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Prescribing Patterns of Methotrexate in Libyan Patients with Rheumatoid Arthritis

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ABSTRACT

Chronic rheumatoid arthritis (RA) is a systemic inflammatory disease that leads to cartilage and bone erosion. Untreated disease is linked with joint deformity and substantial health care related costs. Conventional disease-modifying anti-rheumatic drugs (DMARDs) are the main tool to treat any form of RA. Methotrexate (MTX) is the key conventional DMARDs. It is recommended as a first-line treatment for patients with RA. However, MTX is potentially associated with various toxicities. No clear pattern of MTX use in patients with RA in Libya, since no national guideline has been implanted so far. The aim was to investigate the prescribing patterns of MTX in Libya. A hundred and twenty patients who were on treatment with MTX and follow up in RA clinic of Tripoli University hospital were evaluated for therapy during the period of 2018 and 2019. Patient distribution data, disease duration, other related diseases and drug prescribed as well as adverse drug reactions were considered to analyze the pattern of drug use. The demographic distribution findings indicate that female patients are more than male patients and the ratio of disease among female to male was 1:9. A range of age between 41 - 60 years was the highest affected compared with other ages. Among of these about 75% of patients were no occupational works. RA related diseases were found to be more with diabetes mellitus, hypertension and osteoporosis. Low use of NSAIDs in this group of patients but with high use of steroid. A high group of patient's use of low dose of MTX for up to five years. This study concludes that MTX is an effective drug in controlling the disease with less and tolerated incidence of side effects.

Keywords-- Disease-modifying anti-rheumatic drugs, Methotrexate, Libya, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that may lead to erosion of cartilage and bone. Uncontrolled RA is associated with joint deformity and significant health care related expenses [1]. RA is an inflammatory condition of synovial tissues with involvement of some peripheral joints mostly wrists, hand and feet that commonly affected. Rheumatoid arthritis can also affect non-articular muscular structures such as tendons, ligaments, and fascia [2]. Four different pharmacological classes of drugs are used for RA treatment: namely, analgesics (Non-steroidal anti-inflammatory drugs, NSAIDs), corticosteroids, disease modifying anti rheumatic drugs (DMARDs) and biological DMARDs. NSAIDs are important for symptomatic relief, they have immediate analgesic and anti-inflammatory effects, but may not affect the disease process [3]. The gastrointestinal toxicity of NSAIDs is major issue of RA patients, who often have multiple risk factors for gastrointestinal toxicity. Glucocorticoids can be dramatically and rapidly effective in patients with RA. They can rapidly relieve joint symptoms and control systemic manifestations, but their chronic use can cause many complications. Glucocorticoids are more effective than NSAIDs [3, 4]. Conventional DMARDs are the main tool to treat any form of RA. There is no immediate analgesic action for DMARDs, however, by repeating uses, RA activity can be controlled: decrease joint erosions and increase life quality of the patient with RA [5]. MTX is the key conventional DMARDs. It is recommended by international medical associations (ELAR & ACR) as a first-line treatment for patients with RA. However, MTX is potentially associated with various toxicities. Gastrointestinal adverse event such as nausea, vomiting, dyspepsia, ulcers, diarrhea and hepatotoxicity may also occur. Other conventional DMARDs including hydroxychloroquine, sulfasalazine and leflunamide have also been successfully used in RA patients and remain important therapies [6]. The use of DMARDs and other drugs for RA are also

associated with number of adverse drug reactions such as gastritis, leucopenia, hepatotoxicity, stomatitis, pruritus, and thrombocytopenia [7]. Combination therapy with DMARDs is indicated in patient who fail mono-therapy and have persistent disease activity. MTX is also highly effective in combination with other DMARDs [6], including other conventional DMARDs or conventional DMARDs with biologic DMARDs [8]. No clear pattern of MTX use in patients with RA in Libya, since no national guideline has been implanted so far. Thus, this study aims to investigate pattern of RA in Libya with regard to efficacy, safety and side effects of the low doses of weekly MTX treatment in Libyan patients.

MATERIALS AND METHODS

This mode of this method is a retrospective study that contains patients (n = 120) with known RA who were treated with MTX. All patients were recruited from outpatient RA clinic of Tripoli University hospital, Tripoli-Libya. Approved from local ethic committee was obtained (202/2019). Date was randomly collected from medical records in period from April 2018 to August 2019. Different variable that were extracted from medical records including: (1) demographic details (age, sex, marital status, city, occupation). (2) Details about patient's disease and treatment (duration of disease, activity of disease, drug history, dose and frequency of methotrexate and duration of

treatment) and any recorded side effects. (3) Concomitant illness. (4) Biochemical markers for liver and renal functions of each patient and any extra articular manifestation were also recorded. Data were analyzed using descriptive statistical measures such as frequency distribution, percentage, mean and standard deviation.

RESULTS

One hundred twenty RA patients were enrolled in the study. The socio-demographic characteristics of patients are shown in Table 1. One hundred eight patients were females representing 90% and 12 (10%) were males; with female to male ratio 9: 1. The peak age group was between 41-50 years representing 30.8% of patients and the lowest was for teenager (10 - 20 years) and elderly (71 - 90 years). Furthermore, 80% were married and 12 % were single while 8% patients have no available data and 77% are non-worker. With regards to geographical distribution of patients with RA out of 120 patients with RA, 72% were local inhabitants of Tripoli city, 24% of patients came from other Libyan cities and only 4% of patients have no available data. The duration of rheumatoid arthritis in our patients shows that, the highest group 43.3% is suffering from RA for 2 - 5 years while the lowest group (0.8%) has RA for more than 20 years. The details about clinical characteristics of RA patients and treatment are shown in Table 2.

Table 1: Socio-demographic characteristic of RA patients.

Study variables	Number and percentage of patients: n (%)
Gender	
Female	108 (90)
Male	12 (10)
Age group	
10-20	01 (0.8)
21-30	09 (7.5)
31-40	15 (12.5)
41-50	37 (30.8)
51-60	33 (27.5)
61-70	19 (15.8)
71-80	4 (3.3)0
81-90	1 (0.8)0
Unknown	1 (0.8)0
Marital status	
Single	15 (12)
Married	96 (80)
Unknown	9 (08)0
Occupation	
Worker	28 (23)
Non-worker	92 (77)
Geographic distribution	
City	86 (72)
Out of city	29 (24)
Unknown	(04)50

Table 2: Clinical characteristics of RA patients.

Patient characteristics	Number and percentage of patient: n (%)
Duration of disease (years)	
< 02	18 (15)
02-05	52 (43.3)
06-10	28 (23.3)
11-15	12 (10)
16-20	07 (5.8)
> 20	01 (0.8)
Unknown	02 (1.7)
Doses of MTX per week	
08 mg	02 (1.7)
10 mg	64 (53.5)
12 mg	1 (0.8)
13 mg	1 (0.8)
15 mg	45 (37.5)
20 mg	7 (5.8)
Duration of using low dose of MTX (years)	
< 02	23 (19.2)
02-05	45.8(55
06-10	23 (19.2)
11-15	9.2)(11
16-20	(3.3) 40
Unknown	3.3)(04

Regarding treatment of RA in this study, a total of 83 patients (69%) were receiving MTX as monotherapy and 37 (31%) receiving MTX as combination therapy with other conventional DMARDs. No drug was prescribed from the class of

biologics DMARDs. Of the study patients only 18 (15%) of the patient were used NSAIDs at the first evaluation and 83 patient (69%) were received corticosteroids concomitantly at the first evaluation (Fig. 1).

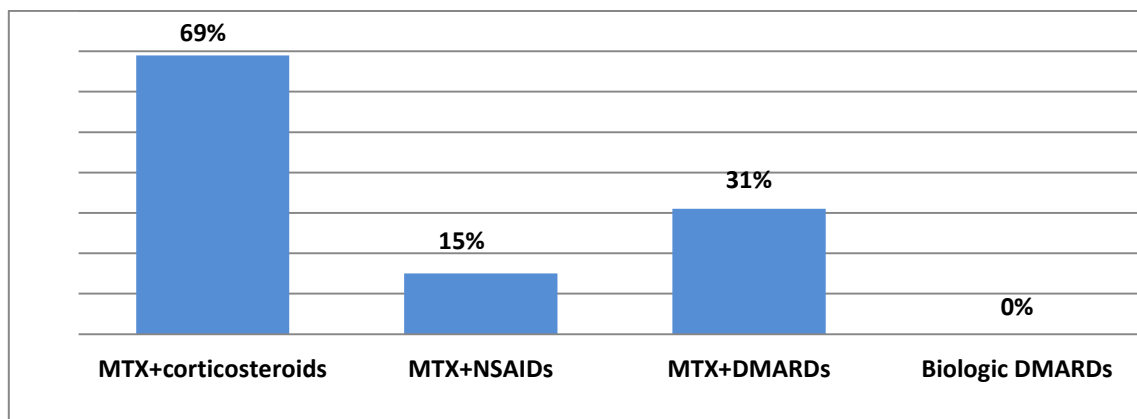


Figure 1: Pattern of treatment of Libyan patients with rheumatoid arthritis.

Different doses of MTX administered per week in each rheumatoid patients (Table 2 and Fig. 2). The highest group of study patients (n = 64, 53.5%) was receiving low dose of MTX (10 mg/week) and the lowest group (n = 1, 0.8%) was receiving MTX in doses between 12 mg and 13 mg/week. However, the highest group (n = 55, 45.8%) of our patients were using low dose of

MTX for 2 - 5 years and lowest (n = 4, 3.3%) for 16 - 20 years (Table 2). Moreover, the patients who are in the remission state (91.7%) are higher than that the active state (8.3%) data not shown. Regarding side effects of methotrexate, the highest group has no side effect and the remaining has side effects, the highest one was for GIT upset, it forms about 8% (data not shown).

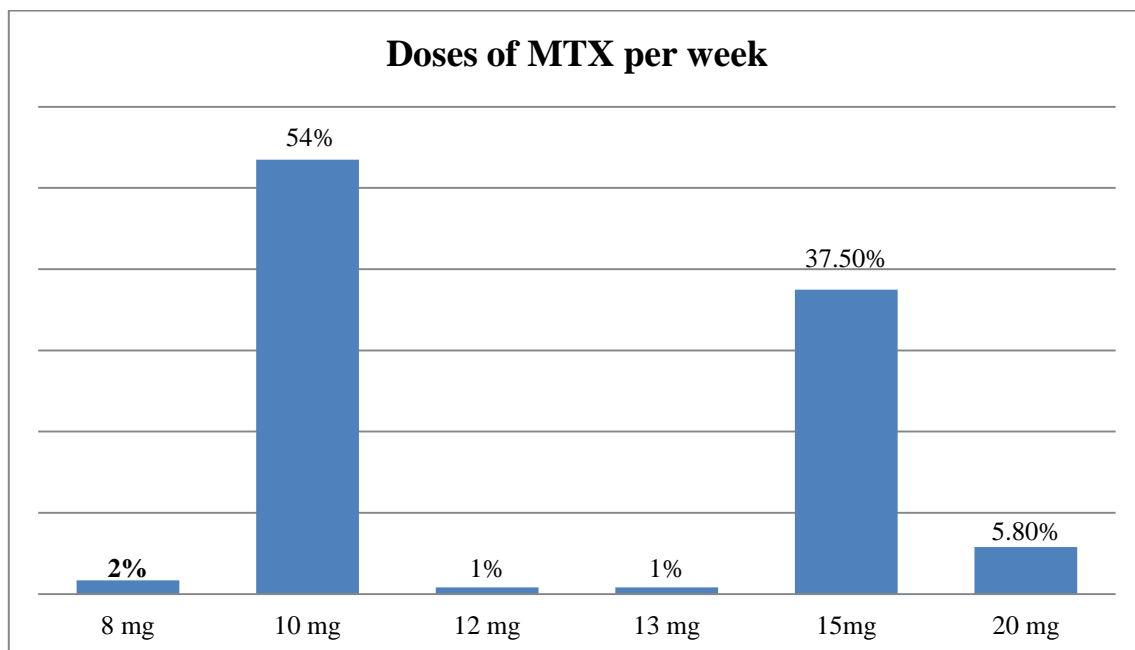


Figure 2: Different doses of methotrexate administered per week in each rheumatoid patients.

In present study out of the studied patients, (n = 43, 35.8%), had other comorbid conditions. Table 3 Shows other diseases associated with rheumatoid arthritis, the highest group 64.2% has only rheumatoid arthritis, and the rest of patients have other chronic diseases in addition to RA ranging from 0.8% up to 5%. Also from our study,

it was found that 14 (12%) patients had extra-articular manifestation of RA, The highest group have articular pattern of RA and the remaining patients have varies extra-articular manifestations, the highest percent for rheumatoid nodule 5% (Table 4).

Table 3: different diseases associated with rheumatoid arthritis in Libyan patients.

Comorbidity	Frequency	Percentage	Valid percent	Cumulative percent
Diabetes mellitus (DM)	06	5.0	5.0	5.0
DM & Osteoporosis	03	2.5	2.5	7.5
Osteoporosis & Lung fibrosis	01	0.8	0.8	8.3
Hypertension (HTN) & Hyperthyroidism	1 0	0.8	0.8	9.2
DM & Lung fibrosis	1 0	0.8	0.8	10.0
DM, HTN & Cardiac disease	40	3.3	3.3	13.3
Abnormal CBC	10	0.8	0.8	14.2
HTN & Hypothyroidism	1 0	0.8	0.8	15.0
Non	77	64.2	64.2	79.2
Hypothyroidism	10	0.8	0.8	80.6
HTN	07	5.8	5.8	85.8
Cardiac disease	02	1.7	1.7	87.5
Osteoporosis	05	4.2	4.2	91.7
Fibromyalgia	01	0.8	0.8	92.4
DM & HTN	06	5.0	5.0	97.9
DM & Cardiac disease	03	2.5	2.5	100
Total	120	100	100	

Table 4: Most common extra-articular manifestations of rheumatoid arthritis.

Extra-articular manifestation	Frequency	Percentage	Valid percent	Cumulative percent
Rheumatoid nodule	06	5.0	5.0	5.0
Sjogren's syndrome	02	1.7	1.7	6.7
Lung fibrosis	02	1.7	1.7	8.3
Sjogren's syndrome and rheumatoid nodule	02	1.7	1.7	10.0
Lung fibrosis& rheumatoid nodule	02	1.7	1.7	11.7
No Extra-articular manifestation	106	88.3	88.3	100
Total	120	100	100	

DISCUSSION

The present finding of prescription pattern of MTX study conducted in Tripoli University hospital provides information about the demographic and clinical characteristic (efficacy and safety) of patients with RA, prescribing patterns and the side effects of MTX. In present study, 108 (90%) of the affected patients were females and the ratio of disease among female to male was 1:9. In India, a study reported by Mittal et al. [9] that more than 80% of the RA patients with RA were women. This is in line with our present study. Other more recent study conducted in Spain has indicated that female patients established 70 % of the sample size population [10]. In the present study the most commonly affected age group was 41 - 60 years (58.3%) which found to be older than the expected. A study by Shakti et al. [11] showed that the peak prevalence of RA was in age groups of 31 - 60 (61.3%) years. Among of patients, 92 patients (77%) were with RA affecting physical activities and with no occupational duties. Married RA patients were more dominant to those of single status patients. Moreover, there is 43 patients (35.8%) had associated with other diseases (comorbid conditions). Furthermore, the present findings are in accord with the other published studies [10, 12]. The associated comorbid conditions in present study were Type-2 diabetes mellitus, hypertension, and osteoporosis.

MTX is the preferred initial DMARD recommended in the USA and Europe [13, 14]. It is highly effective when used as monotherapy or in combination with glucocorticoids, other conventional DMARDs, and biologic DMARDs. MTX as anchor drug in RA management is reflected in the majority of studies worldwide [14]. The current treatment at the time of study, shows that, almost of patients 83 (69%) were receiving MTX as monotherapy and 37 (31%) were receiving MTX as combination therapy with other conventional DMARDs. Combination therapy with

DMARDs is indicated in patients who fail monotherapy and have persistent disease activity. The present study shows the combination of conventional DMARD therapy as first line treatment was very infrequent. A high group of patient's use of low dose of MTX 10 mg/week, orally in most of the cases for up to five years. Combination therapy with DMARDs is indicated in patients who fail mono-therapy and have persistent disease activity. Moreover, in our study great proportion of patients were in remission state (91.7%) and 8.3% in active state this results indicate that the MTX highly effective for treatment of RA at low dose.

Of the study patients 18 patients (15%) were used NSAIDs at the first evaluation and 83 patients (69%) were received corticosteroids concomitantly at the first evaluation. The data from this study shows findings similar to those of some European countries and Canada, with high rates of MTX use in combination with corticosteroids as the most common first-line pattern [15, 16]. In present study, no drug was prescribed from the class of biologics DMARDs, this explained by the fact that the treatment with MTX and corticosteroids as effective as with a biologic DMARDs.

About 70% of patients have no methotrexate side effect and the most common adverse effect affecting the patients is gastric upset (about 10%). This finding is in line with the other study [10]. Serious side effects like hepatic failure and bone marrow suppression are not recorded, just mild hepatitis (4%) is seen, in which liver enzymes return to normal level within weeks without stopping the treatment. Only 75% of patients receive folic acid, this indicates that the folic acid reduce incidence of methotrexate side effects. All the patients show normal liver function test, urea and electrolytes before starting and during their follow up.

The extra-articular manifestations of RA remain a common complication of disease that account for substantial morbidity and mortality. Extra-articular signs of RA occur in nearly 40% of

the patients, in the beginning or throughout the progression of disease [17]. In present study, the extra articular manifestations are seen in 14 cases, the most common one is rheumatoid nodule (5%), followed by Sjogren's syndrome and lung fibrosis. This means the disease pattern is mainly articular

CONCLUSION

This study indicates that MXT is effective and safe for Libyan patients with RA and it controls RA with less and tolerated incidence of side effects. However, MTX as DMARD in treatment RA needs more studies regarding their side effects and effective measures or treatment to decrease these side effects in Libyan patients. Thus, disease pattern of RA in Libya needs more consideration and comparison in other countries. A regular and complete liver function, urea, electrolytes and serum creatinine are still recommended for these patients with minimization of side effects of MTX with folic acid intake.

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