An analysis of South African patients with rheumatoid arthritis with reference to methotrexate therapy retention

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Abstract

Background: Methotrexate (MTX) is a Disease-Modifying Antirheumatic Drug (DMARD) for treating various types of inflammatory arthritis, including Rheumatoid Arthritis (RA).
Objective: This article evaluates MTX retention rates and reasons for discontinuation in patients with RA in South Africa. The article also seeks to establish and draw attention to factors that may affect retention.
Method: The study population comprised of 230 patients with RA treated with MTX attending the Rheumatology Department of the Tygerberg Academic Hospital.
Results: Seventy nine patients (34.3%) terminated MTX and 151 patients continued giving a retention rate of 65.7%. The reasons for MTX termination were persistent high disease activity and presumed ineffectiveness (30.4%), nausea and vomiting (25.3%), non-compliance (11.4%), lung toxicity (8.9%), pregnancy-related (7.6%), and hepatotoxicity (5.1%). Clinical factors were not significant predictors of MTX adherence and MTX retention increased with age. Patients aged 65 years and older were twice as likely to have multiple comorbidities and were more likely to continue with treatment.
Conclusions: The duration of MTX treatment correlated with increased age. High retention rate of MTX is encouraging, as it remains the anchor drug among DMARDs in the treatment of RA. Further large scale, prospective, multicenter studies are needed to clearly understand MTX retention rates in patients with RA.

Key words: Methotrexate, Therapy, Retention, Rheumatoid Arthritis, Patients, South Africa

Introduction

Rheumatoid Arthritis (RA) is a chronic multiorgan autoimmune inflammatory disease. If untreated, RA results in poor clinical outcomes, including severe progressive structural joint damage, functional disabilities, and increased morbidity and mortality[1]. To avoid joint damage, inflammation in patients with RA should be suppressed as much as possible. The main goal of treating RA in patients is to improve their quality of life by reducing the symptoms and clinical disease[2]. This will lead to improving the functional outcome of patients with RA in the long term.

Methotrexate (MTX) is the most frequently used Disease-Modifying Antirheumatic Drug (DMARD) and remains an anchor therapy despite the advent of biological agents for treating RA. The combination of effectiveness and a commendable safety record, when compared to other DMARDs, renders MTX as the first-line treatment for most patients with RA[3]. MTX is extensively used for other autoimmune conditions such as psoriasis, uveitis, and inflammatory bowel diseases. Despite these advantages, there are limited reports on MTX retention rates.

To counter potential toxicity, steps are taken to ensure the safe use of MTX. Hepatotoxicity, gastrointestinal side effects (including nausea and diarrhoea), leukopenia and lung toxicity are well-documented side effects[4]. Considering hepatotoxicity, there are recommendations that patients have liver function tests performed before the commencement of MTX therapy, at least three times a year while receiving the therapy[5]. Some centers also perform routine Hepatitis B surface antigen (HBsAg) and Human Immunodeficiency Virus (HIV) screening. Prior to initiating MTX therapy, a history of liver disease or the use of hepatotoxic drugs, including alcohol should be addressed. This history is relevant as these agents may potentiate liver toxicity, in the setting of MTX use[3]. Folic acid is also used when a patient is on MTX. Folic acid protects the healthy cells in a patient's body by reducing the side effects of MTX; it makes a patient less likely to be vomiting or have diarrhoea[6].

Older patients and those with renal impairment should be monitored

more closely for the development of leucopenia[7]. Considering MTX being an immunosuppressive drug, chest radiographs are performed to exclude Pulmonary Tuberculosis (PTB) or co-existing lung disease[8]. Also, MTX being teratogenic, child-bearing females are routinely advised to use effective contraception or avoid its use if a pregnancy is planned. Patients are also informed of MTX's potential to temporarily reduce fertility in males[8].

Agarwal, *et al*[9] undertook a cross-sectional study to evaluate the retention rates of DMARDs in patients with RA. The study included 102 patients, and a total of 375 total DMARD courses were administered to these patients. The average retention time for MTX was found to be 28 months. This was slightly longer compared with the other DMARDs. The most common reason for DMARDs discontinuation was ineffectiveness (51.1%), followed by Adverse Events (AE) (24.3%) and the disease being considered under control (16.3%). The rest of the discontinuations were due to various reasons such as planned pregnancy (2.2%), concomitant comorbidities (2.2%), non-compliance (1.3%), financial reasons (1.1%), preference for alternative medical therapy (1.1%), and planned surgery (0.4%)[9].

A Norwegian study by Lie *et al.*[10] compared the efficacy and retention rates of MTX administered to patients with Psoriatic Arthritis (PsA) and RA. It was found that the 2-year retention rates of MTX treatment for PsA and RA were 65% and 66%, respectively. However, the reasons for treatment termination were similar among the two groups. It was also determined that after 6 months, there was an improvement in assessed disease activity and the patients' quality of life. This study also found out that Adverse Events (AEs) were the main reason for drug termination, followed by lack of efficacy, and that nausea was the most frequently reported AE, including elevated liver enzymes. A slightly higher proportion of patients with PsA (4.7%) than those with RA (3.3%) discontinued MTX because of elevated liver enzymes[10,11]. GIT toxicity related to methotrexate was the most common AE causing drug discontinuation in both groups.

Based on our understanding, no literature was published to address the question on MTX retention rates in South Africa. This study aimed to assess the rate of MTX retention and causes of MTX termination in South African patients with RA at Tygerberg Academic Hospital.

Materials and methods

This was a retrospective cross-sectional study conducted in the Tygerberg Academic Hospital's Division of Rheumatology. We identified 230 RA patients who had been administered MTX as a DMARD, over a six-month period. The study population included RA patients dating back to January 2009. The patients were between the ages of 19 and 90 years, and categorized into three age domains : namely young patients with RA (YRA; ≤ 40 years), middle-aged patients with RA (MRA; 41-65 years), and older patients with RA (ORA; > 65 years). Each enrolled patient was allocated a number under where their data were recorded to ensure anonymity. The details recorded for each participant were name (only on the confidential list linked to the allocated number), folder number, demographics (e.g., age, sex, and race), duration of disease, treatment, complications, and MTX dosage before treatment termination. Additionally, any adverse effects associated with MTX were recorded, and disease activity was monitored using the Clinical Disease Activity Index (CDAI)[12].

Historical information on basic laboratory test monitoring with full blood count tests and the participants' previous results of renal and liver function tests were collected. Screenings for recorded data relating to more specific tests, such as the serological method to determine the Rheumatoid Factor (RF), anti-Cyclic Citrullinated Peptide (anti-CCP test), and patients' HIV and viral hepatitis status were also performed.

The reasons for MTX termination were classified as AEs, ineffectiveness, non-compliance, and pregnancy related. An AE is any side effect, such as nausea and vomiting that resulted in the discontinuation of treatment. In effectiveness was defined as ongoing active disease despite MTX therapy as measured by the CDAI, and requiring a change in the drug regimen. Non-compliance refers to patients not taking their prescribed medication correctly. The three age groups (YRA, MRA, and ORA) are shown in Table 1.

Statistical analysis

Descriptive (summarized) statistics were used to explore our data. We report the measurement of the variability of the numerical variables as "mean" ± Standard Deviation (SD) for the variables following a normal distribution and as median [confidence interval] for the numerical variables that did not follow a normal distribution. The categorical variables were reported as "counts" (% Frequency).

To investigate potential differences of the variables between the "Age groups", and treatment continuity, a Fisher's Exact Test[13] for the categorical variables were conducted. Two survival analyses (Kaplan Meier and Cox Proportionate Hazards regression) were conducted, one for the "Days to treatment" and the other for the "Days to MTX termination", for the two groups of age "Age on diagnosis groups" and "Age groups".

For the survival analyses, the Kaplan-Meier[14] was used to estimate the survival probability each time an event occurs as well as compute survival curves. The statistical method was also used to investigate the null hypothesis of no difference in survival between two or more independent groups the Log Rank test was utilized. Finally, Cox proportional[15] regression models for each of the survival analyses were applied.

Results

Baseline characteristics and measures of associations

Gender: Across all age groups females dominated aged below 40 years (95.6%), 41-65 years (77.4%) and above 65 years (79.2%).

Table 1: Descriptive statistics of the participants stratified by the "Age groups"

Variables	Age groups			
	40 years and younger (N = 23)	41- 65 years (N = 159)	65+ years (N = 48)	P-value sig.
Gender				0.14
Female	22 (95.6%)	123 (77.4%)	38 (79.2%)	
Male	1 (4.3%)	36 (22.6%)	10 (20.8%)	
Ageat time of survey	33.3 ± 5.0	55.2 ± 6.2	72.9 ± 5.6	*< 0.01
Age at diagnosis	27.0% [23.5;30.5]	47.0% [40.0;54.0]	63.0% [56.0;66.5]	**< 0.01
Duration of treatment	248.0 [120.5;1355.0]	248.0 [11.0;620.5]	283.5 [113.0;887.5]	0.44
Starting †MTX dose (mg/W)				0.42
10/W	0 (0.0%)	3 (1.9%)	3 (6.3%)	
12.5/W	2 (8.7%)	23 (14.5%)	11 (22.9%)	
15/W	14 (60.9%)	88 (55.3%)	20 (41.7%)	
20/W	5 (21.7%)	27 (16.9%)	6 (12.5%)	
22.5/W	0 (0.0%)	0 (0.0%)	1 (2.1%)	
25/W	0 (0.0%)	1 (0.629%)	0 (0.0%)	
30/W	0 (0.0%)	1 (0.629%)	0 (0.0%)	
7.5/W	2 (8.7%)	16 (10.1%)	7 (14.6%)	
Other ‡DMARDS				0.39
§AZA	0 (0.0%)	2 (1.3%)	0 (0.0%)	
¶LEF	1 (4.3%)	9 (5.7%)	3 (6.3%)	
††MMF	1 (4.3%)	2 (1.3%)	0 (0.0%)	
None	15 (65.2%)	86 (54.1%)	34 (70.8%)	
Rituximab	1 (4.3%)	0 (0.0%)	0 (0.0%)	
‡‡SSZ	5 (21.7%)	51 (32.1%)	10 (20.8%)	
SSZ, LEF	0 (0.0%)	8 (5.0%)	1(2.1%)	
Treatment stopped	0.98			
No	15 (65.2%)	103 (64.8%)	30 (62.5%)	
Yes	8 (34.8%)	56 (35.2%)	18 (37.5%)	
Disease activity before MTX termination	18.7 ± 5.8	18.0 ± 9.9	18.7 ± 25.4	0.99
Disease activity after MTX termination	8.0 [5.0;11.5]	12.0 [6.5;15.0]	9.0 [6.5;11.5]	0.73
Comorbidity				***< 0.01
Multiple comorbidities	2 (8.7%)	53 (33.3%)	34 (70.8%)	
None	17 (73.9%)	61 (38.4%)	7 (14.6%)	
Single comorbidity	4 (17.4%)	45 (28.3%)	7 (14.6%)	
Complications of disease				0.09
Carpel Tunnel Syndrome	0 (0.0%)	0 (0.0%)	1 (2.1%)	
§§GERD	0 (0.0%)	3 (1.9%)	4 (8.3%)	
Multiple bone deformity	0 (0.0%)	1 (0.6%)	0 (0.0%)	
Necrotizing autoimmune myopathy	0 (0.0%)	1 (0.6%)	0 (0.0%)	
Nodular rheumatoid disease	0 (0.0%)	2 (1.3%)	0 (0.0%)	

Variables	Age groups			P-value
	40 years and younger (N = 23)	41- 65 years (N = 159)	65+ years (N = 48)	sig.
None	23 (100.0%)	145 (91.2%)	36 (75.0%)	
Osteoporosis	0 (0.0%)	3 (1.9%)	5 (10.4%)	
Panniculitis, Ruptured Baker Cyst	0 (0.0%)	1 (0.6%)	0 (0.0%)	
¶¶RA – †††ILD	0 (0.0%)	3 (1.9%)	2 (4.2%)	
Rheumatic disease				0.49
Giant Cell Arteritis/RA overlap syndrome	0 (0.0%)	1 (11.1%)	0 (0.0%)	
‡‡‡JIA/RA overlap syndrome	3 (75.0%)	1 (11.1%)	0 (0.0%)	
Psoriasis/RA overlap syndrome	0 (0.0%)	1 (11.1%)	0 (0.0%)	
Scleroderma/RA overlap syndrome	0 (0.0%)	1 (11.1%)	0 (0.0%)	
Seronegative RA	0 (0.0%)	2 (22.2%)	0 (0.0%)	
§§§ SLE / RA overlap syndrome	1 (25.0%)	1 (11.1%)	0 (0.0%)	

Note: Numerical variables that follow a normal distribution are expressed as mean ± standard deviation, and the numerical variables that do not follow a normal distribution are expressed as median [Confidence Interval]; the categorical variables are expressed as counts (%). The significant results ($p < 0.05$) are indicated as *p-value for Age, **p-value for Age at diagnosis, and ***p-value for Comorbidity. †Methotrexate; ‡Disease-modifying antirheumatic drugs;§Azathioprine; ¶Leflunomide; ††Mycophenolic acid;‡‡Sulfasalazine;§§Home conditions;¶¶Rheumatoid arthritis; †††Interstitial lung disease; ‡‡‡Juvenile idiopathic arthritis; §§§Systemic lupus erythematosus

Age at time of survey: Twenty-two participants were within the age of 28.3 and 38.3 years, 159 participants were within 49.0 and 61.4 years, and 48 participants were within 67.3 and 78.5 years.

Age at diagnosis: Sixty-three per cent were >65 years of age, 47% were 41-65 years, and those aged below 40 years (27%).

The retention rates of MTX: Retention rates were similar among different age groups (65.2% (young people) vs 64.8% (41-65 years) vs 62.5% (65+ years). Those who discontinued treatment also did not differ in terms of age groups.

Comorbidities: Participants who had multiple comorbidities were twice as likely to be aged above 65 years (70.8%), compared to those aged 41-65 years (33%), and those aged below 40 years (8.7%). Those with single comorbidities were more likely to be aged 41-65 years (28.3%), compared to other age groups. Those who had no comorbidities were more likely to be younger than 40 years of age.

Complications of disease: Only 10% of patients experienced complications of their disease ($p<0.1$). The older age group (65+ years) have experienced more complications (75%) compared to those aged 41-65 years (91.2%) or those aged less than 40 years (100%). Carpel Tunnel Syndrome, GERD (Gastroesophageal Reflux Disease), osteoporosis, Ruptured Baker Cyst, multiple bone deformity, and most other complications did not occur among those aged less than 40 years.

Non-significant factors

Starting MTX dosage: The most common MTX starting dose was 15mg per week. Although 12.5mg was more common in older patients. A starting dose on >20mg/ week of MTX was rarely used.

Disease activity before MTX termination: The results suggest that there were no differences between the three age groups, YRA (18.6%) and those aged 41-65 years (18.7%) or those aged 65+ years (18.7%) in terms of disease activity before MTX termination.

Disease activity after MTX termination: The results suggest that there were no differences between the YRA (8%) and those aged 41-65 years (12%), or those aged 65+ years (9%) in terms of disease activity after MTX termination.

Other DMARDs: The results show that other DMARDS used in combination with MTX were not predominant in this sample. MTX monotherapy was more likely among the aged 65+ years (70%) as compared to the other two groups (54% and 65.2%, respectively). The combination of DMARDs, namely: MTX, SSZ & LEF and MTX and LEF were more likely to be used in the MRA (41-65 years) age group. Rituximab was used in one patient only aged below 40 years.

Rheumatic disease association: The association with other rheumatic diseases were observed more among those aged less than 40 years (75%), followed by those aged 41-65 years (11.1%) and none among patients aged

Table 2: Tabularized illustration of treatment stopped

Variables	Treatment stopped		P-value sig.
	No	Yes	
	(N = 148)	(N = 82)	
Gender			0.497
Female	119 (80.95%)	63 (76.83%)	
Male	28 (19.05%)	19 (23.17%)	
Age	56.58 ± 11.83	56.84 ± 12.62	0.876
Age at diagnosis	48.45 ± 12.44	45.59 ± 12.95	0.101
Duration of treatment (Days to treatment)	249.50 [55.00;603.00]	258.00 [11.00;620.50]	0.995
Starting †MTX dose (mg/W)			0.592
10/W	4 (2.70%)	2 (2.44%)	
12.5/W	20 (13.51%)	16 (19.51%)	
15/W	79 (53.38%)	43 (52.44%)	
20/W	28 (18.92%)	10 (12.20%)	
22.5/W	1 (0.68%)	0 (0.0%)	
25/W	1 (0.68%)	0 (0.0%)	
30/W	0 (0.0%)	1 (1.22%)	
7.5/W	15 (10.14%)	10 (12.20%)	
Comorbidity			0.501
Multiple comorbidities	53 (35.81%)	36 (43.90%)	
None	57 (38.51%)	28 (34.15%)	
Single comorbidity	38 (25.68%)	18 (21.95%)	
Other ‡DMARDS			*0
§AZA	1 (0.68%)	1 (1.22%)	
¶LEF	1 (0.68%)	12 (14.63%)	
††MMF	2 (1.35%)	1 (1.22%)	
None	107 (72.30%)	28 (34.15%)	
Rituximab	1 (0.68%)	0 (0.0%)	
‡‡SSZ	35 (23.65%)	31 (37.80%)	
SSZ, LEF	1 (0.68%)	8 (9.76%)	
SSZ, MMF	0 (0.0%)	1 (1.22%)	
Complications of disease			0.073
Carpel Tunnel Syndrome	1 (0.68%)	0 (0.0%)	
§§GERD	7 (4.73%)	0 (0.0%)	
Multiple bone deformity	0 (0.0%)	1 (1.22%)	
Necrotizing autoimmune myopathy	0 (0.0%)	1 (1.22%)	
Nodular rheumatoid disease	1 (0.68%)	1 (1.22%)	
None	131 (88.51%)	73 (89.02%)	
Osteoporosis	6 (4.05%)	2 (2.44%)	
Panniculitis, Ruptured Baker's Cyst	0 (0.0%)	1 (1.22%)	
¶¶RA – †††ILD	2 (1.35%)	3 (3.66%)	

The significant results ($p < 0.05$) are indicated as *p-value for DMARDS, †Methotrexate; ‡Disease-modifying antirheumatic drug;§Azathioprine; ¶Leflunomide; ††Mycophenolic acid; ‡‡Sulfasalazine; §§Home conditions; ¶¶Rheumatoid arthritis; †††Interstitial lung disease

65+ years. Seronegative RA was observed only among those in the MRA (41-65 years) age group and JIA in the YRA (<40 years) age group only.

Measures of associations between correlates of MTX and duration of treatment

When the treatment stoppage/continuation is the dependent variable, observation shows that other DMARDS and complications of disease were associated with treatment continuity as illustrated in Table 2.

Significant factors

Exposure to DMARDS: The majority of patients were prescribed MTX monotherapy and a third (34.2%) combination DMARD therapy. Out of the 95 patients who were prescribed other DMARDS, 67 received SSZ and 22 received LEF as add on therapy. MTX & SSZ, MTX & LEF, and the combination of MTX/SSZ & LEF were the three most prevalent DMARD combinations in this study.

The complications of disease: Ten percent of patients experienced complications of their disease ($p<0.1$), 6/8 patients with osteoporosis (75%) all seven with GERD complications and other complications all patients with multiple bone deformities, necrotizing autoimmune myopathy, panniculitis or Ruptured Baker's Cysts were more likely to continue with treatment. There were no differences in terms of retention rates of MTX among patients with RA related-ILD, and those with rheumatoid nodules.

Comorbidities: The results show that there were no differences overall between patients who had comorbidities and those without, for retention of MTX treatment. Patients with multiple comorbidities however were more likely to discontinue treatment (43.9% vs 35.8%), compared with those with a single comorbidity (25.7% vs 22%).

Starting MTX dose(mg/week): Results indicate that overall the initial MTX dose was not associated with treatment continuation or stoppage.

Table 3: Tabularized illustration of causes of termination

Variables	N	Descriptive statistics	Class
Cause of termination	79		Categorical
†GIT toxicity, nausea and vomiting		20 (25.32%)	
High disease activity - ineffectiveness		24 (30.38%)	
Hepatotoxicity		4 (5.06%)	
Lung toxicity		7 (8.86%)	
‡MTX induced leucopoenia		4 (5.06%)	
Non-compliance		9 (11.39%)	
Pregnancy-related		6 (7.59%)	
§PTB		3 (3.80%)	
Renal toxicity		1 (1.27%)	
Skin infection		1 (1.27%)	

Demographic factors: Neither gender or age were associated with retention in MTX; the same applies to days to treatment/duration of treatment, those whose mean days of duration was higher, were more likely to continue with treatment (258 days vs 249 days). Results suggest that the longer the duration of treatment, the more likely the patient would be to continue with MTX treatment.

Reasons for termination

Seventy-nine (34%) of the 230 patients stopped and 151 (66%) continued taking MTX. High disease activity (ineffectiveness) (30.4%) and GIT toxicity (nausea and vomiting) (25.3%) were the main reasons for termination and other causes are listed in the Table 3.

Survival analysis

The study sought to investigate factors that were predictors of MTX treatment duration and termination. MTX termination was classified as AEs, ineffectiveness, non-compliance, and pregnancy related. The following two models provide the results in Tables 4 and 5, respectively. For 'days to treatment', age on diagnosis group (60, 80) were 2.2 times more likely to associate with days to treatment ($\beta=2.2$, $p<0.05$), compared to the younger age groups, while the age group (20,40) demonstrated the lowest times to be associated with days to treatment ($\beta=0.7$, $p<0.05$). The older the age group, the more the number of days to treatment shown in Table 4. For 'days to MTX termination', age on diagnosis group (60,80) were nine times more likely to experience fewer days to MTX termination ($\beta=9.0$, $p<0.05$), while the youngest

Table 4: Cox proportional hazards regression model for the "Days to treatment"

Variables	coef	se(coef)	Z-value	P-value sig.
Gender (Male)	0.062	0.165	0.375	0.708
Age groups (41- 65 years)	-0.546	0.294	-1.858	0.063
Age groups (65+ years)	-1.319	0.390	-3.378	*0.001
Age on diagnosis groups (20,40)	0.688	0.556	1.238	0.216
Age on diagnosis groups (40,60)	1.459	0.591	2.470	**0.014
Age on diagnosis groups (60,80)	2.236	0.667	3.353	***0.001

Score (logrank) test = 27.11 on 6 df, $p < 0.01$ The significant results ($p < 0.05$) are indicated as *p-value for Age groups (65+ yrs.), **p-value for Age on diagnosis groups (40,60), and ***p-value for Age on diagnosis groups (40,60).

Table 5: Cox proportional hazards regression model for the "Days to MTX termination"

Variables	Coef	Z-value	P-value sig.
Gender (Male)	-0.611	-1.617	0.106
Age groups (41-65yrs.)	-2.026	-2.796	*0.005
Age groups (65+ yrs.)	-5.383	-4.907	**9.23E-07
Age on diagnosis groups (20,40)	2.712	2.528	***0.011
Age on diagnosis groups (40,60)	4.647	3.806	****0.000
Age on diagnosis groups (60,80)	9.068	5.432	*****5.57E-08
First †MTX dose (12.5/W)	0.927	0.77	0.442
First MTX dose (15/W)	1.846	1.574	0.115
First MTX dose (20/W)	1.829	1.497	0.134
First MTX dose (22.5/W)	NA	NA	NA
First MTX dose (25/W)	NA	NA	NA
First MTX dose (30/W)	0.856	0.542	0.588
First MTX dose (7.5/W)	1.347	1.145	0.252
Comorbidity (None)	0.097	0.232	0.816
Comorbidity (Single comorbidity)	-0.578	-1.39	0.164
Other ‡DMARDs (§LEF)	-0.291	-0.234	0.815
Other DMARDs (¶MMF)	-0.164	-0.089	0.929
Other DMARDs (None)	0.022	0.018	0.986
Other DMARDS (Rituximab)	NA	NA	NA
Other DMARDs (††SSZ)	0.051	0.042	0.967
Other DMARDs (SSZ, LEF)	-0.533	-0.432	0.666
Other DMARDS (SSZ, MMF)	NA	NA	NA
Complications of disease (‡‡GERD)	NA	NA	NA
Complications of disease (Multiple bone deformity)	-1.306	-0.928	0.353
Complications of disease (Necrotizing autoimmune myopathy)	1.605	1.000	0.317
Complications of disease (Nodular rheumatoid disease)	-1.342	-1.003	0.316
Complications of disease (None)	0.1789	0.205	0.838
Complications of disease (Osteoporosis)	2.033	1.515	0.129
Complications of disease (Panniculitis, Ruptured Baker Cyst)	2.927	1.851	0.064
Complications of disease (§§RA – ¶¶ILD)	NA	NA	NA

Note: Score (logrank) test = 60.72 on 24 df, $p < 0.01$ The significant results ($p < 0.05$) are indicated as *p-value for Age groups (41-65yrs.), **p-value for Age groups (65+ yrs.), ***p-value for Age on diagnosis groups (20,40), ****p-value for Age on diagnosis groups (40,60), and *****p-value for Age on diagnosis groups (60,80). †Methotrexate; ‡Disease-modifying antirheumatic drugs;§Leflunomide; ¶Mycophenolic acid; ††Sulfasalazine; ‡‡Home conditions; §§Rheumatoid arthritis; ¶¶Interstitial lung disease.

age group (20,40) were least likely to experience fewer days to MTX termination (β=2.7, $p<0.05$) as shown in Table 5.

Discussion

In RA, medication adherence is highly variable and typically suboptimal, with reports of adherence to conventional Disease-Modifying Antirheumatic Drugs (DMARD) ranging from 22% (underuse) to 107% (overuse)[18]. Also given the prevalence of MTX use and its usage in combination treatment with other agents including increasingly with biologics, it is important to understand factors that may cause patients to be non-adherent or to discontinue MTX treatment[17,20,21].

In our study, the large majority (65.7%) of patients continued with MTX either alone or in combination with MTX & SSZ, MTX & LEF, and the triple combination of MTX/SSZ & LEF being the most prevalent. Two causes of MTX termination dominated this sample, high disease activity, ineffectiveness (30.4%) and GIT toxicity, nausea and vomiting (25.3%). Other factors for MTX termination included non-compliance (11.4%), lung toxicity, pregnancy related and liver toxicity.

While only 10% of our study population had complications of their disease, the most common being osteoporosis and GERD. Continuation of MTX therapy was the rule including all the patients with GERD. The presence of a comorbidity was not a predictor of the duration of MTX treatment. Those with a single comorbidity were marginally more likely to continue with MTX treatment compared to patients with multiple comorbidities. The most common starting dose for MTX in our study was 15mg/week. Older patients usually commenced with 12.5mg/week, rarely 20mg. While the starting dose of MTX was not in itself a predictor for MTX retention patients receiving the higher starting dose of 20mg/week were more likely to continue with treatment.

Gender was not associated with MTX retention rates although females were slightly more likely to continue with treatment and males were slightly more likely to discontinue treatment. There were no differences at all in terms of age; and results indicate that there were no differences between age at diagnosis and MTX retention rates. The same applies to duration of treatment, but patients with a longer treatment duration are more likely to continue with treatment.

A statistical association between two variables merely implies that knowing the value of one variable provides information about the value of the other. It does not necessarily imply that one causes the other[18], hence the following sections use survival analysis to compliment the association results.

Predictors of days to MTX termination

In this study, reasons for MTX termination were classified as AEs, ineffectiveness, non- compliance, and pregnancy related. A previous narrative review found no clear pattern in factors that influence medication adherence in patients with RA[17]. The Cox proportionate results indicate that the age group of patients was a significant predictor of days exposure to MTX termination (duration of MTX treatment). These results imply that days to MTX termination (duration of MTX treatment) increased with age group). Additionally, MTX termination decreased with age as chances of exposure to MTX termination among those diagnosed at age 40-60 years was 4.6 times, and least among those diagnosed at age 20-40 years. Given the prevalence of MTX use and its usage in combination treatment with biologics, it is important to understand factors that may cause patients to be non-adherent or to discontinue MTX treatment[16,19,20].

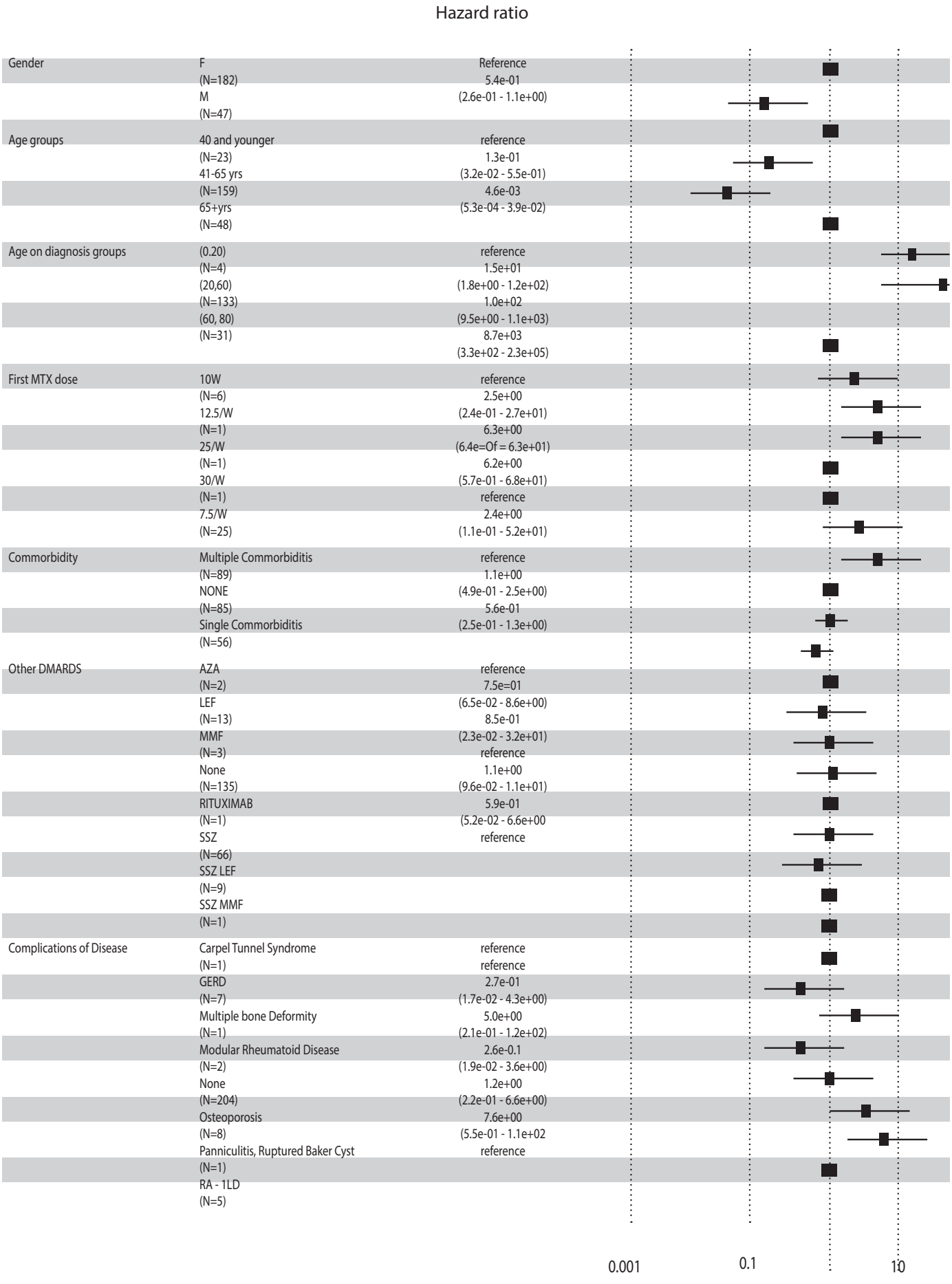
This study provides evidence that MTX dose was not a predictor of duration of treatment (months). However, the study findings highlight that the initial MTX dose was likely to occur between 15 and 20mg/week. In addition, comorbidity was not a predictor of duration of MTX treatment. The results, however, provide clinically relevant insights that those with a single comorbidity were less likely to have a shorter treatment duration, compared to those who had no comorbidity. Further results indicate that all categories of other DMARDS did not predict duration of treatment in this sample. Complications of disease categories were not significant predictors of duration of MTX treatment. Studies suggest that three complications (Panniculitis, Ruptured Baker Cyst, and Osteoporosis) had between 2-3 times greater possibility of increasing the duration of MTX treatment. In contrast, multiple bone deformity complications decreased MTX treatment duration by as much as 1.3 times. Despite these results, it should be noted that MTX is recommended as a first-line treatment in patients with active RA[19], and comorbidity and other DMARDS could be important factors to consider.

Predictors of duration of MTX treatment (Table 5)

The Cox proportionate Hazard results indicate that the older the patient, the more likely they were to remain on MTX treatment. In comparison, younger age groups are more likely to be exposed to shorter treatment duration (Appendix Figure 1).

The Cox proportionate Hazard results indicate that the older the patient, the more likely they were to remain on MTX treatment. In comparison, younger age groups are more likely to be exposed to shorter treatment duration.

Figure 1: A graphical representation of the 'days to MTX termination'



#Events: 75; Global p-value (Log-Rank): 1.8509e-05
AIC; 488.03; Concordance Index 0.78

Limitations and potential shortcomings

The main limitations of this study are its retrospective single-center design. Furthermore, this study did not include demographic factors such as marital status, education level, and other socioeconomic factors, and we could not assess corticosteroid use. Other important factors such as HIV and TB were also not assessed in this study. Lastly, this sample is most unlikely to be a representative of the general population. However, it included a relatively large number of patients who underwent MTX treatment in tertiary level referral hospitals.

Conclusions and recommendations

This study observed that demographic and clinical factors were not significant predictors of MTX adherence. The study provides evidence that age group was a predictor of clinical outcomes with regards to RA. The duration of MTX treatment correlated with increased age. Further results indicate that those who were aged above 65 years, were twice as likely to have multiple comorbidities, and those with multiple commodities were more likely to continue with treatment.

The retention rate for MTX is 65.7%. Adverse events were the most common reason for MTX termination among South African RA patients at TBH, followed by ineffectiveness. Two causes of MTX termination dominated this sample, high disease activity, ineffectiveness (30.4%) and GIT toxicity, nausea and vomiting (25.3%). Other factors for MTX termination included non-compliance (11.4%), lung toxicity, pregnancy related and liver toxicity. The fact that MTX has a high retention rate is encouraging, as it remains the anchor drug among DMARDs in the treatment of RA in resource constrained settings like SA.

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