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Response time and safety profile of pulsed oral methotrexate therapy in idiopathic retinal periphlebitis

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PURPOSE. To evaluate the response time and safety profile of low-dose oral methotrexate pulsed therapy in idiopathic retinal periphlebitis (Eales' disease).

METHODS. A tertiary care center-based prospective interventional study, based on visual acuity grading, was undertaken. Twenty-one consecutive patients with idiopathic retinal periphlebitis were administered 12.5 mg methotrexate as a single oral dose, once per week for 12 weeks (cumulative dose = 150 mg). Each patient was assessed for change in visual acuity grades. Time of first therapeutic response was also noted. Drug safety was monitored by laboratory tests that included twice-weekly white blood cells and differential counts, twice-weekly platelet counts, and monthly liver function tests.

RESULTS. Twenty-one eyes were assessed. Mean follow-up period was 6 months. All showed improvement in visual acuity grades. An excellent visual outcome (6/6 or better) was achieved in 18 (69%) eyes. Time of first therapeutic response varied from 2 to 6 weeks with a majority of eyes (80%) showing response by 4 weeks (median = 3 weeks). All the side effects of methotrexate were mild or moderate in severity and rapidly reversible on dose reduction or discontinuation. No patient had any constitutional symptoms severe enough to necessitate cessation of therapy.

CONCLUSIONS. Low dose oral methotrexate pulse therapy (at a dose of 12.5 mg/week) is clinically effective within 4 weeks, and is associated with an acceptable safety profile. (Eur J Ophthalmol 2005; 15: 374-8)

KEY WORDS. Methotrexate, Pulsed therapy, Retinal periphlebitis, Eales' disease

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INTRODUCTION

Idiopathic retinal periphlebitis (Eales' disease) primarily affects the peripheral retina in young adults. Eales' disease was first described by Henry Eales, in 1880 and 1882 (1, 2).

He found it in seven young, male patients ranging in age from 14 to 29 years with recurrent vitreous hemorrhages. In addition, these patients had histories of headache, variation in peripheral circulation, chronic constipation, and epistaxis (2). In the next century, the disease was redefined by several investigators (3-6).

Retinal antigens (retinal S-antigen and interphotoreceptor retinoid binding protein) (7) and free radicals (8-14) have been found to play a role in the etiopathogenesis. Recently, a new staging system of idiopathic retinal periphlebitis was proposed by Saxena and Kumar (15).

Predominantly T-cell involvement has been demonstrated in the lymphocytic infiltration of epiretinal and subretinal membranes in such patients (16). Hence, treatment

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should be directed to the downregulation of the activated T-cells. Methotrexate, a folic acid antagonist, has anti-inflammatory and immunomodulatory actions. The drug reduces the synthesis of DNA by acting on the enzyme dihydrofolate reductase.

It has a marked effect on rapidly proliferating cells and causes B-cell and T-cell suppression. Oral methotrexate pulsed therapy, directed towards the downregulation of the effects of activated T-cells, can reset an aberrant immune response in cases presenting with retinal periphlebitis (17). The efficacy and safety of this therapy has been proved in active rheumatoid arthritis (18). It has also been shown to be effective in ocular inflammatory diseases (19-22). However, the response time and safety profile of low dose oral methotrexate pulsed therapy in idiopathic retinal periphlebitis still remains to be evaluated. Hence, a tertiary care center-based prospective interventional study was undertaken.

MATERIALS AND METHODS

Twenty-one consecutive patients with idiopathic retinal periphlebitis presenting between September 2001 and September 2002 at this tertiary care center were included in this study, after informed consent and institutional ethical committee clearance. Systemic disorders such as diabetes mellitus, sickle cell hemoglobinopathy, blood dyscrasias, sarcoidosis, and collagen vascular diseases were ruled out after proper history, examination, and investigations (chest x-ray, fasting and post prandial blood sugar, Sickle cell preparation, hemoglobin, hematocrit, total red blood cell and white blood cell [WBC] count, differential count, erythrocyte sedimentation rate, serum angiotensin converting enzyme, and antinuclear antibody). A complete ophthalmologic assessment (including slit lamp biomicroscopy, indirect ophthalmoscopy, and fluorescein angiography) of the patient was done at baseline. Patients were eligible for this study if they

1) had retinal periphlebitis,
2) had no underlying chronic infectious disorder, major organ dysfunction, or neoplasm,
3) had not undergone laser photocoagulation in the past or had not received oral steroids within 3 months before the study period,
4) did not have dense vitreous hemorrhage,
5) had not been on any immunosuppressive therapy, and
6) had a platelet count above 150,000 per mm^3, a WBC count above 3500 per mm^3, and no elevation of liver enzyme levels.

Each patient was prescribed 12.5 mg methotrexate as a single oral dose, after breakfast, once per week for 12 weeks (cumulative dose = 150 mg) along with a H_2 blocker. Patients were asked to avoid alcohol and sulfa containing antibiotics during the treatment period. Drug safety was monitored by laboratory tests that included twice-weekly WBC and differential counts, twice-weekly platelet counts, and monthly liver function tests.

Therapy was suspended if any of the following side effects were observed: 1) WBC counts below 4000 cells/mm^3, 2) platelet counts below 100,000/mm^3, 3) serum hepatic aminotransferase levels more than twice normal, and 4) febrile episodes. Folic acid (1 mg/day) was added if the patient had side effects. No other immunosuppressive agent was permitted during this period though the dose of methotrexate could be reduced if the patient had intolerable side effects. Patients were asked not to plan any children for at least 6 months after the treatment period. Compliance was verified at each visit. Median follow-up period was 7 months (range, 2 to 10 months).

Outcome variables were 1) improvement in best-corrected visual acuity and 2) resolution of retinal periphlebitis. Patients were reviewed at twice-weekly intervals. Each patient was assessed by two independent observers for disease activity at every visit. As the outcome variable, pre- and post-treatment Snellen visual acuity was recorded by an ophthalmic technician, and visual acuity grades were determined, according to the method of Palmer et al (23) (Tab. I).

Each patient's visual outcome was assessed in terms of changes in visual acuity by the end of the treatment period. A successful visual outcome was defined as either maintenance of visual acuity of 6/12 or better or improvement by one or more grades as determined by the last clinical examination. Patients who did not fulfill these criteria were defined as having a poor visual outcome (2). Resolution of retinal periphlebitis was judged by a decrease/absence of leakage of dye from vessel wall on fluorescein angiography, by a retina specialist masked to the treatment status of the patient.

Time to first therapeutic response, after initiation of therapy, was assessed by improvement in visual acuity and a decrease in retinal periphlebitis. If no ocular inflammation was present at the end of the treatment period the patient was considered to be in remission.

RESULTS

The age of the patients in this study ranged from 16 to 38 years (mean = 25.1±12.6 years). All patients were male. Low dose methotrexate pulse therapy was effective in the resolution of periphlebitis. Methotrexate therapy improved or maintained the visual acuity in all 21 eyes, with 71% achieving an excellent visual outcome (visual acuity <6/6). Eighteen eyes out of 21 (85.7%) attained complete remission of their disease at the end of the treatment period. Visual acuity grades, before and after oral methotrexate pulsed therapy, is shown in Table I. Time of first therapeutic response, after initiation of therapy, varied from 2 to 6 weeks. Eighty percent of the eyes started to show a response by 4 weeks (median = 3 weeks) (Fig. 1). The relapse rate during the follow-up period was very low and only one case showed recurrence after cessation of therapy.

WBC counts (range, 4500–9800 cells/mm^3), platelet counts (range, 130,000–250,000/mm^3), and serum hepatic aminotransferase (range, 19–66 IU/L) during methotrexate therapy were within acceptable range. The most common side effects were gastrointestinal symptoms, which included anorexia (28.6%), nausea (19.0%), gastric irritation (14.2%), and vomiting (4.8%). Most of the cases of anorexia and nausea appeared after the second week of initiation of therapy. Four patients experienced mild nausea and anorexia, lasting several hours after taking the drug. This however resolved between the fifth and sixth week of therapy in three patients, while one patient experienced nausea and three had anorexia throughout the treatment duration. Only two patients with discomfiting symptoms were given folic acid (1 mg) on the day of treatment.

Gastric irritation occurred in 14.2% of cases. Episodic vomiting appeared in one patient early in treatment but resolved after 6 weeks. One patient noticed a pruritic rash on his shins 6 to 12 hours after taking methotrexate, which cleared in a day. One patient each experienced body ache and photophobia while on therapy.

Four patients had a transient increase in SGOT (range, 45 to 66 IU/L) between 3 and 6 weeks of therapy. These values returned to normal within 8 weeks in three patients, without altering the methotrexate dosage, while in one patient who had a level of 66 IU/L at 3 weeks, the level returned to normal on dose reduction.

Mild leukopenia was noticed in one patient (4500 cells/mm^3) 4 weeks after start of therapy. As this patient also had gastrointestinal symptoms, the drug was temporarily discontinued. WBC count increased to 6400 cells/mm^3 after 4 weeks of discontinuation of the drug. Methotrexate was then restarted at a reduced dose of 7.5 mg/week and the WBC count remained stable (6800 cells/mm^3) at this dose.

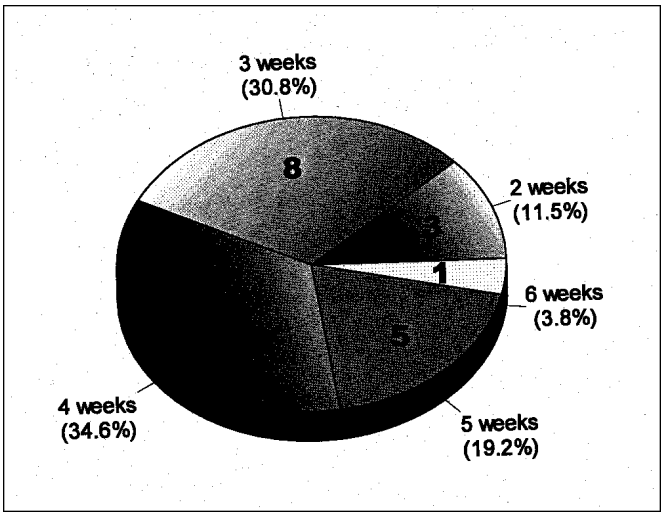

Fig. 1 - Response time of methotrexate pulsed therapy in idiopathic retinal periphlebitis.

DISCUSSION

Anti-inflammatory corticosteroid drugs are potent therapeutic agents for a wide range of ocular and systemic disorders and remain the mainstay of therapy in idiopathic retinal periphlebitis (24, 25). Search for safer and more specific forms of treatment have led to certain immunosuppressives, like methotrexate, which have found a role in patients with immunologically driven systemic diseases. As opposed to the more cytostatic effects of corticosteroids, the cytotoxic immunosuppressives exert their beneficial effects by actually killing the rapidly dividing

TABLE I - VISUAL ACUITY GRADES BEFORE AND AFTER ORAL METHOTREXATE PULSED THERAPY (N=21)

Grade	Visual acuity	Pre-treatment (%)	Post-treatment (%)
Grade I (excellent)	6/6 or better	4 (19)	15 (71.4)
Grade II (good)	6/9 – 6/12	8 (33.3)	4 (19.0)
Grade III (fair)	6/18 – 6/36	5 (23.8)	1 (4.76)
Grade IV (poor)	6/60 or worse	4 (19)	1 (4.76)

clones of lymphocytes that are responsible for inflammation. Various studies describing the role of immunosuppressives in ocular inflammation generally concur with reports of low incidence and reversibility of toxic effects when patients are selected and monitored carefully. According to studies by Hemadi et al (26) and Tamesis et al (27), immunosuppressives may be as efficacious and even superior to corticosteroids in the treatment of certain immune-mediated inflammatory eye diseases and produce fewer long-term side effects if administered at properly adjusted doses.

Methotrexate was used as a weekly pulsed therapy in this study. A pulse differs from chronic moderate dose therapy in its ability to reset an aberrant immune response. Inhibition of the proliferating lymphocyte clones, the temporary removal of recirculating T-lymphocytes from the blood and eye, and the profound suppression of peripheral inflammation all occur simultaneously. Antigens exposed by viral, bacterial, or autoimmune injury are normally perpetuated by the inflammatory response but in such a system a pulse may abolish the source of antigen at the same time as it suppresses the immune response. When memory T-cells recirculate, the disease falters in the absence of the antigen (28).

In the present study, all the side effects of methotrexate were mild or moderate in severity and rapidly reversible on dose reduction or discontinuation. No patient had any evidence of methotrexate induced pulmonary disease during the study or had constitutional symptoms severe enough to necessitate cessation of therapy.

Tamesis et al (27) noted abnormal liver function tests (15.2%), leukopenia (3.8%), and thrombocytopenia (1.9%) in patients with ocular inflammatory diseases treated with long-term oral methotrexate. Possible explanations for the lack of significant side effects in the present study, such as hepatotoxicity and bone marrow suppression, include the short duration of the trial, the administration schedule of a single dose per week, and the low cumulative dose to which the patients had been exposed.

Although mild elevations of serum hepatic aminotransferases above the normal were common (range, 45 to 66 IU/L), no patient had markedly elevated (more than two times the upper limit of normal) enzyme levels. According to various studies, such mild elevations have been found not to correlate with histologic findings at examination of the liver and the development of cirrhosis appears to be unlikely without the concomitant use of alcohol. However, long-term use of methotrexate (or approximately 1.5 g cumulative dose) may rarely cause fibrosis and cirrhosis of the liver. As in the present study schedule, the cumulative dose was only 150 mg; there was a very low risk of hepatic toxicity. The fear of hepatic toxicity has been tempered by data on nearly 1000 liver biopsies by rheumatologists of patients treated with methotrexate over a 5-year period. This treatment failed to show collagen accumulation or significant fibrosis (29). Thus, previous fears over the hepatic toxicity of methotrexate may have been exaggerated (30). Patients should however be asked to refrain from drinking alcohol, and sulfa drugs should be used carefully. Both men and women on methotrexate should avoid conception until 4 to 6 months after the last dose (18), because of risk of possible teratogenicity. In spite of the low rate of side effects, an intimate knowledge of the potential complications and careful laboratory monitoring during methotrexate therapy is essential for its safe use.

On the basis of this study, low dose oral methotrexate pulse therapy (at a dose of 12.5 mg/week) appears to be clinically effective with an acceptable safety profile.

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