TREATMENT OF RHEUMATOID ARTHRITIS IN BASRAH: CLINICAL EFFICACY AND TOXICITY OF METHOTREXATE USED ALONE OR IN COMBINATION WITH DICLOFENAC SODIUM

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ABSTRACT

Background: The present study is based on two assumptions. First is the racial and ethnic differences in the presentation of rheumatoid arthritis (RA) and its response to drugs. And the second is the interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and the disease modifying antirheumatic drugs (DMARDs) particularly methotrexate (MTX) with the possibility of enhanced toxicity.

Objectives: to investigate the efficacy and toxicity of MTX alone or in combination with diclofenac in the treatment of RA.

Methods:

Design: A three month randomized comparative clinical trial

Setting: Rheumatology Unit at the Teaching Hospital and the Department of Pharmacology, College of Medicine, University of Basrah, Basrah, Iraq.

Patients: Patients with moderate to severe RA were classified into, Group I: received MTX (7.5 mg orally as a single weekly dose). Group II: received MTX single weekly dose plus diclofenac sodium 100 SR tablets once daily

Measurements and evaluation

Pain, morning stiffness, joint function (number of the swollen and tender joints), patients and physician global assessment, radiological evaluation (according to modified Sharp score for joint space narrowing and erosions), ACR criteria for progression and remission of RA, laboratory findings (complete blood picture and ESR, blood groups, Hb electrophoresis, AST, ALT, blood urea) and drug adverse effects were evaluated.

Results: Twenty eight patients with moderate to severe RA were randomly allocated into two treatment groups as cited in the Methods. Only 25 patients managed to complete the 12 week treatment course. Oral MTX (7.5 mg) resulted in a statistically significant clinical improvement after 12 weeks of treatment. The improvement seems to be time dependent. The average percent improvement in six clinical parameters mounted to about 35% compared to the baseline measurements. The 20% improvement at 12 weeks of treatment using ACR criteria involved 42.8% of patients. Radiological findings (joint space narrowing and erosion) increased slightly by only 5.7% over the 12 week treatment period. No significant change in all laboratory parameters measured. No important side effects peculiar to MTX could be figured out. Concurrent administration of diclofenac (sustained release formulation) with MTX resulted in a paradoxical finding. Instead of enhancing efficacy or toxicity of MTX, diclofenac reduced the efficacy of MTX from 35.25% to only 15.78% at the end of the treatment period. The two groups, however, differed in some aspects e.g. disease duration and severity, and the type of blood groups which might possibly have contributed to this difference. The ACR20 in the combination group is 36.3% (compared to 42.8% in MTX group). Radiological findings progressed by 48.3% in the joint space narrowing and erosion. When results of MTX and MTX+diclofenac groups were analyzed according to disease severity and blood groups, it was found that the response of patients with severe but not moderate disease was comparable in the two groups. Blood group (A) seems to be associated with enhanced response and group (O) with a reduced one.

Conclusion: Methotrexate 7.5 mg as a single oral dose per week produced a significant clinical improvement over the 12 week treatment period. The drug seems to be well tolerated with no important adverse effects. In contrast to what is expected, sustained formulation of diclofenac sodium reduced the efficacy of MTX. The latter finding, if proved to be true, could have an important clinical implication.

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease of unknown cause, primarily affects the peripheral joints in symmetrical pattern.[1] It affects around 1% of adults; two to three times more prevalent in women than in men. Few groups have much higher prevalence rates (e.g. 5-6% in some Native American groups) and some have lower rates (e.g. black persons from Caribbean region). There are racial and ethnic differences in drug response and also in the RA disease itself. For example, Hispanics in the USA tend to have more pain when they are first diagnosed, while African-Americans have more physical disability that translates into difference in the drug response. [2] Pharmacological treatment of

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RA,[3-8] include among many others the use of disease modifying antirheumatic drugs (DMARDs) which can retard or prevent disease progression and, thus, joint destruction with subsequent loss of function. The most active of these in terms of remission and onset of action, is methotrexate and sulfasalazine. Other drugs used for treatment of RA include leflunamide, tumor TNF-alpha blockers (e.g. etanercept, infliximab), minocycline and anakinra (IL-receptor antagonist). Methotrexate is an antifolate drug that, in recent years, has been largely employed in the early treatment of rheumatoid arthritis as a first line treatment. The mechanism of action of low weekly dose of methotrexate in rheumatoid arthritis is still unclear, but it might be more anti-inflammatory than immunosuppressive.[3] Disease suppression starts earlier than with other slow-acting antirheumatic drugs. However, response to methotrxate treatment cannot be expected before 2 months and may not occur until after 6 months of treatment.[9,10] Current expectations of adverse reactions are more common in the elderly and in patients with advanced stage disease.[11] Pancytopenia is a rare adverse effect associated with low dose MTX therapy for RA. It is a potentially serious complication that may occur at any time during therapy; and this adverse effect is more likely to occur in patients with renal impairment.[12] Although high-dose of MTX is known to be nephrotoxic, data on low dose MTX renal effects are scanty. Patients on low dose of MTX should, thus, be monitored for creatinine levels periodically.[13] NSAIDs can interact with MTX; they reduce renal tubular excretion and glomerular filtration of MTX and also its protein binding. This can increase the concentration of MTX to toxic levels.[14] However, even with low doses of MTX used in the treatment of RA, such an interaction may still seem to be clinically significant.[15] One may, therefore, expect that addition of diclofenac could increase the efficacy and probably, the toxicity of MTX.Thus, this study is intended to investigate the clinical efficacy and toxicity of MTX as a monotherapy or in combination with the NSAID: diclofenac sodium, in treatment of patients with moderate to severe RA.

PATIENTS AND METHODS

A 3-month randomized, comparative clinical trial was conducted at the Rheumatology Unit at the Teaching Hospital, Basrah, and the Department of Pharmacology, College of Medicine, University of Basrah (Iraq) during the period from October 2005 to June 2006.

Patients with moderate to severe RA were classified into*:*

Group I: received MTX, Ebewe Drug Company, orally (7.5mg as a single weekly dose)

Group II: received MTX 7.5 mg once weekly plus diclofenac sodium 100 mg sustained release, enteric coated tablets (Hemofarm) once daily.

Measurements

- Clinical evaluation (including laboratory investigations and monitoring of adverse effects)
- Radiological evaluation

Clinical and laboratory evaluation

Pain (using 11-point numerical rating scale), morning stiffness (duration in minutes), joint function (number of tender and swollen joints, and patient and physician global assessment), laboratory investigations (including complete blood picture and ESR, liver enzymes, blood urea, Hb electrophoresis and blood groups), American College of Rheumatology (ACR) criteria, and drugs adverse effects (according to a check list).

Radiological evaluation

X-rays before and 3 months after treatment were assessed blindly by a specialist in radiology using modified Sharp score (Van der Heijde DM. Bailliere's Clin Rheumatol 1996; 10:435-453) involving joint space narrowing and erosion.

Treatment allocation

Drugs were randomly allocated according to a randomization list. Follow-up was made by two rheumatologists: the first prescribed the drugs, and the second, blindly, assessed the patient response and the adverse effects

Ethical approval

The study design was approved by the College Council and the ethical committee of the College of Medicine, University of Basrah (Iraq).

RESULTS

Clinical response expressed as percent improvement in six clinical parameters (joint pain, morning stiffness, number of swollen joints, number of tender joints, patient global assessment, physician global assessment) in the two treatment groups (methotrexate (MTX), and MTX+Diclofenac). The overall average of improvement in the six clinical parameters showed that MTX alone resulted in 15.33%, 22.8%, and 35.25% improvement at 2, 6, and 12 weeks of treatment respectively in comparison to pre-treatment measurements. While combination of MTX and diclofenac resulted in only 11.3%, 10.5%, and 15.78% improvement over the same periods of treatment (Figure-1).

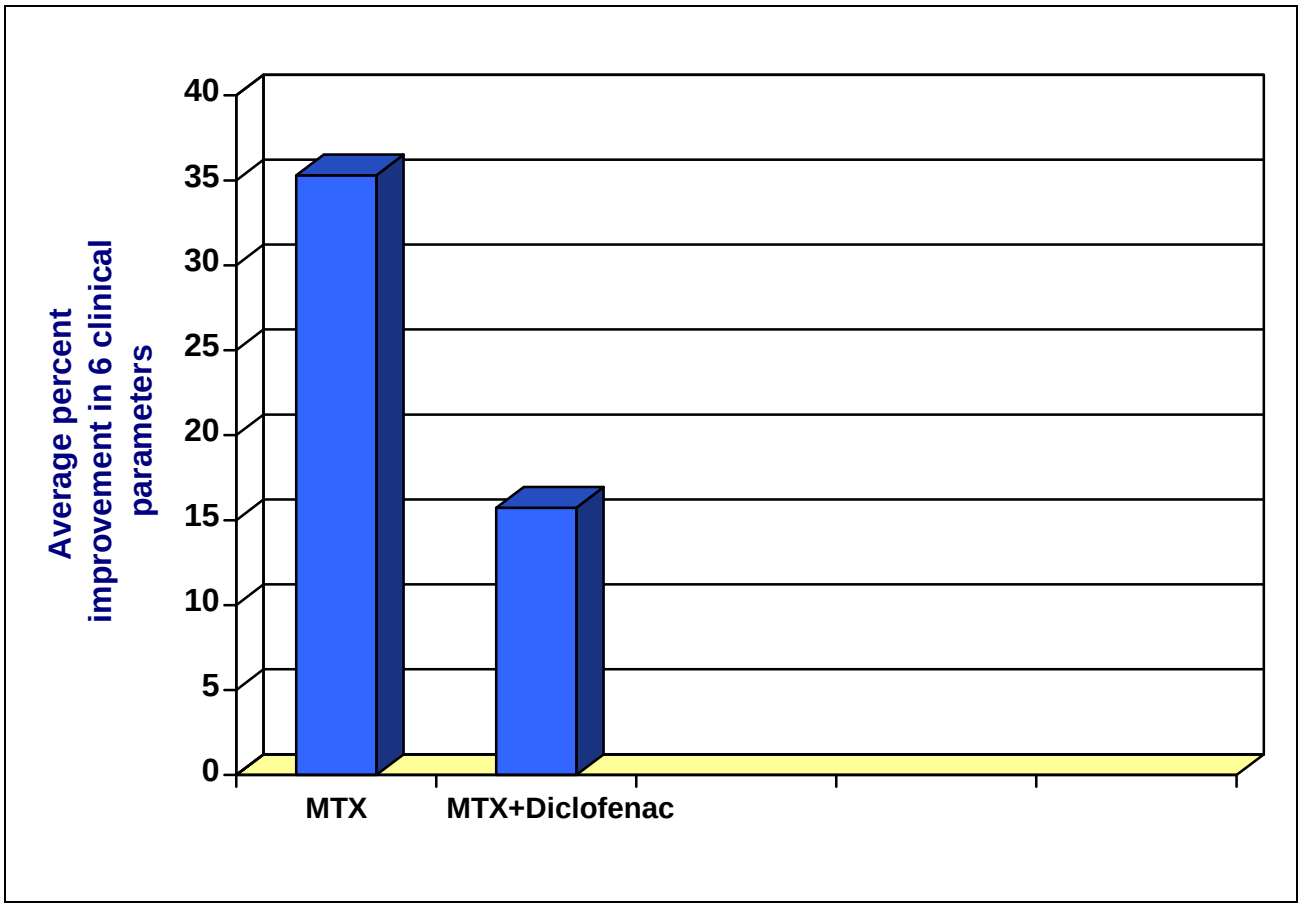

Fig 1. Average percent improvement in six clinical parameters (joint pain, morning stiffness, number of swollen joints, number of tender joints, patient global assessment, physician global assessment) in the two treatment groups (methotrexate (MTX), and MTX+Diclofenac) after 12 weeks of treatment.

However, there are three main differences between the group of MTX and that of MTX+ Diclofenac; these are: differences in duration and severity of disease, and in the type of blood groups. An analysis was, therefore, made to see whether these factors had contributed to the difference between the two groups or not. Comparison between female patients and disease of moderate severity in the two groups, and between blood groups within each type of treatment had shown that the type of blood group and disease of moderate severity might have, partially, contributed to this difference. Blood group 'O' seems to contribute to the reduction and blood group 'A' to the enhancement of response to drugs. The high percentage of improvement was found in patients with disease of moderate severity rather than high severity.

Table 1. The mean percentage of improvement in the six clinical parameters at 12 weeks of treatment with MTX or MTX+diclofenac analyzed according to disease severity.

	Type	MTX group (N=13)	MTX + diclofenac (N=12)
Severity (% improvement with respect to pre-treatment measurement)	Moderate	42.35% (n=8)	16.4% (n=7)
	Severe	18.23% (n=5)	14.24% (n=5)
	Total	35.25%	15.25%

Improvement after 12 weeks of treatment assessed according to the American College of Rheumatology Criteria (ACR-20)

Twenty percent improvement using the ACR criteria was found in 42.8% of patients receiving MTX alone compared to 36.3% when MTX and diclofenac are used concomitantly.

Radiological assessment

Radiological changes, 12 weeks after treatment with MTX, or with its combination with diclofenac

There was no significant progression in the radiological changes (joint space narrowing and erosion) when assessed before and three months after treatment with MTX. On the other hand, the radiological changes progressed by 48.3% in the group received MTX and diclofenac after 3 months of treatment. However, this result is also not statistically significant.

Adverse effects of the drugs used in the study (Symptoms reported by patients before and after treatment)

There was a consistent trend towards reduction in the incidence of symptoms reported by patients after 12 weeks of treatment when compared to before treatment in both groups of patients. MTX treatment reduced the incidence of reported symptoms by 60.3%, while its combination with diclofenac reduced it by only 31.6% especially the CNS, GIT and respiratory systems

DISCUSSION

Methotrexate has been reported to demonstrate good efficacy and tolerability and is currently, used early in treatment of RA as a first line treatment.[15] There are racial variation in the clinical presentation of RA, and in its response to treatment.[1,2,14] This ethnic and racial variations have led to the question whether patients with RA, here, in Basrah (Iraq) with their different genetic constitution, differ in their response to antirheumatic drugs or not. In the present study, MTX produced a good clinical response (35.2%) as measured by joint pain score, morning stiffness, number of swollen and tender joints, and patient and physician global assessment. Laboratory parameters of efficacy (ESR) and toxicity (Hb, total and differential WBC counts, AST, ALT, blood urea, and platelet counts) were not changed significantly over the 12 week treatment with MTX. Kent et al[16] and Shiroky[17] found that lack of folate supplementation is one of risk factor for transaminases elevation and other toxicities. Despite that our patients were not given folate supplementation, serum transaminases were not increased. This may be due to the short duration of treatment (3 months). Swier et al[8] found that at the end of 60 month treatment with oral 7.5 mg once weekly MTX dose, 64% of patients had adverse effects. The problem with the assessment of adverse drug reactions is that they are intermingled with the signs and symptoms of the disease itself. Signs and symptoms assessed in the present study at baseline before starting treatment were higher than those assessed 12 weeks after treatment. This may reflect the improvement in the disease process after using MTX. Most studies followed radiological progression of RA over 1-4 years as it had been reported by Wick et al,[18] Van et

al[19], Stenger et al[20] and Dixey et al.[21] Wick et al[18] found that MTX retarded the radiological progression by 71% during the first year after diagnosis. Therefore, it is expected that the 3-month follow up period planned for the present study may not be enough to show clear radiological changes in patients with RA treated with MTX. NSAIDs can interact with MTX through different mechanisms. These include displacement of MTX from its protein binding sites increasing the unbound fraction of MTX, and also a decrease in MTX renal clearance.[7,16] These interactions can lead to MTX toxicity which include enhanced hemopoietic toxicity and immunosuppression.[8] Severe, sometimes, fatal MTX toxicity can also occur when NSAIDs were used concurrently with low to moderate doses of MTX which are routinely used in treatment of RA or psoriatic arthropathy.[14,15] Contrary to the expected results from the interaction between NSAIDs and MTX cited above, diclofenac in combination with MTX produced a clinical response lower than MTX used alone. The type of diclofenac formulation used is the sustained release formulation. Thus, a question may be raised whether or not a sustained release type of NSAIDs differs in its interactions with MTX from the immediate release one. So far, this finding may be a coincidental one because of the limited number of RA patients studied and the short period of follow up (which may reflect the difficulty of following up our patients). However, it could be an important and clinically significant finding if proved by other larger studies.

In conclusion, the finding that diclofenac may reduce the efficacy of MTX if given concurrently to patients with RA, could be an important finding, but because of limitations of the present study (duration and patient number it should be investigated in the future regarding the following aspects: Does SR-formulation of diclofenac differ from immediate release tablet? Does severe form of RA differ from mild to moderate one with respect to the effect of the combination of diclofenac and MTX? Is the effect of blood groups a real or coincidental finding? And finally; are males and females different in their responses to these drugs?

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