a response despite therapy. It remains a challenge to predict which patients will respond. Our study aims to investigate early predictors of primary TNFi failure in RA patients. Patients were categorized into two groups based on TNFi therapy (responder/non-responder) and then compared to detect the most significant predictors of treatment failure.

Results This study included 87 RA patients treated with TNFi for the first time after conventional disease-modifying anti-rheumatic drugs (DMARDs) failed. This study showed that compared to those with successful treatment, patients with overall primary failure were significantly higher in older age, females, smokers, obese, younger age at the onset of the disease, or those with deformity. In addition, the drug failure was significantly related to erythrocyte sedimentation rate (ESR) (100 vs 68 mm/h), C-reactive protein (CRP) (48 vs 12 mg/dl), rheumatoid factor (RF) positivity (29% vs 16%), anti-cyclic citrullinated peptide (anti-CCP) positivity (39% vs 23%), and non-methotrexate (MTX) concomitant use (33% vs 40%).

Conclusion The increased age, being a smoker, earlier age at onset, presence of a deformity, and positive anti-CCP at baseline were predictors of overall failure. At the same time, concomitant MTX intake increased the success rate by 9.6%.

Highlights

- The increased age, being a smoker, earlier age of disease onset, and the presence of a deformity were predictors of overall TNFi primary failure.
- The overall primary failure of TNFi treatment was significantly related to ESR, CRP, RF positivity, anti-CCP positivity.
- The regression analysis showed that these combined factors predict 70.1% of the TNFi failure rate.
- Concomitant MTX intake increased the success rate by 9.6%.

Keywords Rheumatoid arthritis, Tumor necrosis factor inhibitors, Predictors, Treatment failure, Disease activity score

Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease (AID). It is characterized by persistent synovitis and is accompanied by pain, joint damage, disability, and poor quality of life (QoL) [1].

The primary target for RA management is disease remission or low disease activity (LDA). Remission is the state in which there are no longer any noticeable clinical

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signs of a serious inflammatory illness. Low-disease activity could be considered another satisfactory therapeutic goal, particularly in long-standing disease [2]. According to disease activity score-28 (DAS-28) (ESR), the disease activity cut-offs for remission and LDA are < 2.6 and ≤ 3.2, correspondingly [3].

Disease remission in refractory RA with specific biological medications is one of the optimum goals. Comprised in such agents are tumor necrosis factor-alpha inhibitors (TNFi), often used as the first biological drugs employed for RA management after the failure of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) [4].

To date, TNFi includes five distinctive agents: infliximab (IFX) and its bio-similar (bs-IFX), etanercept (ETA), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP). These five TNFi vary in structures, half-lives, route of administration, dosage intervals, immunogenicity, and pharmacokinetic characteristics [5].

However, the response differs among patients; in other words, not every case gives the same reaction to the same medication. In addition, the response rate of TNFi in RA is erratic and often unpredictable, which makes therapeutic decisions quite complicated [6]. About 35% of cases stop TNFi therapy owing to primary failure, secondary loss of response, or intolerance. In addition, they could induce complications such as infections, malignant tumors, acute infusion and injection hypersensitivity, autoimmunity, and cardiovascular (CV) effects [7, 8]. The therapeutic modalities to manage TNFi failure involve switching to another TNFi, perhaps a different kind of tailored medication with a variety of action mechanisms [5].

Studies that addressed the primary response to TNFi therapy and the predictors of its failure in RA patients are scarce [9–11]. In addition, reviewing the available current literature reveals a lack of recent and up-to-date Egyptian studies in this area. Therefore, this study was done to fill this gap for better disease treatment outcomes and to forecast the patients who will react to a specific method.

The current study aimed to investigate early predictors of primary TNFi failure in RA patients. This could help to enhance the risk–benefit ratio (RBR) and cost-effectiveness in individual cases and the overall therapeutic success.

Subjects and methods

This was a retrospective, record-based, descriptive study with an analytic component. The study was conducted at the Rheumatology and Rehabilitation Department, xxxxxxxxxx.

Inclusion criteria

It included all RA classified according to the 2010 rheumatoid arthritis classification criteria [12] biological naive patients who received anti-TNF as primary biological therapy.

Exclusion criteria

1. Patients received biological treatment other than TNFi.
2. patients developed severe side effects that limited continuous use of TNFi.
3. Patients had an acute or active infection.
4. Patients had congested heart failure or other contraindications to TNFi.
5. Biosimilars were excluded due to limited experience.

Method

The data listed below were gathered:

1. Demographic data: age, sex, body mass index (BMI), tobacco smoking
2. Co-morbidities: such as diabetes, hypertension, CV diseases, lung diseases, and renal dysfunction.
   Disease characteristics: age of diagnosis, disease duration, time from diagnosis to the initiation of therapy with biological drugs, extra-articular manifestations, such as rheumatoid nodules, pulmonary affection, ocular manifestations, and vasculitis. Besides, previous and concomitant treatments.
   Failure to respond is defined as failure to achieve remission or LDA according to DAS28-ESR, while treatment response is the fulfillment of remission or LDA according to the DAS28-ESR.
3. Laboratory analysis (done at baseline and 3 months later), including complete blood count (CBC), rheumatoid factor (RF), anti-citrullinated peptide antibodies (Anti-CCP), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).
4. The disease activity score-28 (DAS-28) was measured at baseline and three months following starting the first biological disease-modifying anti-rhematic drugs (bDMARD). The DAS28 is a composite score derived from the following four variables [13]: (A) determination of swollen joint count (SJC) (out of 28), (B) determination of tender joint count (TJC) (out of 28), (C) measurement of the ESR, and (D) determination of the patient global assessment (PGA).

Based on this score, three months after starting the therapy, patients were divided into two groups: responder and non-responder to their first TNFi therapy. This included IFX, ETA, ADA, and GOL.

Ethical consideration

The Medical Research Ethics Committee gave their approval to the research protocol, (code number: MS.21.10.1698). Consent is not applicable because the

study was retrospective and was based on patients' data collection which was anonymized. Personal privacy and confidentiality were upheld.

Statistical analysis

Using SPSS (Version 21) for Windows, the gathered data was coded, processed, and examined. program. A descriptive statistical analysis of all patients was performed. Patients were categorized into two groups based on TNFi therapy (responder/non-responder). The baseline demographics, as well as clinical and disease characteristics, were compared between the two groups to identify overall possible predisposing factors and predictors of TNFi failure in these cases.

These groups were compared using Pearson's chi-square, Fisher's exact tests, Student's *t*-tests, Monte Carlo, or Mann–Whitney *U* tests according to the data distribution. Using the "failure to response" (failure to achieve remission or LDA according to DAS28 ESR) as the dependent variable, multiple univariate logistic regression was conducted to recognize which features were accompanied by such outcomes and to be considered in the multivariate analyses. For modeling the response to each TNFi, a binary logistic regression model was used. With parameter (B) Beta regression coefficient. *A p* value of 5% or less was taken to be statistically significant.

Results

This is a record-based study which included 87 RA patients who were managed with TNFi for the first time after the failure of csDMARDS.

As regards the characteristics of studied RA patients as shown in Table 1, among the studied 87 RA patients, the mean age was 47.8 ± 13.1 years, 77% of them were females, 35.6% were obese, and the diagnosis was delayed for one or more years for about 60% of them. Among these patients, the median age (interquartile range) (IQR) was 31 (25–44) years at disease onset, 32 (25–44) years at diagnosis, and 8 (5–15) years from diagnosis to the first biological treatment.

Drug-related response in Table 2 showed that the overall primary failure (OPF) of the biological treatment in the studied patients was 49.4%. In addition, Table 2 showed that, according to the type of biological treatment, the primary failure was 35.3% for IFX, 58.3% for ETA, 50% for ADA, and 50% for GOL. Methotrexate (MTX) was given to 83.9% of patients, with a good response of 54.8%. At the same time, concomitant MTX intake increased the success rate by 9.6%.

Table 3 revealed, in comparison with patients with successful responses to biological treatment, patients with OPF were significantly older (51.7 ± 12.9 years vs

Table 1 The characteristics of the studied rheumatoid arthritis (RA) patients

Characteristics of the studied RA patients	*N* (%)
Total number of cases:	87 (100.0)
Age: (mean ± SD)	47.8 ± 13.1 years
Sex:	
- Males	20 (23.0)
- Females	67 (77.0)
Smoking:	
- Never smoke	64 (73.6)
- Ex-smoker	2 (2.3)
- Smoker	21 (24.1)
BMI: (kg/m^2) (mean ± SD)	30.5 ± 8.9
Obesity:	
- Non-obese	56 (65.4)
- Obese	31 (35.6)
Parent consanguinity:	
- Yes	10 (11.5)
- No	77 (88.5)
Age at disease onset: median (IQR)	31 (23.0–39.0) years
Age at diagnosis: median (IQR)	32 (25–44) years
Delay of diagnosis: (years)	
- No delay/less than 1 year	35 (40.2)
- 1 year	43 (49.5)
- 2 years and more	9 (10.3)
Duration after diagnosis and **before biological treatment:** median (IQR)	8 (5–15) years

N number, *BMI* body mass index, *IQR* interquartile range

Table 2 The overall and drug-related response among the studied patients

Drug-related response	*N* (%)
Total number of cases:	87 (100)
Overall response to biological treatments:	
- Success:	44 (50.6)
- Primary failure:	43 (49.4)
Primary failure with each type of biological treatment:	
- Infliximab (***n*** = 17)	6 (35.3)
- Etanercept (***n*** = 24)	14 (58.3)
- Adalimumab (***n*** = 36)	18 (50.0)
- Golimumab (***n*** = 10)	5 (50.0)
Methotrexate intake:	73 (83.9)
Biological response to concomitant methotrexate use[a]**:**	
- Good response	40 (54.8)
- Poor response	33 (45.2)
-The percent of the biological response difference when combined with methotrexate	9.6%

N number

[a] response defined as the fulfillment of remission or LDA according to the DAS28-ESR

43.9 ± 12.1 years, $p = 0.005$), females than males (88.4% vs 11.6%, $p = 0.013$), smokers (44.2% vs. 4.5%, $p < 0.001$), obese (48.8% vs. 22.7%, $p = 0.01$), and aged younger at the onset of the disease (29.9 ± 10.4 vs. 34.9 ± 11.2, $p = 0.038$). There was no significant difference between the two groups as regards parent consanguinity, family history of RA, age at diagnosis, delayed diagnosis, or duration after diagnosis and before the biological treatment.

Table 4 showed that deformity was statistically higher among patients with primary failure than those with successful treatment (38.5% vs. 6.8%, $p = 0.0007$). There was no statistically significant difference between the two subgroups regarding arthritis pattern, number of painful joints, and other studied parameters. Moreover, non-concomitant MTX use was associated with biological therapy failure.

Regarding laboratory findings in Table 5, the OPF of biological treatment was significantly related to ESR, CRP, RF positivity, and anti-CCP positivity. In contrast, there was no statistically significant difference between the OPF of biological treatment and other lab parameters.

Concerning the concomitant intake of steroids, as demonstrated in Table 6, there was no statistically significant difference between patients with successful responses to biological treatment and patients with OPF.

As we can find in Table 7, the increased age, being smoker, earlier age at onset, presence of deformity, and positive anti-CCP at baseline were statistically significant predictors of overall failure (odds ratios are1.11, 32.3, 0.855, 8.5, and 6.48 respectively) in the studied cases, with the overall percentage predicted 70.1% by the combination of the previous factors.

Discussion

RA is a chronic inflammatory autoimmune disease that has a debilitating nature and a great effect on one's health. TNFi is one of the various lines of RA treatment usually used after failure of csDMARD with the aim of remission or LDA.

Table 3 The relationship between the overall primary failure (OPF) of biological treatment and characteristics of the studied RA patients

Characteristics of the studied cases	TNFi responder (44) *N* (%)	TNFi non-responder (43) *N* (%)	Test of significance
Age in years: (mean ± SD)	43.9 ± 12.1	51.7 ± 12.9	$t = 2.89$, $p = 0.005$*
Sex:			
- Males	15(34.1)	5(11.6)	$\chi^2 = 6.19$,
- Females	29(65.9)	38(88.4)	$p = 0.013$*
Smoking:			
- Never smoke	42(95.5)	22(51.2)	MC = 22.0,
- Ex-smoker	0 (0.0)	2(4.7)	$p < 0.001$*
- Smoker	2(4.5)	19(44.2)	
BMI:(kg/m^2)			
- Non-obese	34(77.3)	22(51.2)	$\chi^2 = 6.46$,
- Obese	10(22.7)	21(48.8)	$p = 0.01$*
Parent consanguinity:			
- Yes	4(9.1)	6(14.0)	$\chi^2 = 0.51$,
- No	40(90.9)	37(86.0)	$P = 0.477$
Family history of RA:			
-Positive	3(6.8)	2(4.7)	$\chi^2 = 0.18$,
-Negative	41(93.2)	41(95.3)	$p = 0.664$
Age of disease onset (years)	34.9 ± 11.2	29.9 ± 10.4	$t = 2.17$, $p = 0.038$*
Age at diagnosis (years)	33.6 ± 11.1	34.9 ± 11.4	$t = 0.55$, $p = 0.581$
Delayed diagnosis:			
-No delay/less than 1 year	18(40.9)	17(39.5)	
-1 year	21(47.7)	22(51.2)	$\chi^2 = 0.15$,
-2 years or more	5(11.4)	4(9.3)	$p = 0.927$
Duration after diagnosis and before biological treatment	Median (IQR) in years		
	8 (5–15)	9 (6–15)	$z = 0.49$, $p = 0.619$

TNFi tumor necrosis factor inhibitor, *N* number, *BMI* body mass index, *RA* rheumatoid arthritis, *IQR* interquartile range, *t* Student's *t* test, χ^2chi-square test, *MC Monte Carlo test*, *Z* Mann–Whitney *U* test

* $P \leq 0.05$ is considered statistically significant

Table 4 The relationship between the overall primary failure (OPF) of biological treatment and clinical presentation of the studied RA patients

Clinical presentation	TNFi responder (= 44) *N* (%)	TNFi non-responder (= 43) *N* (%)	Test of significance
Arthritis pattern:			
-Typical	43(97.7)	43(100)	FET = 0.98,
-Atypical	1(2.3)	0(0.0)	*P* = 1.0
Number painful joint:			
median (IQR)	11(8–16)	10(8–13)	*Z* = 0.99, *P* = 0.319
Number swollen joint:			
median (IQR)	6(4–8)	5(4–9)	*Z* = 0.17, *P* = 0.868
Morning stiffness:			
-1 h or less	2(4.5)	2(4.7)	
-2 h	24(54.5)	18(41.9)	MC = 2.75,
-3 h	17(38.6)	23(53.5)	*p* = 0.432
-4 or more hours	1(2.3)	0 (0.0)	
Weight loss:	3(6.8)	5(11.6)	$\chi^2 = 0.60, p = 0.438$
Fatigue:	34(77.3)	35(81.4)	$\chi^2 = 0.23, p = 0.635$
Pallor:	20(45.5)	26(60.5)	$\chi^2 = 1.97, p = 0.161$
Carpal tunnel syndrome:	0 (0.0)	1(2.3)	FET = 1.04, *P* = 0.494
Vasculitis& skin ulcers:	1(2.3)	0 (0.0)	FET = 0.98, *P* = 1.0
Deformity:	3(6.8)	17(38.5)	$\chi^2 = 11.37, p = 0.0007$*
Nodules:	3(6.8)	2(4.7)	$\chi^2 = 0.19, p = 0.67$
Co-morbidities:			
DM:	4(9.1)	9(20.9)	$\chi^2 = 2.39, p = 0.121$
Hypertension:	9(20.5)	7(16.3)	$\chi^2 = 0.25, p = 0.783$
Thyroid diseases:			
- Hypothyroidism	2(100)	3(75)	FET = 0.60,
- hHyperthyroidism	0 (0.0)	1(25)	*P* = 1.00
Cardiovascular	1(2.3)	1(2.3)	FET = 0.0, *P* = 1.0
Lung disease	2(4.5)	1(2.3)	FET = 0.32, *P* = 1.0
Osteoporosis	11(25)	4(9.3)	$\chi^2 = 3.76, p = 0.053$
Methotrexate concomitant use	40(90.9)	33(76.7)	$\chi^2 = 5.72, p = 0.016$*

TNFi tumor necrosis factor inhibitor, *N* number, *IQR* interquartile range, *DM* diabetes mellitus, *FET* Fisher's exact test, *Z* Mann Whitney *U* test, *MC* Monte Carlo test, χ^2 chi-square test

* $P \leq 0.05$ is considered statistically significant

In the current study, the OPF of the biological treatment in the studied patients was 49.4%. The primary failure was 35.3% for IFX, 58.3% for ETA, 50% for ADA, and 50% for GOL.

In Wijbrandts and Tak., 2017 [14] study, it was reported that the failure rate of TNFi was 30–40% in patients who formerly failed csDMARD therapy, including MTX. In addition, there was no specific factor that explains or predicts response to TNFi. Generally, about 40% of RA cases do not give a response to the first biologic or gradually lose responsiveness [5, 15].

In this study, compared to patients with successful responses to biological treatment, patients with primary failure were significantly older patients, females, smokers, obese, aged younger at the onset of the disease, and had a deformity.

A systematic review and meta-analysis reported that old age (more than 55 years), females, obesity, and smoking were the main variables accompanied by poor response to TNFi. This can be explained by the fact that older patients are at a higher risk of having a prolonged duration of disease and usually have co-morbidities at baseline that induce early biological agents' discontinuation [16]. It was also found that the innate and adaptive immune systems are impacted by aging. As we age, the innate immune system becomes less focused on its activity; this participates in increased chronic inflammation and co-morbidities [17]. Also, the adaptive immune

Table 5 The relation between the overall primary failure (OPF) of the biological treatment and the laboratory findings of the studied RA patients

Laboratory findings		TNFi responder (= 44) *N* (%)	TNFi non-responder (= 43) *N* (%)	Test of significance
HB	(1) Baseline:			
	- Normal	5(11.4)	6(14.0)	$\chi^2 = 0.13$,
	- Anemic	39(88.6)	37(86.0)	$p = 0.716$
	(2) After			
	3 months:	5(11.4)	7(16.3)	$\chi^2 = 0.44$,
	- Normal	39(88.6)	36(83.7)	$p = 0.506$
	- Anemic			
Platelets	(1) Baseline:			
	- Normal	41(93.2)	42(97.7)	FET, $p = 0.616$
	- Thrombocytosis	3(6.8)	1(2.3)	
	(2) After			
	3 months:	43(97.7)	42(97.7)	FET, $p = 1.0$
	- Normal-	1(2.3)	1(2.3)	
	- Thrombocytosis			
WBCS	(1) Baseline:			
	- Normal	43(97.7)	43(100)	FET, $p = 0.320$
	- Leukocytosis	1(2.3)	0 (0.0)	
	(2) After			
	3 months: - normal	44(100)	43(100)	
ESR	(1) Baseline:	68.5(15–83.6)	100(56–110)	$z = 2.5$, $p = 0.01$*
	(2) After 3 months:	36(20–59.8)	55(30–80)	$z = 2.28$, $p = 0.02$*
CRP	(1) Baseline:	12(6–25)	48(16–48)	$z = 2.68$, $p = 0.007$*
	(2) After 3 months:	10(6–12)	12(4.7–48)	$z = 1.14$, $p = 0.255$
SGPT	(1) Baseline:	22(2025–24)	22(21–24)	$z = 0.29$, $p = 0.804$
	(2) After 3 months:	22(20–23)	22(21–23)	$z = 0.74$, $p = 0.46$
SGOT	(1) Baseline:	22(21–24)	22(20–24)	$z = 0.03$, $p = 0.976$
	(2) After 3 months:	22(21–23.8)	22(21–24)	$z = 1.46$, $p = 0.143$
Serum creatinine	(1) Baseline:	0.720 ± 0.097	0.731 ± 0.187	$t = 0.34$, $p = 0.738$
	(2) After 3 months:	0.734 ± 0.101	0.752 ± 0.161	$t = 0.62$, $p = 0.538$
RF positivity	(1) Baseline:	16(36.4)	29(67.4)	$\chi^2 = 8.41$, $p = 0.004$*
	(2) After 3 months:	33(75.0%)	37(86.0%)	$\chi^2 = 1.69$, $p = 0.194$
Anti-CCP positivity	(1) Baseline:	23(52.3)	39(90.7)	$\chi^2 = 13.04$, $p = 0.001$*
	(2) After 3 months:	29(65.9)	37(86.0)	$\chi^2 = 4.82$, $p = 0.028$*

TNFi tumor necrosis factor inhibitor, *N* number, *WBCs* white blood cells, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SGPT* serum glutamic pyruvic transaminase, *SGOT* serum glutamic oxaloacetic transaminase, *RF* rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide, χ^2 chi-square test, *FET* Fisher's exact test, *Z* Mann–Whitney *U* test, *t* Student *t* test, *MC* Monte Carlo test

* $P \leq 0.05$ is considered statistically significant

system develops flaws and changes in phenotype with age, participating in the breakdown of immunological tolerance that results in an increased prevalence of AIDS [16]. In contrast, different researchers recorded no effects of age on response to TNFi [18, 19].

Along the same line, many researchers recorded that, with the same treatment, females had a worse prognosis of RA compared to males [20–22].

In addition, obesity was reported as an indicator of poor remission in patients receiving TNFi. The adipose tissue releases pro-inflammatory cytokines, which include TNF-α and interleukin-6 (IL-6). The high fat mass and levels of such cytokines could interfere with the medicinal responses [23]. In addition, being a current or ex-smoker reduces the response to TNFi. Chronic cigarette smoking triggers different morphological,

Table 6 The relation between overall primary failure (OPF) of the biological treatment and steroid intake in the studied RA patients

Steroid intake	*N*	TNFi responder (*n* = 44) *N* (%)	TNFi non-responder (*n* = 43) *N* (%)	Test of significance
Before biological therapy:				FET = 0.19, *P* = 0.664
- Yes	82	41(93.2)	41(95.3)	
- No	5	3(6.8)	2(4.7)	
Dose: median (IQR)		10(5–20)	10(5–20)	*Z* = 0.34, *P* = 0.731
After biological therapy:		*N* (%)	*N* (%)	$\chi^2 = 0.002$, *p* = 0.963
- Yes	73	37(84.1)	36(83.7)	
- No	14	7(15.9)	7(16.3)	
Dose: median (IQR)		5(5–10)	5(5–10)	*Z* = 1.15, *P* = 0.252

TNFi tumor necrosis factor inhibitor, *N* number, *IQR* interquartile range, *FET* Fisher's exact test, *Z* Mann–Whitney *U* test

Table 7 Predictors of the overall failure among studied cases

The predictors	*B*	*P* value	Odds ratio (95% CI)
Age: (years)	0.101	0.001*	1.11(1.04–1.17)
Sex:			
-Male(R)	1.09	0.179	21.98(0.606–14.68)
-Female			
Smoking:			
-Never smoke(R)	1		
-Ex-smoker	23.51	0.999	Undefined
-Smoker	3.48	0.002*	32.30(3.62–38.47)
Age of disease onset (years)	-0.122	0.001*	0.855(0.824–1.03)
BMI: (kg/m^2)			
-Non-obese	0.950	0.173	2.58(0.658–10.14)
-Obese			
Deformity:	2.14	0.049*	8.5(1.02–74.42)
ESR baseline:	0.01	0.197	1.01(0.994–1.03)
CRP baseline:	0.008	0.475	1.01(0.987–1.03)
RF baseline:	1.24	0.058	3.47(0.961–12.53)
Anti-CCP baseline:	1.87	0.018*	6.48(1.38–30.56)
Methotrexate use:	-21.72	0.99	Undefined
Overall % predicted = 70.1			

Binary logistic regression test

B beta regression coefficient, *CI* confidence interval, *BMI* body mass index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *RF* rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide

* $P \leq 0.05$ is considered statistically significant

physiological, and enzymatic changes. These changes impair inflammatory responses [24]. It acts on cellular and humoral immunity, causing systemic proinflammatory state [25].

The present study showed no difference between both groups as regards parent consanguinity, family history of RA, age at diagnosis, delayed diagnosis, duration after diagnosis and before the biological treatment, arthritis pattern, extra-articular manifestations, or disease complications.

Another study [16] concluded that disease duration, high TJC, and high SJC score at the diagnosis time were not significantly accompanied by a lower remission rate. In contrast, other studies reported that disease duration and disability were accompanied by lower remission rates [26, 27].

In this study, the OPF of biological treatment was significantly related to ESR, CRP, RF positivity, anti-CCP positivity, and non-MTX concomitant use. Similarly, a study [16] concluded that a lower remission rate accompanied by increased ESR and positive anti-CCP at the diagnosis time. On the other hand, regarding the relationship between both RF and anti-CCP at baseline and response to TNFi treatment, many studies reported contradictory results. Two studies [28, 29] reported that RF and anti-CCP at baseline significantly correlate with better response to TNFi. In contrast, other studies [30, 31] said the presence of RF or anti-CCP antibodies was accompanied by a decreased response to TNFi drugs.

In recent years, there has been no biomarker identified to predict response to TNFi in RA cases. RF was not significantly accompanied by poor response to TNFi; on the other hand, increased ESR was demonstrated to be a significantly poor predictor of remission, and cases with positive anti-CCP showed a high remission rate as a response to TNFi as concluded in a recent study [16]. Other research recorded no correlation between RF or anti-CCP positivity and the response to the therapy [32–34].

The anti-CCP positivity was accompanied by better responses to abatacept and adalimumab [35]. The anti-CCP binds to the Fc receptors, shown by immunological cells of the myeloid lineage, stimulating the complement system [36]. Most TNFi work on suppressing T cells, B cells, and their products of antibodies and cytokines; this partly clarifies their comparative efficiency in cases with positive anti-CCP [37].

In the current study, MTX was given to 83.9% of patients, with a good response of 54.8%. This agreed with a study [26] which reported that concurrent MTX therapy with TNFi therapies improves TNFi efficacy. Furthermore, a meta-analysis revealed that concurrent MTX therapy with TNFi improved the clinical response compared to biologic monotherapy [38]. Moreover, the combination of MTX to biological agents reduces the production of anti-drug antibodies and improves drug persistence [39].

The simultaneous MTX therapy improves the efficiency of low-dose IFX. However, the advantages of greater dosages of IFX are not clear [40]. Disease duration did not appear to interfere with the positive impact of IFX on radiological progression in RA patients [41]. In contrast, a recent study [16] concluded that prior or concurrent utilization of MTX was not significantly accompanied by a lower remission rate.

Although this study included all the available records of the patients who received TNFi, the sample size was small owing to financial limitations and neglected recording of some cases. Therefore, further studies with larger sample sizes are recommended.

Despite these limitations, this study has strengths; our prediction model used routine investigations, history taking, and clinical examination, which can be easily done without too much cost. Also, there is a lack of recent and up-to-date Egyptian studies in this area.

Conclusion

This record-based study demonstrated that increased age, being a smoker, earlier age of disease onset, presence of deformity, and positive anti-CCP at baseline were predictors of overall failure in the studied cases. Meanwhile, concomitant MTX intake increases the success rate by 9.6%.

Abbreviations

ADA	Adalimumab
AID	Autoimmune disease
Anti-CCP	Anti-cyclic citrullinated peptide
bDMARDS	Biologic disease-modifying anti-rhematic drugs
BMI	Body mass index
bs-IFX	Biosimilar infliximab
CBC	Complete blood count
CRP	C-reactive protein
csDMARDS	Conventional synthetic disease-modifying anti-rheumatic drugs
CV	Cardiovascular
CZP	Certolizumab pegol
DAS28	28-Joint disease activity score
DMARDS	Disease-modifying anti-rheumatic drugs
ESR	Erythrocyte sedimentation rate
ETN	Etanercept
GOL	Golimumab
IFX	Infliximab
IL	Interleukin
IQR	Interquartile range
LDA	Low disease activity
MTX	Methotrexate
OPF	Overall primary failure
PGA	Patient global assessment
QoL	Quality of life
RA	Rheumatoid arthritis
RBR	Risk-benefit ratio
RF	Rheumatoid factor
SJC	Swollen joint count
TJC	Tender joint count
TNFα	Tumor necrosis factor-alpha
TNFi	Tumor necrosis factor inhibitor

Acknowledgements

We thank the participants for their cooperation.

Authors' contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by A.K, D.M, S.H, and E.A. The first draft of the manuscript was written by A.K, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

All data is available upon request.

Declarations

Ethics approval and consent to participate

The Institutional Research Board (IRB), Faculty of Medicine, Mansoura University, Egypt (R.21.03.1276) approved this study.

Consent to participate

Consent is not applicable because the study was retrospective and was based on patients' data collection which was anonymized

Competing interests

The authors declare that they have no competing interests.

Received: 13 February 2024 Accepted: 21 May 2024
Published online: 30 May 2024

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