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Methotrexate as Remission Inducing Agent in Rheumatoid Arthritis.

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Abstract

Rheumatoid arthritis is a chronic multi-system disease of unknown etiology with remissions and exacerbations of inflammatory attacks leading to joint destruction and deformity. The patient becomes crippled within due course of time. NSAID's give temporary relief of inflammation and have side-effects. Steroids induce remissions but have to be continued for a long time and gradually toxic effects develop. Second line drugs are costly and have delayed onset of action. Methotrexate has been used to induce remission early and has less side effects. It can be continued for a long period of time.

20 patients with active rheumatoid arthritis and in early synovial or arthritic stage, were given low dose methotrexate along with NSAID's. Patients with normal hepatic, renal, cardiac and other systemic functions, of either sex, were given the drug at 7.5 mg weekly dose and the signs of symptoms monitored at weekly intervals for first three months and then biweekly for another three months. The toxic effects of drug were also monitored. The results were encouraging at 24 weeks in terms of control of pain, disappearance of swelling of joints, improvement in morning stiffness and increase in ROM of joints. These patients did not develop any major toxic effects and could be subjected to physiotherapy easily and their joint functions and muscles were maintained for full activity. Few patients developed gastrointestinal side effects and were given foliate derivatives to overcome it. Hence it is concluded that Methotrexate at weekly dose of 7.5 mg could be used safely for rheumatoid arthritis patients along with NSAID's for inducing remission.

Introduction

Rheumatoid arthritis is a chronic multisystem disease of unknown etiology with a prevalence rate of approximately 1%. The remissions and exacerbations of synovial inflammation lead to cartilage destruction and bony erosions, resulting in joint deformity. The patient becomes crippled and bedridden in due course of time and this is the hallmark of disease. Hence the primary aims in the treatment of Rheumatoid arthritis are to reduce joint pain and inflammation, maintain joint mobility and range of motion, and prevent deformity. A potential goal is to retard disease progression. These aims can be achieved by a drug which induces remission earlier and is less toxic. The first line therapy, consists of non-steroidal anti-inflammatory drugs(NSAID's) i.e., aspirin. It was used first in 1938. These drugs give symptomatic relief of pain and inflammation rapidly but cannot halt the progression of disease. They have adverse side-effects including allergic reactions, G.I. disturbances, renal toxicity and cannot induce remission.

Second line drugs known as disease-modifying anti-rheumatic drugs (DMARD's) and slow-acting anti-rheumatic drugs (SAARD's)

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e.g., antimalarials, D-pencillamine, Cyclosporin and methotrexate, have the potential to retard disease progression and induce remission but they have slow onset of action. They have severe toxic effect, minimal analgesic activity and are costly. Steroids have been used in combination with other drugs to induce remission, but due to their adverse effects, especially in elderly patients and long term maintenance therapy, they are not ideal for use.

Hence a drug which has minimal toxic effects, modifies the course of disease, halts progression of bony erosions and has rapid onset of action, is ideal for preventing morbidity and crippling condition of the patient. Methotrexate (amethopterin) a foliate analogue, fulfils most of the above needs and is currently in large use for rheumatoid patients. It inhibits dihydrofoliate reductase and thymidylate synthetase and has oral bioavailability of approximately 15 to 20 % less than intermuscular or I/V route. 35-50% is bound to albumin and elimination rate is 7.1 to 7.4 hrs, mainly through kidneys. It has emerged as a highly useful agent, being used at a very low dose, with a more rapid onset of action (two to six wks.) than other second-line drugs.

Material and Methods

Patients of either sex attending the department of Physical Medicine and Rehabilitation, IMS Srinagar from 1996 till date with classical or definite Rh. arthritis and with active disease having synovial or early arthritis stage, were taken up for this randomized study. These patients were treated with low dose methotrexate either on OPD basis or were admitted in the ward. The criteria for selection of cases was as under :

- Age : between 18-60 years
- Sex : both males and females
- Pts. with classical or definite

Rh. arthritis as diagnosed by revised ACR criteria 1987.

- Patients with active arthritis e.g. : Rithchie's score of 5 with six swollen joints and raised ESR and without joint deformity or systemic involvement.

The following patients were excluded from the study :

- Patients having advanced disease and crippled with multiple joint deformities.
- Proceeding treatment with sulphasalazine or other second line drugs.
- Patients with contraindications to MTX therapy i.e., hepatic, renal, cardiac, G.I. or haemopoitic disorders and other systemic diseases.
- Very old patients, uncontrolled diabetics, malignancy, pregnant women and blood dyscrasias.

These patients were evaluated on OPD or indoor basis and a complete history and clinical examination done, important signs and symptoms such as pain and swelling of joints, morning stiffness, ROM of joints, stiffness and contracture of joints and general well being noted. All the laboratory investigations for haemopoitic system, kidneys, liver, heart, lungs and other systems were done and recorded. Immunological assay for Rh. arthritis such as RF, CRP, ASO, ANA and other immunoglobin profiles were also done. These tests served as a baseline and for watching any toxic effects of the drug subsequently when these tests were repeated.

Dosage

Methotrexate was given as a single dose of 7.5mgs per week. Three tablets of 2.5mg were given together or in divided dose in one day/week. Other NSAID's such as nimesulide (100mg) or diclofenac (50 mg) were given along with MTX initially. The tolerability of the drug and development of any toxic effects was monitored

and dose increased gradually to 10-15 mg/week for full response, in some patients. The drug was given at weekly single dose for 12 weeks initially and the dose reduced to 5mg/week in those patients who achieved good response. No steroid or second line drug were given concomitantly. The drug was continued at a minimum dose for 24 weeks and results analysed. The base line investigations were repeated at two weekly intervals for first three months and then monthly for another 3 months to know the development of toxic effects of the drug.

Evaluation

These patients were followed up at weekly intervals for Ist three months and then two weekly intervals for another 3 months and results finalised at 6 months. The evaluation was carried out on clinical basis i.e. in terms of control of pain and swelling of joints, decrease in morning stiffness and contracture of joints, increase in ROM of joints and general well being of patients. The tolerability of drug and development of any side-effects was monitored, various laboratory investigation of liver, kidneys, heart, haemopoitic system, lungs and G.I. tract were repeated at two weekly intervals for first 3 months and then monthly for next three months, for detecting any toxic reaction to the drug. The role of drug as remission inducing agent was finalised at 6 months therapy.

Observations

This study explored the efficacy of MTX as remission inducing agent due to its significant effect on primary outcome variable-the DAS. Difference was significant at the mean DAS corrected at 0 weeks as well as the difference between 0 weeks and 24 weeks. The individual components of DAS all changed in favour of MTX as primary remission inducing agent.

This randomised study was conducted on 22 patients of classical or definite Rh. arthritis patients attending the department of PM&R of SKIMS Srinagar from 1996-1997. The age or patients ranged between 18 to 60 years with maximum number of patients in the 4th decade (9 patients). There were 17 female and 5 male patients and all except one girl of 18 years age were married. All of these patients had multiple joint involvement especially of hands, wrists, feet, ankles, elbows etc. with swelling of these joints and decreased ROM. Other large joints such as knees, shoulders, hips and spine were involved in a few cases only. Maximum number of patients (17) had morning stiffness. The involved joints were swollen and tender, with decreased ROM. Only few patients (5) had joint deformities such as flexion contracture of fingers, wrist and elbow and boutonnaire deformity of fingers.

The R.F. was positive in 18 patients and 4 patients were seronegative. The X-rays of hands of these patients were almost normal expect for osteoporosis and decreased joint space in 8 patients.

The other associated diseases observed in this series were hypertension in three cases NIDDM in one case, OA knees and Cushing's Syndrome in one patient each. The various joint areas involved were mainly of hands and feet bilaterally. In hands the MTP joints followed by PIP joints were involved. Similarly in feet joints of intertarsal region and MTP joints and PIP joints were involved. The other joints involved in order of frequency were wrists, elbows, ankles and knees. Shoulders, Hips and Spine were not involved much.

Results

MTX was given at low weekly doses with the primary aim of inducing remission at an early stage. These patients were followed up at 2,4,6,8,10,12,16,20 and 24 weeks and their

symptoms and signs assessed. The clinical criteria applied for assessment of remission was as under :

A. Full Control of pain and morning stiffness.
B. Reduction of swelling of joints.
C. Increase in ROM of joints.
D. No tenderness of joints and periarticular tissues.
E. Overall well being of patients and useful return of function of joints.

In all these 22 patients there was no response at two weeks follow up. Only few patients (five) started showing clinical improvement at 4 weeks. There was reduction in pain and morning stiffness and swelling had started becoming less. Tenderness of joints continued and ROM was still painful in these patients. At 6 weeks maximum number of patients (10) had clinical response to the drug. Two patients out of 22 were lost to follow up after 6 weeks. At 8-10 weeks all the 20 patients had improved and were in complete remission. There was no swelling of joints. Pain and morning Stiffness was absent. ROM of joints was full and painless. Soft tissues contractures had become less and therapeutic exercise and passive stretching was possible easily in these patients. These patients had returned to their job. After 6 weeks of therapy the dose was increased to 10mg/week in 10 patients for achieving full response and at 12 weeks it was again reduced to 7.5 mg/week. From 12 weeks onwards the dose of the drug was again reduced to a minimum level of 7.5 mg/Week in all these patients. The patients were followed up at 4 weekly intervals after 12 weeks and were investigated for any toxic effects to liver, kidneys heart and blood etc. Two patients out of 20 developed gastrointestinal upsets and there was epigastric sensation and mild upper abdominal pain. They were given foliate derivatives and antacids to overcome such side effects. No other major side effects were seen upto 24 weeks. Retrospectively 6 patients were followed-up for one year and it was observed that are they having complete remission and without any toxic effects of the drug.

Discussion

Rh. arthritis is a chronic inflammatory process with remissions and exacerbations. The inflammation of synovial tissue and periarticular tissues continues till joint structures including articular cartilage and bone is destroyed and joint develops contracture and ankylosis thus rendering the patient crippled. Hence there is need for a drug to arrest inflammation and stop further progression and recurrence of disease. The disease being immune-mediated an immunosuppressive drug like MTX can reverse the above phenomenon and the patient can be saved from being crippled. This should be achieved early in the disease process before permanent damage to the joint structure occurs. In this randomised study on 20 patients MTX has given encouraging results and it was used at a very low dose, in patients with early stage active disease. NSAID's were also used for short duration till remission occurred. The patients were of either sex with 15 females and 5 males and between 18-60 yrs. of age. Females were usually housewives. Maximum patients (13) were between 30-50 years of age.

A low dose of MTX i.e. 7.5 mg/week was used in these patients and remission was observed between 6-8 weeks in maximum number of cases. Few patients showed response at 2-4 weeks only. Hoffmeister R.T. (1972) studied 29 patients using MTX 10-15 mg/wk and observed beneficial results. Steinsson K. Weinstein A (1982) studied 21 patients for a mean duration of 38 weeks with 7.5-25.0 mg/wk dose of MTX 52% patients were responders. 17 patients showed a

sustained response after 42 months of treatment completion. Michaels RM, Nashel DJ (1982) reported marked improvement in 79% of patients in 4 weeks with a dose of 50 mg/wk of MTX with total duration of treatment for 7-20wks. Thus our observations are consistent with the above author's and the role of MTX as remission inducing agent is clinically acceptable.

Randomized placebo controlled trials were conducted in patients who had failed to respond second-line therapies, including gold salts and D-pencillamine by Thompson RN (1984) in 48 patients with significant improvement in 6 weeks with 10-25 mg/wk dose of MTX, Weinblatt ME (1985) in 35 patients with 7.5-15.0 mg of MTX/wk for 24 weeks and observed beneficial results within 12 wks, William's HJ and Willkins RF in (1985) observed good results with 7.5-22.5 mg/wk of MTX for a period of 3 months to 10 years.

MTX has been found superior to other second-line drugs like Azathioprine, Cyclosporin. A and parental gold as observed by Hamdy H, Liver JA (1987) in 40 patients; Arnold MH (1990) in 53 patients; Weinblatt ME, Kaplan H (1990) in 281 patients and Cohen S. Rustein J (1993) in 264 patients for 34 weeks.

* MTX induces remission in patients resistant to sulphasalazine as observed by C.J. Haagsma, C.M. Vanriel in (1994) in 24 weeks with a dose of 5-15 mg/wk.
* Intramuscular MTX is more efficacious than oral administration in patients of rheumatoid arthritis as observed by R.A. Halminton (1997) over a period of 6-18 months.
* Supplementation of folic acid during MTX therapy reduces the risk of toxicity as observed by Surah L Morgan (1994) in 79 patients between 19-78 years of age.

In the present study MTX was used safely without any untoward side effects to the patients. No major toxic effect was seen. However, two patients developed gastrointestinal upsets which was corrected by folic acid derivatives and antacids and the drug was not discontinued.

Bannwarth B. Labat L (1994) has observed adverse effects like GI upsets in 60% patients, cytopenia in 5-25% patients, respiratory symptoms in 0.7-7.7% patients and alopecia in some patients which were successfully managed with temporary discontinuation, dose reduction or by administration of folic acid derivatives, Bridges SL Jr (1989) observed hepatotoxicity in 25.6% patients. MacDonald DR (1991) observed dizziness, vertigo, headache and congnitive dysfunction in his study with MTX.

Conclusion

This randomized study conducted on 20 patients with low dose MTX i.e. 7.5-15mg/week for a period of 6 months has given encouraging results with remission occuring between 4-8 weeks of therapy in maximum number of patients. These patients were in synovial or early arthritic stage with active diseases and without much deformities. They were not suffering from any other systemic illness which would be a contraindication to the drug. No untoward side effects were seen except for mild upper GI discomfort in few cases only. The idea of using MTX as first line drug inducing remission has been achieved in this short duration trial. Hence MTX is recommended as first line drug along with other NSAID's to arrest inflammation and further progression of disease so that the integrity of the joints and periarticular tissues is maintained and reasonably good function and overall well being of patient is achieved.

References

1. Arnold MH O'Callaghan J, Mccredie M, Beller EM, Kelly DE Brooks PM. Comparative controlled trial of low dose weekly MTX versus azathioprine in

rehumatoid arthritis. 3 yrs prospective study. Br. J. Rheumatol 1991;29:120-5.
2. Bridges SL Jr, Alarcox GS, Koopman WJ. MTX induced liver abnormalities in rh.arthritis J.Rheumatol 1989; 16 : 1180-3.
3. Bannwarth B, Labat L, Moride Y, Schaverbeke T. MTX in Rh.arthritis. An update. Drugs 1994 ; 47 : 25-30.
4. BN Cronstein. The antirehaumatic agents sulphasalzineand MTX share an anti inflammatory mechanism. BJR 1995:34 (supp.2):30-32
5. CJ Haagsma, PLCM Vanriel, DJ Derooji, T.B. Vrea F.J.M. Russels. A randomized open clinical trial in rh. arthritis patients resistant to sulphasalazine therapy. BJR 1994 ; 33 : 1049-1055.
6. Cohen S, Rutstein J, Luggen Metal. Comparison of the safety and efficacy of cyclosoprin A and MTX in refractory rh. arthritis. A randomized multi-centered placebo controlled trial. Arthritis Rehum 1993; 336 : 356 (Abstract).
7. D.E. Furst. Practical Clinical pharmacology and drug interaction of low dose MTX therapy in rheumatoid arthritis. BJR 1995 : 34 (supl 2) : 20-25.
8. DM Sandoval, GS Alarcon and S.L. Morgan, Adverse effects of MTX-related rheumatoid arthritis patients, BJR 1995; 34 (supp.2) : 49-56.
9. Hoffmeister RT. MTX in rheumatoid arthritis. Arthritis Rheum 1972 ; 15 : 114 (abstract).
10. Handy H, Mckendry RJ, Mierins E, Liver JA. Low dose MTX compared with azathioprine in rehumatoid arthritis-a twenty four week controlled trial. Arthritis Rheum 1987 ; 30 : 361-8.
11. JM Kremmi. Possible mechanism of action of MTx in patients with rh. arthritis. BJR 1995 ; 34 (suppl.2) 26-29.
12. Michaels RM, Nashel DJ, Leonard A, Siliwinksi AJ, Derbes SJ. , Weekly intravenousMTX in the treatment of Rh.arthritis.Arthritis Rheum 1982 : 25 : 339-41.
13. M.E. Weinblatt. Efficacy of MTX in rheumatoid arthritis. 1995 ; 34 (Suppl.2) : 43-48.
14. RA Halminton and JM Kremer.Why I/M MTX may be moreefficacious than oral dosing in patients with rh. arthritis. BJR 1997;36 : 86-90.
15. Steinsson K, Weinsten A, Korn J, Abeles M. Low dos MTX in rheumatoid arthritis. J. Rheumatol 1982 : 9 : 860-6.
16. Sarah L Morgan, Joseph E. Bagglot, William H. Vaughan, Supplementation with folic acid during MTX therapy for rh.arthritis. Ann Intern Med 1994 ; 121 : 833 -41.
17. Thompson RN, Watts C, Edelman J, Esdaile J, Russel AS. A Controlled two-centrer trial of parentral MTX therapy for refractory rehumatoid arthritis. J Rheumatol 1984 ; 11 : 760-3.
18. T. Pinctus. Long term outcome in rheumatoid arthritis. BJR 1995;(Suppl.2) : 59-73.
19. Weinblatt ME, Cablyn TS, Fox DA et al. Efficency of low dose MTX in rheumatoid arthritis. NEJM 1985 : 312 : 818-22.
20. Williams HJ, Willkens RF, Samuelson CD, Jr et al.Comparison of low dose oral pulse MTX and placebo in the treatment of rheumatoid arthritis. A Controlled Clinical trial. Arthritis Rheumatol 1985 ; 25 : 721-30.
21. Whiting-D Keefe QE, Fye KH, Sack KD. MTX and histologic hepatic abnormalities. a meta analysis. Am J Med 1991 ; 90 : 711-6.