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Improvement in Compliance of Patients with Rheumatoid Arthritis to Methotrexate by Concomitant Use of Folic Acid

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SUMMARY

Methotrexate is an important and a commonly prescribed second-line and disease-modifying drug in the treatment of Rheumatoid Arthritis (RA). It is a folate antagonist through its effect on enzyme dihydrofolate reductase. Many patients stop using this medicine due to its gastrointestinal side effects that occur early in the course of treatment. We performed this study to see if folic acid supplementation can reduce these gastrointestinal side effects thus improving the compliance of patients in the initial period. 133 patients of RA were studied in two groups. Group I (65 patients) received only Methotrexate and Group II (68 patients) were also given Folic acid 5 mg daily for 5 days a week. Both the groups received Methotrexate 7.5 mg per week in two divided doses. Folic acid was given to Group two patients on days when they were not using methotrexate to avoid any possible interaction that might reduce its efficacy. Patients were followed up for a period of three months. About 48% patients in the group I as compared to about 9% in the Group II developed the side effects. Most common side effects observed were stomatitis, abdominal pain, diarrhoea and vomiting. Comparison of the side effects in the two treatment groups demonstrated statistically significant reduction in the frequency of occurrence in the Group II ($P < 0.001$). It was interesting to note that patients who dropped out of the study due to these early side effects did so within the first three weeks of the methotrexate therapy. Therefore, it is concluded that folic acid supplementation is an effective way of reducing early GI side effects of Methotrexate therapy in Rheumatoid Arthritis and due to this favourable effect, it improves the compliance of these patients to this drug.

Key words: Rheumatoid Arthritis, Methotrexate, Folic acid.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic progressive destructive inflammatory polyarthritis associated with substantial disability, long standing debility and economic losses. It is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis, arthritis and sometimes multisystem involvement.[1] RA affects 1% of the adult population and is 3 times more common in females.[2] It has been found that patients with active, polyarticular, rheumatoid factor (RF)-positive RA have a >70% probability of developing joint damage or erosions within 2 years of the onset of disease.[3] Therefore, early diagnosis and treatment are imperative. It has been shown that early aggressive treatment may alter the disease course and may limit the joint damage and functional loss by using the so-called, Disease Modifying Anti-Rheumatic Drugs (DMARDs) or Slow Acting Anti-Rheumatic Drugs (SAARDs).[4]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the initial drug treatment of RA to reduce joint pain, swelling and improve function by reducing inflammation in and around affected joints. NSAIDs, however, do not alter the course of the disease nor do they prevent joint erosion and destruction. Disease Modifying Anti-

Rheumatic Drugs (DMARDs) are used for all patients in whom the disease remains active despite adequate treatment with NSAIDs, usually for a period not exceeding six weeks. DMARDs have the potential to reduce or prevent joint damage by preventing erosions, preserve joint integrity and function, and, ultimately, to reduce the total cost of health care and maintain economic productivity of the patient with RA.[4]

Methotrexate (MTX), a DMARD, has shown the most predictable benefit to patients with RA. It is a structural analogue of folic acid and is a competitive inhibitor of dihydrofolic acid (FH2) to the enzyme dihydrofolate reductase (DHFR). Being an anti-metabolite it is associated with various side effects. Common toxicities associated with MTX include gastrointestinal adverse effects (stomatitis or oral ulcers, nausea and vomiting, abdominal pain, and loose stools in addition to griping abdominal pain), central nervous system side effects (headache, fatigue, or impaired ability to concentrate), skin rash, alopecia, fever and haematologic abnormalities. Gastrointestinal complaints usually occur within 24 to 48 hours after the weekly MTX dose.[5] Rare but potentially serious toxicities associated with MTX include pulmonary, hepatic[6] and lymphoproliferative disorders.[7]

About 30% of the patients of RA taking MTX show non-compliance due to adverse effects especially related to gastrointestinal tract[8] as these side effects appear early during the treatment. Folate depletion is considered to be the cause of most of the gastrointestinal adverse effects. Studies have supported that many of these side effects can be alleviated or prevented by the addition of supplemental folic acid, without changing the efficacy of MTX.[8] Stomatitis, nausea, diarrhea, and perhaps alopecia from MTX use may decrease with concomitant folic acid treatment. However, there is no evidence that the hepatic or pulmonary toxicity are related to folate depletion.[9]

PURPOSE OF THE STUDY

We performed this study to see the effect of folic acid supplementation in Pakistani patients started on methotraxate for the treatment of RA and to see if it improves compliance to the therapy. We compared the results with international figures to see if some differences exist in our population due to ethnic and geographical variability.

PATIENTS AND METHODS

Inclusion criteria

Patients fulfilling the following criteria were included in our study:

1. Patients of both sexes and all ages
2. Patients diagnosed as a case of Rheumatoid Arthritis according to American Rheumatology Association (ARA) criteria[10] as shown in Table 1

Table 1: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis[10].

1) Morning stiffness in and around joints lasting at least 1 hour before maximal improvement.
2) Soft tissue swelling (arthritis) of 3 or more joint areas observed by a physician.
3) Swelling (arthritis) of the proximal interphalangeal, metacarpophalangeal, or wrist joints.
4) Symmetric swelling (arthritis).
5) Rheumatoid nodules.
6) The presence of rheumatoid factor.
7) Radiographic erosions and/or periarticular osteopenia in hand and/or wrist joints.

Rheumatoid arthritis is defined by the presence of 4 or more criteria.
Criteria 1 through 4 must have been present for at least 6 weeks.

Exclusion criteria

Following patients were excluded from the study

1. Patients who were already taking methotrexate
2. Patients who had taken methotrexate in the past 2 years
3. Patients of RA who were on other disease modifying agents such as Sulphasalazine
4. Patients with concomitant pulmonary, hepatic or haematological pathology

Study Protocol

The study was performed at Shaikh Zayed Hospital affiliated with Federal Postgraduate Medical Institute, Lahore.

All patients with Rheumatoid Arthritis

presenting to Rheumatology and Medical outpatient clinics and Casualty department during the period from July 1999 to October 2000, who met the inclusion criteria were enrolled in the study.

After selection of the case, informed consent was obtained from each patient for enrolment. Patient was either admitted in the medical floor or investigated on outpatient basis. Detailed history including joint symptoms was obtained from each case. Complete physical examination was done including general physical and systemic examination with particular attention to musculoskeletal system. Routine haematological investigations (haemoglobin, total leucocyte count, differential leucocyte count and erythrocyte sedimentation rate), radiographs of hands and chest, RA factor including the titre (dilution method) and liver function tests were done in each case before commencement of Methotrexate.

The patients were divided randomly into two groups:

Group 1 received Methotrexate alone without any folate supplementation. (MTX 5mg on day 1 and 2.5 mg on day 2)

Group 2 received Methotrexate in dosage as above alongwith folate supplementation (folate 5 mg for 5 days a week, day 3 through 7)

No other disease-modifying drugs were given. Patients were allowed to take non-steroidal anti-inflammatory drugs but oral glucocorticoid was only given to those already using them.

Clinical Response

The patients were monitored for gastrointestinal side effects on weekly basis for the first month and then fortnightly for next two months. Following gastrointestinal adverse effects were monitored:

- Oral ulcers
- Abdominal pain
- Nausea
- Vomiting
- Diarrhoea

Statistical Analysis

The gastrointestinal side effects of methotrexate were compared by evaluating differences in the proportions in the two treatment groups. We used the chi-square test to evaluate categorical variables and to analyze the proportion of patients who had a response. The statistical analysis was done by using Bivariate analysis on SPSS version 10.0.

RESULTS

Characteristics of the patients

- **Both groups combined**

  A total number of 133 patients were enrolled in the study. There were 21 male and 112 female patients. The female to male ratio observed in the study was approximately 5.3:1. The ages of the patients ranged from 16 to 55 years with mean age of approximately 33 years.

- **Group 1 (methotrexate without folate supplementation)**

  This group included a total number of 66 patients - 55 female and 11 male patients. The female to male ratio in the group was 5:1. The ages of the patient in this group ranged from 16 years to 52 years with mean age of about 32 years.

- **Group 2 (methotrexate with folate supplementation)**

  This group included a total number of 67 patients - 57 females and 10 males with female to male ratio of 5.7:1. The ages of the patient in the group ranged from 17 to 55 years with mean age of about 34 years.

Gastrointestinal adverse effects

- **Both groups combined**

  The adverse effects were noted in a total of 38 out of 133 (28.5%) patients. The commonest side effect was vomiting reported in 12 out of 133 (9%) patients followed by nausea and oral ulceration in 11 (8.27%) and 10 (7.5%) patients respectively. Abdominal pain was reported in 9 (6.76%) patients and diarrhoea in 8 (6%) patients. 13 patients had more than one side effect.

- **Group 1 (methotrexate alone)**

  Adverse effects were noted in 32 out of 66 (48.5%) patients. Most common side effects noted were oral ulceration and vomiting found in 9 out of 66 (13.63%) patients. Abdominal

pain and diarrhoea were noted in 7 out 66 (10.6%) patients, as shown in Table 2. Ten patients had more than one side effect.

Table 2: Adverse effects noted in Group 1 (methotrexate alone) (n=66)

Adverse effect	*Frequency*	*Percentage*
Oral ulceration	9	13.63
Nausea	8	12.12
Vomiting	9	13.63
Abdominal pain	7	10.6
Diarrhoea	7	10.6

Note: 10 patients had more than one adverse effect.

Group 2 (methotrexate alongwith folate supplementation)

In this group, side effects were noted in 6 out of 67 (9%) patients. The commonest side effects were nausea and vomiting reported in 3 patients followed by abdominal pain and oral ulceration (Table 3).

Table 3: Adverse effects noted in Group 2 (methotrexate with folate supplementation) (n=67)

Adverse effect	*Frequency*	*Percentage*
Oral ulceration	1	1.5
Nausea	3	4.5
Vomiting	3	4.5
Abdominal pain	1	1.5
Diarrhoea	0	

Note: 3 patients had more than one adverse effect.

Comparison of Group 1 and Group 2

Group I consisted of 66 patients and was given methotrexate without any folate supplementation. Adverse effects were noted in 48.5% of the patients in this group. However, in Group II who were given folate supplementation developed adverse effects in only 9% of the patients. The comparison of individual adverse effect in the two groups is shown in Table 4. The results were compared statistically by applying Chi Square test. The result of Chi Square test obtained was 25.46 that was significant statistically ($P<0.001$).

Table 4: Comparison of adverse effects between Group 1 and Group 2.

Adverse effect	*Group 1*		*Group 2*		*P value*
	No.	*%*	*No*	*%*	
Oral ulceration	9	13.63	1	1.5	P<.001
Nausea	8	12.12	3	4.5	P<.001
Vomiting	9	13.63	3	4.5	P<.001
Abdominal pain	7	10.6	1	1.5	P<.001
Diarrhoea	7	10.6	0	0	p<.001

DISCUSSION

Methotrexate (structural analogue of folic acid) is a competitive inhibitor of dihydrofolic acid (FH2) to the enzyme dihydrofolate reductase (DHFR). Methotrexate emerged at the same time as corticosteroids, but was not used in the treatment of rheumatoid arthritis until early 1980s.[11] The efficacy of MTX in the treatment of RA has been established beyond doubt. In one multi-center prospective study, use of methotrexate in RA showed significant improvement in all clinical disease variables (such as joint pain, joint tenderness and joint swelling index), measures of functional status, and the erythrocyte sedimentation rate ($P = 0.0001$).[12]

Common toxicities associated with MTX are related to gastrointestinal tract and central nervous system. Folate depletion is considered to be the cause of most of the gastrointestinal side effects. Studies have supported that many of these side effects can be alleviated or prevented by the addition of supplemental folic acid, without changing the efficacy of MTX.[8]

Morgan et al has demonstrated that folic acid supplementation does not affect the efficacy of methotrexate therapy as judged by joint indices and patient and physician assessments of disease. In addition, patients given folic acid supplements had

lower toxicity scores than did participants given placebo ($P<0.001$).[13] A meta-analysis of randomised controlled trials by Ortiz et al had revealed similar results showing marked reduction in gastrointestinal side effects by supplementation with folic acid. In addition, there was no significant difference between low and high dose folate supplementation.[14]

Folinic acid supplementaion also results in reduction in gastrointestinal side effects but it may also reduce the efficacy of methotrexate at higher doses.[15]

In this study, the effect of Folic acid supplementation in reduction of gastrointestinal side effects of methotrexate was studied in patients with RA. Folic acid supplementation (Group 2) resulted in marked reduction ($P<0.001$) in gastrointestinal side effects compared with Group 1 (methotrexate without folic acid supplementation. The results were quite significant statistically. The results obtained were similar to those demonstrated by Morgan et al[13] and Ortiz et al[14] in their meta-analysis.

Therefore, we strongly recommend the use of folate supplementation while using methotrexate in patients with RA as it results in marked reduction in gastrointestinal adverse effects thus improving the compliance of patients to this drug, which is currently the gold standard in the management of RA.

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