

Treatment Modalities and Comorbidities among Samples of Rheumatoid Arthritis in Baghdad Teaching Hospital, Baghdad, Iraq

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic inflammatory disorder that most commonly affects the joints, causing progressive, symmetric, erosive destruction of cartilage, and bone.

Objectives: To determine the association between comorbidities and treatment patterns (Disease-modifying antirheumatic drugs-DMARDs & biological therapy) in RA patients attending Baghdad teaching hospital, Iraq

Subjects and Methods: A descriptive; cross-sectional study conducted at Baghdad teaching hospital in Baghdad city (convenient sample) included 210 patients already diagnosed with RA. The data collection continued for the period starting on 1st December–2020 ending on 1st April 2021.

Results: Mean of the age of the studied sample was (50.81 years \pm 11 SD), duration of disease (12.7 \pm 8.2 SD) they were more frequently women 173 (82.4%), were married (80%), employed (20%), had primary education (38.6%) and (10.48%) smokers. The age group 50–59 years has the highest prevalence of RA (31.4%). Combination use of DMARDs and biological was reported in (94.3%) of the patients, while only (5.7%) of them use biological therapy without DMARDs. Methotrexate was the most common drug used by patients as a DMARD; it was used by (90%) of patients while other types in decreasing of frequency as a follow: Hydroxychloroquine (23.8%); Leflunomide (10.9%); sulfasalazine (1.4%). The mean duration of DMARDs use was (7.6 \pm 5.7 yr.). Different biological therapy is available in Iraq. The majority of patients on antitumor necrosis factors (86.7%) while only (13.3%) of them use rituximab. The mean duration of biological use was (4.2 \pm 2.5 yr.). Switching among biological drugs was observed in (35.2%) of patients. A significant association was reported between respiratory diseases and receiving biological therapies (Rituximab & TNF- Antagonist) at *P-value* = 0.005. Also, a significant association was detected between ischemic heart disease (IHD) and biological therapy (P.V= 0.003).

Conclusions: Rituximab was used more commonly in rheumatoid arthritis patients with interstitial lung diseases.

Recommendation: larger sample sizes would be needed to confirm this conclusion.

Keywords: Baghdad teaching hospital, Biological therapy, Rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune systemic inflammatory disorder, causing substantial morbidity and decreased quality of life and increased mortality and annual costs of billions of dollars. Prevalence is estimated to affect approximately 0.5 to 1 percent of the population worldwide and be twice as common in women than men.¹ The interaction of genetic and environmental factors results in a cascade of immune reactions, which ultimately lead to the development of synovitis, joint damage, and structural bone damage. These, in turn, lead to pain, disability, and emotional, social, and economic challenges. Several extra-articular manifestations and comorbidities are present in patients with RA, resulting in increased mortality.²

Joints that are mostly affected include the metacarpophalangeal (MCP) joints of the hand and metatarsophalangeal (MTP) joints of the feet.³ At the point of diagnosis, these joints present clinically with tenderness, swelling, and redness. Latterly, tissue degradation, joint subluxation, and fixed deformity can occur, leading to difficulties in walking or quality of life.⁴

Specific classification criteria have been developed used by rheumatologists as guidance to diagnose RA.⁵ These involve clinical indicators and serological tests, including autoantibodies and levels of rheumatoid factor. The recent classification 2010 criteria of RA require the existence of inflammation in at least one synovial joint and fulfill at least 6 out of 10 points from a scoring system with four domains:

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location and number of involved joints (range 0-5), presence of autoantibodies ACPA and or RF (range 0–3), duration of RA symptom ≥ 6 weeks (range 0-1) and raised the acute-phase reactants (range 0-1). These criteria have a specificity of 61% and sensitivity of 82% for RA.⁶

Treatments for RA help to decrease inflammation in the joints, prevent or slow down joint damage, relieve pain, reduce disability and improve quality of life.⁷ The first lines of management of RA are DMARDs; the most important one is methotrexate. Despite the effectiveness of these medications, some patients with RA experience failure even with combination or triple DMARDs and need another line of treatment. The use of biological therapy in the treatment of RA has revolutionized management in the last two decades.⁸

OBJECTIVE OF THE STUDY

To determine the association between comorbidities and treatment patterns (DMARDs & biological therapy) in RA patients attending Baghdad teaching hospital.

SUBJECTS AND METHODS

Study Design

A cross-sectional analytical study was conducted in Baghdad teaching hospital – Medical City – Baghdad.

Duration of Study

The data collection continued for four months, starting on 1st December -2020 ending on 2nd March 2021.

Place of Study

The place of study was in Baghdad teaching hospital in Baghdad city.

Inclusion and Exclusion Criteria of Study

Inclusion criteria: Rheumatoid patients who fulfilled ACR_EULAR 2010 criteria for the diagnosis of RA; who were aged 18 to 75 years received DMARDs & biological therapy of either gender accepted to participate in the study.

Exclusion criteria: those who stopped taking either type of medications (DMARDs & biological therapy) for more than three months, and who have other types of rheumatic diseases, including psoriasis.

Statistical Analysis

Data analysis was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences version 25). Categorical data were presented in simple measures of frequency, percentage whereas quantitative data was summarized by mean, standard deviation, and range (minimum, maximum values). The significance of different percentages (qualitative data) was tested using Pearson Chi-square test. Statistical significance was considered whenever the P-value was equal or less than 0.05.

RESULTS

The majority of RA cases were females 173 (82.4%), and 37 (17.6%) were males. The female to male ratio was 4.6:1. The mean age was (50.81 years \pm 11 SD), duration of the disease

(12.7 \pm 8.2 SD). The age group 50–59 years has the highest prevalence of RA (31.4%). As shown in Table 1; the majority of cases (168; 80.0%) were married, (206; 98.1%) lived in urban area, (42; 20.0%) employed, (81; 38.6%) had primary education and (22; 10.48%) smokers.

Different medications were used for the treatment of RA; DMARDs and biological therapy were mainstay therapy. Combination use of DMARDs and biological were reported in 94.3% of the patients, while only (5.7%) of them use biological therapy without DMARDs. Methotrexate was the most common drug used by patients as a DMARD; it was used by 90% of patients while other types in decreasing of frequency as a follow: Hydroxychloroquine (23.8%); Leflunomide (10.9%); sulfasalazine (1.4%). The mean duration of DMARDs use was (7.6 \pm 5.7 yr.). Different biological therapy is available in Iraq. The majority of patients on antitumor necrosis factors (86.7%) while only (13.3%) of them use rituximab. The mean duration of biological use was (4.2 \pm 2.5 yr.). Switching among biological drugs was observed in (35.2%) of patients, as reported in the Table 2.

This table shows that the highest percentages of those receiving Rituximab and TNF-Antagonist were exposed switching to another type of biological therapy (35.71%, 9.89%), respectively at significant level *P-value* = 0.0001. Similarly, significant associations were detected among those on biological therapy (Rituximab and TNF- Antagonist) with Salazopyrine (*P.V*= 0.006), as shown in Table 3.

Table 1: Distribution of studied sample according to demographic variables

Demographic variables	No.	%	
Age (years)	< 40years	36	17.14
	40–49	57	27.14
	50–59	66	31.43
	≥ 60 years	51	24.29
Gender	Male	37	17.62
	Female	173	82.38
Residency	Urban	206	98.10
	Rural	4	1.90
Occupation	Employed	42	20.00
	Unemployed	168	80.00
Marital status	Single	19	9.05
	Married	168	80.00
	Divorced	3	1.43
	Widow	20	9.52
Educational level	Illiterate	38	18.10
	Primary	81	38.57
	Intermediate	28	13.33
	Secondary	20	9.52
	College	42	20.00
Smoking	High college	1	.48
	Yes	22	10.48
	No	188	89.52

Table 2: Treatment of the studied patients

Type of medication	n=210	%
No DMARD *	12	5.7
DMARD		
Monotherapy	137	65.2
Two DMARD	55	26.2
Three DMARD	6	2.9
<i>Type of DMARDs</i>		
Methotrexate	189	90.0
Hydroxychloroquine	50	23.8
Leflunomide	23	10.9
Sulfasalazine	3	1.4
<i>Duration of DMARDs</i>		
<5DMARD	72	34.3
5---9	70	33.3
≥ 10DMARD	68	32.4
Mean ± SD (Range)	7.6 ± 5.7 yr.	(0–35)
<i>Biological agents</i>		
n=210		
TNF Antagonist**	182	86.7
Rituximab ***	28	13.3
<i>Duration of Biological agent</i>		
<5BIO	126	60.0
5---9	78	37.1
≥ 10BIO	6	2.9
Mean ± SD (Range)	4.2 ± 2.5 yr.	(1–15)
<i>Switching of Biological agent</i>		
Yes	74	35.2
No	136	64.8

*These patients use biological only. ** Include Etanercept, Infliximab, Adalimumab, Golimumab. ***Beta cell depleting agent

A significant association was reported between respiratory diseases and receiving biological therapies (Rituximab & TNF- Antagonist) at P-value=0.005. Also, a significant association was detected between ischemic heart disease (IHD) and biological therapy (P.V= 0.003). No association was found between (hypertension, diabetes mellitus, and thyroid diseases) and biological therapies statistically (P-value= 0.630, 0.372, 0.322).

DISCUSSION

RA is a systemic inflammatory, progressive autoimmune disease that involves peripheral joints, primarily small and medium-size, but large joints involvement such as knee joints occur. It's a worldwide disease 0.5- 1% of the population. This study was conducted on (210) patients with RA who fulfill ACR/EULAR 2010 criteria with mean age (50.8 ± 10.8 years).

Several rheumatic diseases are more frequent in females than males, including RA.¹ The present study showed that female patients were (82.4 %) while male patients were only (17.6%) and female to male ratio was 4.6:1. The finding is consistent with past studies by Faiq et.al.,⁹ Koehn et al.,¹⁰ which conclude that female to male ratio in 2019 in Iraq was 7.6:1. In contrast, Myasoedova et.al.,¹¹ Cross et.al.,¹² Itoh et.al.¹³ found that the ratio of females to males was 2-3:1. The difference in the ratio was due to differences in sample selection, but all showed a higher female to male ratio. The prevalence of RA in females more than males due to sex hormone changes that have been widely investigated based on changes in the clinical phenotypes observed during pregnancy and menopause.¹⁴

Table 3: Distribution of studied sample according to biological therapy and DMARD

		<i>Biological agent</i>						
		<i>TNF-Antagonist (n=182)</i>		<i>Rituximab (n=28)</i>		<i>Total</i>		
		<i>No</i>	<i>%</i>	<i>No</i>	<i>%</i>	<i>No</i>	<i>%</i>	<i>P.V</i>
Switching	Yes	18	9,89	10	35,71	28	13,33	0.0001*
	No	164	90,11	18	64,29	182	86,67	
	No	11	6,04	1	3,57	12	5,71	
<i>Therapy (DMARD)\</i>	Mono- therapy	121	66,48	16	57,14	137	65,24	0.377
	Two drugs	46	25,27	9	32,14	55	26,19	
	Three drugs	4	2,20	2	7,14	6	2,86	
Methotrexate	Yes	143	78,57	23	82,14	166	79,05	0.666
	No	39	21,43	5	17,86	44	20,95	
Arava	Yes	20	10,99	3	10,71	23	10,95	0.965
	No	162	89,01	25	89,29	187	89,05	
Salazopyrine	Yes	1	0,55	2	7,14	3	1,43	0.006*
	No	181	99,45	26	92,86	207	98,57	
Hydroxychloroquine	Yes	10	5,49	4	14,29	14	6,67	0.083
	No	172	94,51	24	85,71	196	93,33	
Predinsolone	Yes	52	28,57	8	28,57	60	28,57	1.000
	No	130	71,43	20	71,43	150	71,43	

Table 4: Biological therapy and comorbidities in RA patients

Comorbidities	Biological therapy						Total	P.V
	TNF- Antagonist (n=182)		RituximabC (n=28)					
	No	%	No	%	No	%		
HT	Yes	63	34,62	11	39,29	74	35,24	0.630
	No	119	65,38	17	60,71	136	64,76	
DM	Yes	27	14,84	6	21,43	33	15,71	0.372
	No	155	85,16	22	78,57	177	84,29	
Respiratory disease	Yes	5	2,75	4	14,29	9	4,29	0.005*
	No	177	97,25	24	85,71	201	95,71	
IHD	Yes	7	3,85	5	17,86	12	5,71	0.003*
	No	175	96,15	23	82,14	198	94,29	
Thyroid disease	Yes	6	3,30	2	7,14	8	3,81	0.322
	No	176	96,70	26	92,86	202	96,19	

The medications used for RA patients can prevent the structural changes of the involved joints and delay the further progress of the disease. Concerning therapies taking by rheumatoid patients in the current study, it was reported that (94.3%) of rheumatoid patients received DMARDs (65% single type of DMARDs, 26% dual therapy, and 3% were on triple therapy). Those patients used different DMARDs, but more than three quarters were used Methotrexate, and the lowest percentage use Sulfasalazine.

The present study was compatible with previous studies^{15,16} that Methotrexate was used by more than 85% of rheumatoid patients. And interfere with another study performed in London,¹⁷ in Japan^{18,19} in Paulo found that DMARDs were used by seventy percent of rheumatoid patients or less.

Another type of DMARDs, including Hydroxychloroquine used in 23% of Iraqi patients, in Egypt study²⁰ found that (>60%) of RA patients were using this type of DMARDs²¹ in Germany report lower than this percentages. Physicians recommend that 11% of the studied sample use Lefluomide compared to 52% of rheumatoid patients in China.²² Concerning Sulfasalazine, only 1% of the studied sample received it²⁰ in Egypt report 17% of patients were on Sulfasalazine.

Moreover; 65% of the studied sample use a single type of DMARDs and 29% in combination of two or three types of DMARDs; this differs from what has been found²³ in Egypt who reports that 11% of rheumatoid patients used monotherapy compared to 86% combined more than one type of DMARDs. In contrast²¹ in Germany report that 12.2% of patients in combining therapy. The variation in receiving DMARDs therapy may be due to differences in the guidelines in different countries.

Regarding biological therapies, this study shows that 86% of rheumatoid patients were on TNF-Antagonist compared to 13% who were using Rituximab. At the same time, 16% of rheumatoid patients were on Biological therapy in London.¹⁷ These differences are related to the tolerability of MTX intake by the patients. All recommendations and guidelines for treating RA worldwide use MTX as a first and mainstay therapy, but some patients cannot tolerate side effects as

it causes gastrointestinal complaints. Iraqi guideline for prescription of biologicals for rheumatoid patient stated use of a combination of two DMARDs; one of them is MTX in maximum tolerable dose, but still, some patients stop MTX by themselves up to 6% in this study. This study found that rituximab was used in 14% of patients with RA and interstitial lung disease (ILD) to slow progression as in Keir *et.al.*²⁴ and Ddruse *et.al.* (Table 4).²⁵

CONCLUSION

Rituximab was used more commonly in RA patients with interstitial lung diseases.

RECOMMENDATION

Earlier diagnosis of RA and effective therapy must be applied to prevent complications and deformities of the disease.

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