Methotrexate Use in Rheumatoid Arthritis-Related Interstitial Lung Disease (RA–ILD): Is It Beneficial?

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Abstract

Background :Rheumatoid arthritis patients often experience complications in their lungs, such as rheumatoid nodules, interstitial lung disease (RA-ILD), obstructive lung disease, bronchiectasis, obliterative bronchiolitis, drug-induced lung toxicity, and opportunistic infections due to immunosuppression. Since ILD plays such a crucial role in the natural history of RA, the role of methotrexate (MTX) as a DMARD for RA-ILD is hotly contested.

Objectives :was to determine whether or not Methotrexate improves lung function in people with interstitial lung disease caused by rheumatoid arthritis.

Patients and Methods :Fifty patients with RA and ILD were recruited from the outpatient clinic and inpatient units of the Physical Medicine, Rheumatology, and Rehabilitation Departments at Qena University Hospitals for this prospective hospital-based study. A complete history and physical examination were performed for all participants. The data collected included vital signs, complete cardio-pulmonary assessment, the related laboratory investigations and HRCT before and after treatment.

Results: The mean age of the study population was 48 years, with a female: male ratio of around 7:1, two thirds were from rural areas, while the other third were from urban ones. Envirnmental exposure of materials blamed to have a relation with ILD development was found in 42% of the cases, and smoking in 5 cases (10%), with 30% had family history of RA only, 10% had family history of ILD only and another 10% had positive family history of both RA and ILD. the mean disease duration was 5.8 years. we found that majority of the cases showed improvement of arthritis on MTX without combination with another DMARD or biologics (94%). The majority of the cases showed ILD improvement (74%). but, 14% of the cases did not improve and only 6 cases (12%) showed deteriorated ILD after MTX , with P value = 0.137.

Conclusion: Methotrexate showed a noticeable improvement of the RA associated ILD which can be attributed to the overall improvement of the disease.

Keywords: Methotrexate; RA; ILD; RA-ILD.

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Introduction

Between 0.5 to 1.0% of the world's population suffers from rheumatoid arthritis (RA), a chronic autoimmune inflammatory condition. While it is commonly associated with the joints, rheumatoid arthritis is also a systemic inflammatory disease that can have far-reaching effects on other organs as well, including the lungs. **(Kelly et al., 2016)**.

Pulmonary involvement encompasses a wide range of conditions, including rheumatoid nodules, interstitial lung disease (RA-ILD), obstructive lung disease, bronchiectasis, bronchiolitis, obliterative bronchiolitis, drug-induced lung toxicity, and opportunistic infections in the context of immunosuppression, which is detected in 40-70% of patients. **(Metafratzi et al., 2007 ; Paulin et al., 2021)**.

There is a substantial morbidity and death rate associated with RA-ILD, making it an important complication to consider. Yet, there is a wide variation in the severity of RA-ILD, with many cases having no symptoms at all or only mild ones despite (radiographic) indicators of ILD. According to statistics, The 1-year incidence of RA-ILD has been reported at 2.8% of population**(Hozumi et al., 2013 ; Hozumi et al., 2022)**.

According to different diagnostic procedures, and criteria employed, as well as the severity of RA in the study group the incidence of ILD in rheumatoid arthritis patients might range from 5% to 58%. The prognosis for ILD in general is depressing, but the prognosis for RA-ILD is particularly dismal, mortality risk of 2.86 times the national average. Among RA patients, among all causes of death, it ranks second, respiratory complications account for 13% of the disease's excess mortality. **(Bongartz et al., 2010 ; Maher et al., 2023)**.

There is a great debate about the effectiveness of methotrexate (MTX) as a disease-modifying antirheumatic medication (DMARD) for rheumatoid arthritis (RA) due to the prominent part ILD plays in the course of RA's natural history. Several researchers have found a link between MTX and ILD in RA, however this is still debatable. However, if RA is not well managed, it can lead to active systemic inflammation, which can then manifest as interstitial lung disease (ILD) or fibrosis in the typical pattern of usual interstitial pneumonia (UIP). Throughout the past few decades, the link between MTX and RA-ILD has received considerable attention. We now know regarding the correlation between MTX and RA-ILD is coincidental rather than causal, and that what really drives ILD is the underlying inflammatory process. In conclusion, RA-ILD is caused by the disease itself and not by the medication. **(Bongartz et al., 2010 ; Conway et al., 2017 ; Raimundo et al., 2019).**

Nowadays, Methotrexate is the cornerstone medication for managing RA, and there is significant evidence suggests that it enhances survival when used in medical treatment. **(Smolen et al., 2014 ; Smolen et al., 2023)**. The current work was to determine whether or not Methotrexate improves lung function in people with interstitial lung disease caused by rheumatoid arthritis**.**

Patients and Methods

Type of the study: A hospital-based prospective study.

Study Setting: The outpatient clinic and inpatient of Physical Medicine, Rheumatology, and Rehabilitation Department at Qena University Hospitals.

Study subjects: A total of 50 Rheumatoid arthritis (RA) patients who were diagnosed as having associated Interstitial lung disease (ILD).

Patients' selection criteria

Inclusion criteria:-

- Patients who have been classified as having RA according to the EULAR/ACR criteria from 2010 **(Aletaha et al., 2010)**.
- High-resolution chest CT scans have been used to diagnose patients with interstitial lung disease (ILD).
- Must be over the age of 18.

Exclusion criteria:-

- Other diseases associated with Interstitial lung disease (ILD).
- Other connective tissue diseases.

Calculating Sample Size

To determine a sufficient sample size, one can apply the following formula:

$$\mathrm{n} = \frac{z^2 p(1-p)}{d^2}$$

In prevalence study: where:

- n is the sample study.
- z is standard normal variant (at 5% type 1 error ($p>0.05$)) = 1.96.
- p is expected proportion in population based on previous studies or pilot studies = 3%.
- d is absolute error or precision = 0.05.

Confidence is the standard to shoot towards 95%. To establish a more representative sample size, we doubled the number of rheumatoid arthritis (RA) patients with ILD from 22 to 50.

Duration of Methotrexate treatment: We used methotrexate in rheumatoid arthritis (RA) patients associated with interstitial lung disease (ILD) for 6 months .

Methods

Each and every one of the participants was subjected to the following:-

- Complete record taking (personal history, drug history, family history, and surgery history).
- Checking of Vitals and Other General Parameters.
- Systematic examinations.
- Full Cardiopulmonary Examination.
- Investigations:
    - Laboratory (CBC, ESR, CRP, Rheumatoid factor, Anti-CCP).
    - Routine Lab (Liver enzymes, Renal function tests, Blood Glucose level).
    - Radiographic investigation (Plain X-ray of both hands and feet (AP view)
    - High Resolution CT chest.

Ethical clearance: A written consent was taken from all participants in the study. **Ethical approval code :** SVU-MED-PRR022-1-21-12-293

Measuring the Results of Research

- Primary (main): Determination Methotrexate's impact on rheumatoid arthritis-related interstitial lung disease using high resolution CT.
- Secondary (subsidiary): Analyzing the effect of methotrexate on Rheumatoid Arthritis using DAS-28.

Statistical analysis

The statistical analysis was done using IBM's Statistical Package for the Social Sciences (IBM-SPSS) version 25.0 (IBM, Chicago, USA, August 2017). Statistics presented include the mean, standard deviation (SD), number, and percentage. Mean and standard deviation were used to characterize quantitative data, whereas numbers and percentages were employed to explain qualitative information. Kappa analysis was used to examine whether or not there was a reduction among patients in RA Activity and ILD after 6 months of MTX treatment. in addition ,we evaluted the effect of MTX subjectively.

Results

Average age amongst participants was 48. **(Table.1)**. The vast majority of cases in the current study were females, with a female: male ratio of around 7:1. Two thirds of them were from rural areas **(Table.2)**.

Environmental exposure of materials blamed to have a relation with ILD development was found in 42% of the cases and 10% of the cases were smokers. Family history was seen in half of the cases, with thirty percent only have a family history of RA, 10% had family history of ILD only and another 10% had a positive family history of both RA and ILD **(Table.2)**.

Disease duration among the study population ranged from 1-15 years on average, with a mean of 5.8 years. **(Fig.1)**.

Table 1. Age of the study population.

Mean	48.04
Median	48.00
Std. Deviation	12.988
Minimum	24
Maximum	75

(Std : srandard)

Regarding the number of large joints involved in the study population, more than half of the studied cases had either no large joints (36%) or only one joint (16%), with a mean large joints involved of 1.4±1.3. On the other hand, regarding the small joints involved, most of the cases (96%) had at least 5 involved joints, and 40% had over 10 involved joints; with a mean small joint involved

of 9.1±3.3. Morning stiffness was seen in all of the cases and subcutaneous nodules in 16% of them (**Table 3**).

Table 2. Sex distribution , residence, Environmental exposure, family history and smoking of the study group.

Variables		No	Percent
Sex	**Male**	6	12%
	Female	44	88%
Residene	**Rural**	33	66%
	Urban	17	34%
Environmental exposure	**Yes**	21	42%
	No	29	58%
Family history (FH)	**FH of RA**	15	30%
	FH of ILD	5	10%
	FH of RA + ILD	5	10%
	Non	25	50%
Smoking	**Yes**	5	10%
	No	45	90%

(No: number , FH: family history , RA:rheumatoid arthritis , ILD: interstitial lung disease)

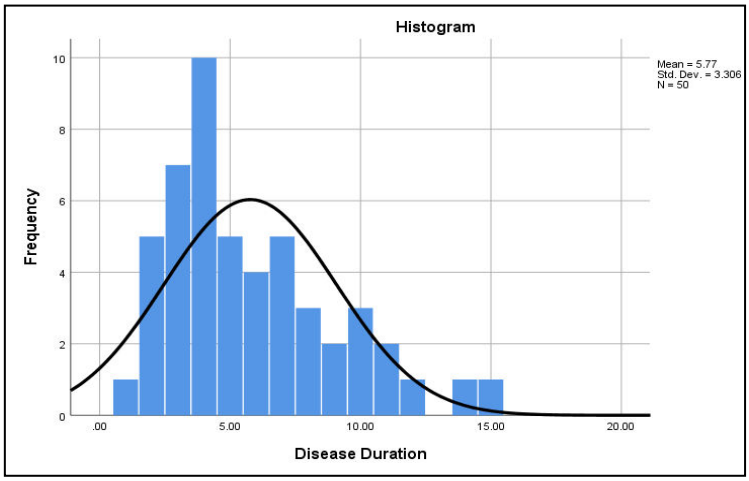

Fig. 1. Disease duration of Rheumatoid Arthritis among the study population (in years)

Table 3. Rheumatoid Arthritis manifestations.

Variables		No	Percent
Number of large joints involved	**0**	18	36%
	1	8	16%
	2	17	34%
	3 or more	7	14%
	Mean±SD	1.38±1.34	
Number of small joints involved	**0**	0	0
	1-4	2	4%
	5-9	28	56%
	10-15	18	36%
	16 or more	2	4%

	Mean±SD	9.08±3.28	
Morning stiffness > 60 minutes	**Yes**	50	100%
	No	0	0
Duration of symptoms	**> 6 weeks**	50	100%
	< 6 weeks	0	0
Subcutaneous nodules	**Yes**	8	16%
	No	42	84%

(SD : srandard deviation)

Most of the studied cases had very high ESR and CRP levels with a mean ESR of 66±33.4 mm/h (range 5-134) and a mean CRP of 48.6±38 mg/dL (range 5.2-174). Rheumatoid factor was positive in 64% of the cases and anti CCP in 76% of them **(Table.4)**.

Table 4. Laboratory investigations

Variables	Mean	Median	Std. Deviation	Minimum	Maximum
HGB	11.472	11.200	1.873	6.9	15.6
TLC	8.711	8.805	2.964	2.40	18.40
PLT	280.92	296.00	96.334	104	453
ESR	65.96	65.50	33.372	5	134
CRP	48.620	38.500	37.985	5.2	174.0
ALT	19.44	18.50	6.964	7	35
AST	21.20	20.50	6.649	8	33
Serum Creatinine	0.876	0.800	0.365	0.50	2.70
Serum Uric acid	4.758	4.800	0.975	2.99	6.50
RBS	144.06	131.00	53.670	75	277

(Std : srandard , HGB: hemoglobin , TLC: total leucocyte count , PLT: platelet , ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine Aminotransferase, AST: Aspartate Transferase, RBS: random blood suger)

Regarding the ILD manifestations, the most common manifestation was chronic dry cough and basilar fine crackles, seen in all cases. Also, dyspnea was present in all cases, with different grades ranging from grade 2 (44%), grade 3 (46%) and grade 4 (10%). On the other hand, chest pain was seen in 22% of the cases and hypoxia in 20% of the cases **(Table.5).**

Table 5.Interstitial Lung Disease manifestations

Variables		No	Percent
Chronic dry cough	**Yes**	50	100%
Dyspnea	**Grade 2**	22	44%
	Grade 3	23	46%
	Grade 4	5	10%
Chest pain	**Yes**	11	22%
	No	39	78%
Hypoxia	**Yes**	10	20%
	No	40	80%
Basilar fine crackles	**Yes**	50	100%

Regarding the rheumatoid arthritis response to MTX treatment, we found that the vast majority of cases improved on treatment (94%) **(Fig.2).**The vast majority of cases showed ILD improvement on treatment (74%). On the other hand, 14% of cases did not improve and only 6 cases (12%)

showed deteriorated ILD after therapy **(Fig. 3 , Table. 6 and Table.7).**

Table 6. Response of Rheumatoid Arthritis and Interstitial Lung Disease to Methotrexate.

Variables		No	Percent
RA	Improved	47	94%
	Not improved	3	6%
ILD	Improved	37	74%
	Not improved	7	14%
	Worsened	6	12%

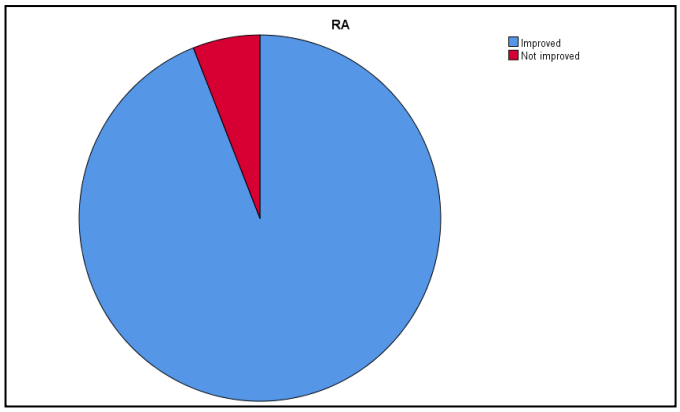

Fig.2. Rheumatoid arthritis treatment response after six months.

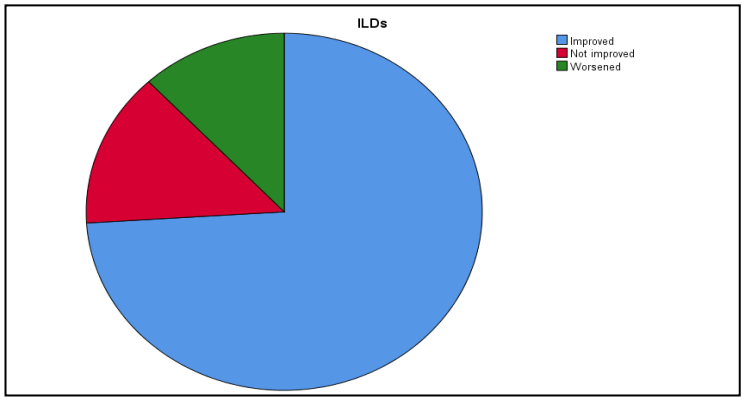

Fig.3. Interstitial lung disease treatment response after six months.

Table 7. Comparison between Rheumatoid arthritis and Interstitial Lung Disease response to treatment after 6 months.

Variables			RA		Total
			Improved	Not improved	
ILDs	Improved	No	37	0	37
		%	74.0%	0.0%	74.0%
	Not improved	No	7	0	7
		%	14.0%	0.0%	14.0%
	Worsened	No	3	3	6

		%	6.0%	6.0%	12.0%
Total		**No**	47	3	50
		%	94.0%	6.0%	100.0%

Kappa test = 1.468, P value = 0.137

Discussion

Rheumatoid Arthritis, or RA, is a autoimmune systemic inflammatory disorder that causes chronic joint pain with articular and extra-articular manifestations. pulmonary involvement is the most prevalent extra-articular symptom of RA, most of respiratory manifestations occur within the first 5 years of disease, although respiratory symptoms may precede onset of articular symptoms in 10–20% of cases (**Marigliano et al., 2013**). Although there is extensive heterogeneity among prevalence studies of pulmonary manifestations in RA depending on criteria for diagnosis, as well as radiographic imaging, ILD has the greatest estimated prevalence, followed by airway disease, pleural effusion and rheumatoid nodules (**Hyldgaard et al., 2017**).

ILD is the most common lung manifestation of RA, being detected in up to 60% of patients with RA on high-resolution computed tomography (HRCT), clinically significant in 10% of cases, and is a leading cause of illness and death in patients with RA (**Koduri et al., 2010 ; Juge et al., 2018**). It's important to note that there may be a relation between RA-ILD and the medications used to treat the disease as well (drug-induced ILD–DI-ILD). Methotrexate (MTX), leflunomide, and biologics all have been linked to DI-ILD. **(Alarcon et al., 1997; Yamazaki et al., 2010; Furukawa et al., 2013)**.

Clinical and radiological aspects distinguish DI-ILD from RA-ILD, with the former typically presenting with an acute or subacute course marked by cough, dyspnea, and fever and the latter typically presenting with bronchiolitis obliterans organized pneumonia. However, due to the non-specificity and overlap of clinical, radiological, and histological features, distinguishing RA-ILD from DI-ILD can be challenging in clinical practice. **(Fragoulis et al., 2019)**.

Before initiating DMARDs therapy, some individuals may have had mild ILD abnormalities (not seen on a standard chest X-ray). Furthermore, since many patients are given multiple DMARDs, Linking a specific DMARD to ILD may be difficult to prove (sequentially or in a combination therapy). There is still some uncertainty over whether or not DMARD use increases the risk of ILD. This is a very important question to answer, as stopping DMARDs therapy or opting for less aggressive treatment may have a detrimental effect on long-term prognosis and paradoxically raise the likelihood of RA-ILD and other extra-articular symptoms.**(Kur-Zalewska et al., 2021)**.

The current study's objective was to assess the impact of methotrexate on interstitial lung disease in RA patients so as to provide an estimate of the drug's potential positive effect.

In the current study only 10% of the cases were smokers. This was much different from the study of **(Kur-Zalewska et al., 2021)** where up to 55% of the cases were smokers. In the study of **(Juge et al., 2021)**, more than half of the cases were smokers, and this was more evident among RA-ILD cases compared to non ILD cases.

Disease duration among the study population ranged from 1-15 years on average, with a mean of 5.8 years. The study of **(Kur-Zalewska et al., 2021)** found that the disease duration was much longer, around 9.94 years.

In the current study, rheumatoid factor was positive in 64% of the cases and anti CCP in 76% of them. These figures were much lower than those of the **(Kur-Zalewska et al., 2021)** study, where the RF was positive in 83% of the cases and anti CCP in 86% of them. In the study of **(Juge et al., 2021)**, RF was positive in 77% of the cases and anti CCP in 86% of them, with non-significant association between serology and ILD development.

Regarding the rheumatoid arthritis response to MTX treatment in the current study, when patients were given appropriate care, we discovered that 94% showed considerable improvement. The vast majority of the cases showed ILD improvement on treatment (74%). On the other hand, 14% of the cases did not improve and only 6 cases (12%) showed deteriorated ILD after therapy.

According to the study of **(Kur-Zalewska et al., 2021)**, the risk of ILD development among their cases was significantly reduced in those who received methotrexate. Moreover, they found that this was a dose dependent effect of methotrexate, with more beneficial effect with rise of the MTX dose. However, they concluded that their results need to be confirmed by more studies.

Barrera et al., 1994 reported that treatment with DMARDs should protect against development of RA-ILD, as high disease activity is a very important risk factor. In contrast, ILD was recorded following almost all DMARDs, albeit its true scope is hard to gauge. DI-ILD is among the most worrisome MTX-related adverse effects. The highest prevalence found in research was 11.6%.

However, recent research suggests that this phenomenon occurs far less frequently. In a massive cohort study, there were only 6 occurrences of MTX-induced pneumonitis, or 0.9%. (673 patients, 1402 patient-years of treatment) **(Kinder et al., 2005)**.

0.43 % of patients on long-term MTX monotherapy developed MTX pneumonitis (15 instances among 3463 patients) (15% of 3463 patients) **(Salliot et al., 2009 ; van der Heijde et al., 2009)**.

Several DMARDs, including leflunomide and biologics, appear to carry a similar risk of drug-induced pneumonitis as MTX. There is some worry that DMARDs, and notably MTX, could cause or worsen rheumatoid arthritis-induced lung disease (RA-ILD). Yet, there is mounting evidence to support the idea that MTX use is not associated with the onset or worsening of RA-ILD. In addition, MTX has been shown to have a positive impact on the risk and course of RA-ILD in a number of trials. **(Roubille et al., 2014; Kur-Zalewska et al., 2021)**. Conway et al. reported that there was no association between MTX use and ILD in RA or non-RA inflammatory disorders, as shown by two meta-analyses of randomized controlled trials (**Conway et al., 2014 ; Conway et al., 2015)**.

Patients who received MTX as part of RA-ILD therapy had a better survival rate than those not receiving MTX (**Rojas-Serrano et al., 2017**).

After all, **Kiely et al., 2019**, discovered that not only was MTX treatment unrelated to an increase in the prevalence of RA-ILD diagnosis, but it also appeared to delay the development of ILD.

Juge et al., 2021 found similar results, concluding that MTX use did not correlate with an elevated risk for RA-ILD and that ILD was diagnosed much less frequently and later among MTX users than among non-MTX users.

Conclusion

Methotrexate showed a noticeable improvement of the RA associated ILD which can be attributed to the overall improvement of the disease.

List of Abbreviations

ACR : American College of Rheumatology.
Anti-CCP : Anti-citrullinated protein antibody.
AP : Antero-posterior.
CBC : Complete blood count.
CRP : C-Reactive protein.
DAS : Disease activity score.
DI-ILD : Drug induced interstitial lung disease.
DMARDs : Disease modifying antirheumatic drugs.
ESR : Erythrocyte sedimentation rate.
EULAR : European Alliance of Associations for Rheumatology.
FH : Familiy history.
HRCT: High resolution computed tomography.
ILD : Interstitial lung disease.
MED : Medical.
MTX : Methotrexate.
RA : Rheumatoid Arthritis.
RA-ILD : Rheumatoid Arthritis-Related Interstitial lung disease.
RF : Rheumatoid factor.
SD : Standard deviation.
SVU : South valley university.
UIP : Usual interstitial pneumonia.

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