

# Effectiveness and Predictor Response of Biological Therapy in Rheumatoid Arthritis in Libya

**Aim:** Our study was to estimate effectiveness of biological therapy in Rheumatoid arthritis by using predictor response of function score, disease activity, and Pain score.

**Patient and method:** Follow up study patients were diagnosed as rheumatoid arthritis (RA). Those patients were studied clinically and functional disability assessed by the Health Assessment Questionnaire (HAQ score) and the Disease Activity Score in 28 joints (DAS 28).

**Result:** Ninety three patients with diagnosed rheumatoid arthritis were included in the study. Patients clinical characteristics are the age of the study patients ranged from (24-68years), M=(48 ± 13 year), 80 (86%) were female. The Mean DAS 28 activity at baseline was (4.4 ± 1.2), the mean health assessment questionnaire score (HAQ) of patients (1.2). The management of rheumatoid arthritis be combined methotrexate with biological therapy was 40 (43%) of patient on Infliximab, 24 (25.8%) of patient on Adalimumab, 19 (20.4%) of patient on Etanercept and 10 (10.7%) of patient on Rituximab at follow-up. Mean DAS 28 activity at 6 months in patients was 1.2-3.6 M=(2.3 ± 0.5), and Mean DAS 28 activity at 12 months in patients was 0.6-2.6 M=(1.2 ± 0.4) with significant Pvalue=0.000. Clinical improvement after biological therapy at 6 and 12 months measure by American College of Rheumatology (ACR) and improvement or EULAR Response with significant Pvalue=0.000, in addition greater improvement in health assessment questionnaire score (HAQ) after biological therapy from baseline with significant Pvalue=0.000 and improvement in pain score. Conclusion: The biologics therapy had effective decline disease activity in rheumatoid arthritis, improves function score and pain score and had significant benefits in outcomes for patients.

**Keywords:** biological therapy • disease modified anti rheumatoid drugs (DMARDs) • the Health Assessment Questionnaire (HAQ) • the Disease Activity Score in 28 joints (DAS 28) • rheumatoid factor (IgM-RF) • antibodies against citrullinated antigens (anti-CCP) • radiological score

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## Introduction

In recent years has been the development of novel biologic therapeutics in rheumatoid arthritis and other autoimmunity diseases. Biologic agents are engineered drugs that target specific inflammatory cells, cellular interactions, and cytokines that mediate rheumatoid arthritis related tissue damage [1]. The application of these principles in the management of patients with rheumatoid arthritis has resulted in significant improvement in the outcome [2]. Tight control involves reassessment of disease activity on a regularly with the use of quantitative composite measures and adjustment of treatment to quickly achieve and maintain control of disease activity [3]. Other factors in rheumatoid arthritis management that may influence the target or choice of therapy include Level of disease activity or

the disabilities or progressive joint damage or comorbidities, and prognostic factors [4].

## Patients and Method

Follow up study patients were diagnosed as rheumatoid arthritis (RA) according to 2010 ACR/ European League against Rheumatism (EULAR) Classification Criteria for Rheumatoid Arthritis, assessment clinically and laboratory test every 3 months. Those patients were studied clinically, history of fatigue, morning stiffness, number of joint pain or swollen functional disability assessed by the Health Assessment Questionnaire (HAQ). These questions are organized into eight categories: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Ranging from (0 to 3), 0=no difficulty, 1=some difficulty 2=much difficulty and 3=inability

to do. The Disease Activity Score in 28 joints (DAS 28), Ranges of DAS28 scores that correspond High disease activity DAS28 >5.1, Moderate Activity DAS28 >3.2 to 5.1, Low Disease Activity DAS28 2.6 to 3.2 and Remission DAS28< 2.6, and blood samples were obtained to evaluate the Erythrocyte sedimentation rate (ESR) (normal values ≤ 15 mm/1st hour in men and ≤ 20 mm/1st hour in female) and C-reactive protein (CRP) normal values ≤ 0.40mg/dl level and positive values >6 mg/dl, the presence of Rheumatoid Factor (IgM-RF) whereas a titre of IgM-RF >40 UI/ml was considered as positive and anti-cyclic citrullinated peptide (anti-CCP) antibodies positivity was >20 IU/ml.

**Response criteria**

Defined for both moderate and major changes in disease activity. The European League against Rheumatism (EULAR) response criteria are based upon the DAS28. Improvement into either good the decline in DAS score >1.2 and decline in DAS score 0.6 to 1.2 are moderate also use American College of Rheumatology (ACR)

response criteria ACR70, ACR50 and ACR20.

**Statistical analysis**

Data and statistical analysis was done using the Statistical Package for Social Science (SPSS) version 20. Descriptive Statistics included the mean and Standard Deviation (SD) for quantitative variables, and effective and percentage for categorical variables Differences between the categorical variables were tested using Paired T test and Chi square test.

**Result**

Ninety three patients with diagnosed rheumatoid arthritis were included in the study. Patient’s clinical characteristics are shown below (Table 1). The age of the study patients ranged from (24-68 years), M=(48 ± 13 year), 80(86%) were female, 13(13.9%) were male. the duration disease range from (2-28 year) M=[12 ± 7 year], 84(90.3%) of the patients had positive rheumatoid factors, 80(86%) of the patients had positive anti-cyclic citrullinated peptide (anti-CCP),

Age	24-68 years M=(48 ± 13Y)
sex	80 female (86%) 13 male (13.9%)
Duration disease	2-28year M=[12 ± 7y]
RF+	84(90.3%)
CCP+	80(86%)
Erythrocyte sedimentation rate (ESR)	(50-148)M=98 ± 24
C-reactive protein (CRP+)	88(94.6%)
Sub Cutaneous Nodule	13(13.9%)
Extra Articular Lung Fibrosis	8(8.6%)
Lanser score LS12 (0-5)	12-48 M=[29 ± 12.3]
Pain Score (1-5) Mild pain Moderate pain High pain Very high pain	11(12%) 34(37%) 33(35%) 15(16%)
HAQ(0-3)	0.3-3M=[1.2 ± 0.4]
DAS28	2.60-7.00 M=[4.4±1.2)
High DAS28 >5.1	28(30.1%)
Moderate DAS28 >3.2< 5.1	48(51.6%)
Low DAS28 >2.6< 3.2	17(18.3%)
Methotraxte	86(93%)
Infliximab	40(43%)
Adalimumab	24(25.8%)
Etanercept	19(20.4%)
Rituximab	10(10.7%)

13(13.9%) of the patients had positive Sub Cutaneous Nodule ,8(8.6%) of the patients had lung fibrosis and erythrocyte sedimentation rate (ESR) ranged from (50-148)M=98.1 ± 23.7.

The mean Radiological change assessment by Lanser score (LS12) 28.7 was reflect most of patients had grade in between 2 to 3 (narrow joint space and erosion).

Mean DAS 28 activity at baseline was (4.4 ± 1.2). Most patients had moderate or severe diseaseactivity. The mean health assessment questionnaire score (HAQ) of patients (1.2) was indicated moderate disability and 34(37%) of patients had moderate pain score followed 33(35%) of patients had high pain score, followed 15(16%) had very high pain score and 11(12%) had mild pain score.

Choice of therapy of rheumatoid arthritis according guideline methotrexate (MTX) was the most commonly prescribed 86(92.5%). As stated by recent updated 2016 European League Against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis be combined with biological therapy because of a superior efficacy of combination therapy choice of biological drug was 40(43%) of patient on Infliximab, 24(25.8%) of patient on Adalimumab, 19(20.4%) of patient on Etanercept and 10(10.7%) of patient on Rituximab at follow-up shown below (Table 2). Mean DAS 28 activity at 6 months in patients was 1.2-3.6M=(2.3 ± 0.5), and Mean DAS 28 activity at 12 months in patients was 0.6-2.6 M=(1.2 ± 0.4). Differences between Mean DAS 28 activity at baseline and 6 months or 12 months analyzed by Paired T test with significant Pvalue=0.000. We observed decline DAS 28 activity at 6 month in patients on Infliximab to (2-2.5), Adalimumab to (2.5-3), Etanercept to (2-2.5) and Rituximab to (≤ 2.5) we observed decline DAS 28 activity at 12 month in patients on all biological therapy to (1-1.5).

Clinical improvement after biological therapy at 6 and 12 months measure by American College of Rheumatology (ACR) improvement or EULAR Response shown below (Table 3). Most patient at 6 month follow up had ACR50(42%) follow ACR70(39%) then ACR20(19%) compared with 12 months most patient had ACR70(54%) follow ACR50(29%) then ACR20(17%)

**Table 2. Mean disease activity of RA patients on Biological therapy at Baseline, 6 and 12 months.**

DAS		P value
Baseline	2.6-7M =[4.4 ± 1.2]	0.000
6 Months	1.2-3.6M=(2.3 ± .5)	
12 Months	0.6-2.6M=(1.2 ± .4)	

**Table 3. Improvement criteria in rheumatoid arthritis on biological therapy.**

ACR improvement	6 months	12 months	Pvalue
ACR70	36(39%)	50(54%)	0.000
ACR50	39(42%)	27(29%)	
ACR20	18(19%)	16(17%)	
<b>EULAR Response</b>			0.000
Good	76(82%)	61(65.6%)	
Moderate	17(18%)	32(34.4%)	

with significant P value=0.000 analyzed by chi square test, other categorical EULAR Response at 6 month follow up (82%)patient had good EULAR Response and (18%) patient had moderate EULAR Response compared with 12 months (65.6%) patient had good EULAR Response and (34.4%) patient had moderate EULAR Response with significant P value=0.000, in addition greater improvement in health assessment questionnaire score (HAQ) after biological therapy from baseline with significant P value=0.000, and improvement in pain score.

**Discussion**

Rheumatoid arthritis is a chronic inflammatory disease affecting the synovium and leading to joint damage. Peak age of onset is in the fifth decade and females are two to three times more likely to be affected. Our patients had mean age (48 ± 13 years), (86%) were female affected [5,6]. Our patients had long standing disease with a mean 12 years, patients had disease long duration reflecting Daley referral patient or missed early diagnosis. The earliest predictors of both chronic and erosive disease are the presence of high titer Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Both are very good diagnostic and prognostic value. Our patients had (90.3%) positive Rheumatoid Factor (RF), (86%) positive anti-cyclic citrullinated peptide (anti-CCP) antibodies and (13.9%) positive Sub Cutaneous Nodule which help in diagnosis rheumatoid arthritis and prognostic value. Erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) will both be increased tend to correlate with disease activity in rheumatoid arthritis as well as radiologic progression in rheumatoid arthritis and may be useful for monitoring therapeutic response [7-9]. Our patients had (94.6%) positive C-reactive protein (CRP), mean erythrocyte sedimentation rate (ESR) 98 ± 24 reflecting disease activity in rheumatoid arthritis as well as radiologic progression in rheumatoid arthritis.

Radiographic changes in rheumatoid arthritis (RA) can be assessed by the method of Larsenscore (LS) based on

the analysis of 12 areas. Relevant areas in the hands and wrists and our study mean Larsen score (LS12) was  $29 \pm 12$  reflecting erosions and joint space narrowing.

Assessment of disease activity of rheumatoid arthritis, our patients had mean ( $4.4 \pm 1.2$ ) that reflecting high active disease, mean of Health Assessment Questionnaire (HAQ) was ( $1.2 \pm 0.4$ ) that reflecting moderate disability and our patients had (37%) moderate pain score then (35%) had high pain (16%) had very high pain, both pain score and HAQ are indicated active disease. The treatment of rheumatoid arthritis (RA) is start with conventional disease-modifying anti rheumatic drugs (DMARDs) therapy, methotrexate (MTX) is first drug started as soon as a diagnosis of rheumatoid arthritis (RA) has been made. Our study found (93%) of patient on methotrexate and other of patients non taken methotrexate due to intolerance drug or side effect.

Biological therapies are introduced in treatment of rheumatoid arthritis in Libya, infliximab was the first in 2006, adalimumab and rituximab in 2009, and etanercept was in 2010, According to recent ACR and EULAR recommendations [10], rheumatoid arthritis patients who may be candidates for biologics include patients with high disease activity, and those who have previously failed to respond adequately to conventional DMARD therapy. The choice of biologic treatment for rheumatoid arthritis (RA) depends on several factors, including patient and physician preference and drug availability in our country, (43%) of patients on infliximab, (25.8%) of patient on adalimumab, (20.4%) of patients on etanercept, (10.7%) of patient on rituximab, (93%) of patient combined with methotrexate and small number of patient monotherapy of biological therapy without methotrexate.

Biological therapy efficacy is frequently evaluated using Disease Activity Score (DAS 28) at follow-up we observed decline DAS 28 activity at 6 month, 12 month to  $< 2.6$  that achieved remission in rheumatoid arthritis, Differences between Mean DAS 28 activity at baseline and 6 months or 12 months with significant

Pvalue=0.000 that mean biologics therapy are highly effective in reducing rheumatoid arthritis symptoms and improving Disease Activity Score (DAS 28) [11-14], due to the small number lead to difficult Statistical compared efficacy in between groups of biological therapies.

Clinical improvement after biological therapy at 6 and 12 months measure by American College of Rheumatology (ACR) and improvement or EULAR Response, Most patient at 6 month follow up had ACR50(42%) follow ACR70(39%) then ACR20(19%) compared with 12 months most patient had increase ACR70(54%) follow ACR50(29%) then ACR20(17%) with significant Pvalue=0.000 other categorical EULAR Response at 6 month compared with 12 months EULAR Response with significant Pvalue=0.000, that means biologics therapy are highly effective slowing disease progression, and improving indices of physical function and quality of life [14-16].

All treatment groups showed decreases in HAQ scores with significant P value=0.000, indicating improvement in functional disability, at one year [17,18].

### Conclusion

The use of biologics therapy in the treatment of Rheumatoid Arthritis had significant benefits in outcomes for patients. Biologics therapy had effective decline disease activity in rheumatoid arthritis and improves function score and pain score.

### Limitation of study

1. Due to the small number lead to difficult Statistical Comparisons efficacy in between of etanercept vs infliximab, vs adalimumab and rituximab
2. The study cover the biology currently available for the treatment of Rheumatoid arthritis in Libya
3. Lack of data, monotherapy of biological therapy prescription

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