A Randomized Comparative Study of Oral Corticosteroid Minipulse and Low-Dose Oral Methotrexate in the Treatment of Unstable Vitiligo

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Key Words
Corticosteroids · Methotrexate · Vitiligo

Abstract
Background: Despite continued progress towards elucidation of the biochemical, genetic and immunopathological pathways in vitiligo, a definitive cure remains elusive. The initial therapy must be directed to arrest disease progression. Oral minipulse therapy (OMP) with betamethasone/dexamethasone has been tried and shown to be an effective modality to arrest the disease progression in vitiligo. Objectives: Methotrexate (MTX) is a time-tested effective treatment extensively used in various autoimmune disorders with good efficacy, safety and tolerability on a long-term basis. We intended to compare the efficacy of MTX with that of OMP in patients with unstable vitiligo vulgaris. Patients and Methods: In a prospective randomized open label study, 52 patients with vitiligo were divided into two groups. Patients in group 1 received 10 mg methotrexate weekly. Group 2 patients received corticosteroid OMP which comprised tablets of dexamethasone 2.5 mg (5 tablets), taken on 2 consecutive days in a week (total weekly dose of 5 mg dexamethasone). Results: In the MTX group, among 25 patients analyzed, during the course of treatment for 24 weeks, overall 6 patients developed new vitiliginous lesions. In the OMP group, 7/25 patients developed new lesions. Statistical correlation between the two groups showed no significance in the number of patients who developed new lesions (increasing disease activity) in either of the groups. At the end of the study, it was demonstrated that patients in both groups had a similar reduction in the vitiligo disease activity score. Conclusion: Our study demonstrated that both drugs are equally effective in controlling the disease activity of vitiligo. MTX can be used in patients with active vitiligo, wherever corticosteroids are contraindicated.

Introduction
Vitiligo is an ‘acquired cutaneous achromia characterized by white patches, often distributed symmetrically, corresponding to substantial loss of functioning epidermal and sometimes hair follicle melanocytes’ [1]. This asymptomatic, noncontagious disease is associated with significant psychosocial implications that often lead to an exaggerated sense of humiliation and loss of self-esteem in the patients [2]. The worldwide prevalence of vitiligo is around 0.5–1% with an equal sex distribution [1]. The course of the disease is unpredictable, often progressive with phases of stabilized depigmentation [3]. Approximately half of the affected persons present before 20 years of age [4–7].
Among the various theories proposed regarding the pathogenesis of vitiligo, the autoimmune hypothesis is the best-supported theory. Familial clustering of generalized vitiligo with other autoimmune diseases compels evidence for the same and a common underlying genetic susceptibility to an immunological defect in vitiligo patients [8]. Genetically linked loci like HLA-A2, -DR4, -DR7, -DBQ1 and -0303 have been identified. They appear to mediate susceptibility to both generalized vitiligo and other autoimmune diseases [9], like autoimmune thyroid disease, rheumatoid arthritis, psoriasis, diabetes mellitus, pernicious anemia, systemic lupus erythematosus, Addison’s disease and alopecia areata.

Despite continued progress towards elucidation of the biochemical, genetic and immunopathological pathways in vitiligo, a definitive cure remains elusive. The initial therapy must be directed to arrest disease progression. Corticosteroids given systemically in adequate doses have a profound effect in controlling the disease activity [10]; however, the side effects of corticosteroids are a problem, thus oral minipulse therapy (OMP) with betamethasone/dexamethasone has been tried and shown to be an effective alternative to arrest the disease progression in vitiligo. It also induces simultaneous repigmentation along with arresting disease activity [11].

Methotrexate (MTX) [12] is a time-tested effective treatment extensively used in various autoimmune disorders like psoriasis, psoriatic arthritis, alopecia areata, lupus erythematosus, generalized lichen planus, chronic urticaria and rheumatoid arthritis in low to moderate doses with good efficacy, safety and tolerability on a long-term basis. The reports on the role of MTX in vitiligo are scarce. We intended to compare the efficacy of MTX with that of OMP in patients with unstable vitiligo vulgaris.

**Materials and Methods**

It was a prospective, randomized open label study which included 52 vitiligo patients fulfilling the inclusion criteria, attending the pigmentation clinic of our department as per inclusion and exclusion criteria given below.

**Inclusion Criteria**

Patients with unstable vitiligo, i.e. 1–5 lesions in the last month, 1–15 lesions in the last 3 months, either sex with age >14 years.

**Exclusion Criteria**

Stable vitiligo patients, leukoderma secondary to other causes, pregnancy/lactation, patients with a severe hepatic, renal or other systemic disorder, immunosuppression, alcohol abuse, aphakia or cataract, segmental vitiligo, history of spontaneous repigmentation of lesions, age <14 years and patients with weight <35 kg were excluded from the study.

Patients receiving topical or systemic therapy like antioxidants and vitamins for vitiligo were kept off treatment for 2 weeks prior to recruitment into the study. Patients under phototherapy or on other immunosuppressives were excluded. A detailed history and clinical examination were performed and noted on a predesigned form. Patients were randomly assigned using a random number table to one of the two treatment groups of 25 patients each.

- **Group 1** patients received low-dose tablets of MTX, i.e. 10 mg/week, folic acid 2.5 mg a day prior to and on the day after the MTX dose.
- **Group 2** patients received corticosteroid OMP which comprised tablets of dexamethasone 2.5 mg (5 tablets), taken on 2 consecutive days in a week.

On follow-up, the patients were assessed for:

- Repigmentation in each topographical area, by a standard protocol of digital photography, and compared accordingly in two groups; repigmentation was graded as no improvement, minimal (less than 25%), mild (26–50%), moderate (51–75%) and marked to complete (more than 75%).
- Repigmentation and depigmentation in each topographical area were also assessed by the Vitiligo Area Scoring Index (VASI).

The percentage of vitiligo involvement was calculated in terms of hand units. One hand unit (which encompasses the palm plus the volar surface of all digits) was approximately equivalent to 1% of the total body surface area. The degree of pigmentation was estimated to the nearest of one of the following percentages: complete depigmentation, no pigment was present (100%); specks of pigment present (90%); depigmented area exceeds the pigmented area (75%); pigmented and depigmented areas are equal (50%); pigmented area exceeds depigmented area (25%); only specks of depigmentation present (10%).

The VASI for each body region was determined by the product of the area of vitiligo in hand units and the extent of depigmentation present (10%): $\text{VASI} = \sum [\text{hand units}] \times [\text{residual depigmentation}]$.

The color of repigmentation obtained was graded as: 1 = somewhat darker, 2 = somewhat lighter, 3 = same.

Disease activity was assessed by using the Vitiligo Disease Activity Score (VIDA).

The VIDA is a 6-point score [13]:

<table>
<thead>
<tr>
<th>Vitiligo activity</th>
<th>Time period</th>
<th>VIDA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>6 weeks or less</td>
<td>+4</td>
</tr>
<tr>
<td>Active</td>
<td>6 weeks to 3 months</td>
<td>+3</td>
</tr>
<tr>
<td>Active</td>
<td>3–6 months</td>
<td>+2</td>
</tr>
<tr>
<td>Active</td>
<td>6–12 months</td>
<td>+1</td>
</tr>
<tr>
<td>Stable</td>
<td>1 year or more</td>
<td>0</td>
</tr>
<tr>
<td>Stable + spontaneous repigmentation</td>
<td>1 year or more</td>
<td>−1</td>
</tr>
</tbody>
</table>

All patients were followed up at 2-weekly intervals during the first 2 months and later at 4-weekly intervals during the subsequent 4 months. Photographs of the observed clinical lesion/new lesions were taken during follow-up visits. Hemogram, renal function tests, liver function tests, chest X-ray, serology for hepatitis B and C, electrocardiogram and urine pregnancy test (in females)
were done at baseline and repeated at 2-weekly intervals in the first 2 months after the start of treatment and 4-weekly intervals during the subsequent 4 months in group 1.

The statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, Ill., USA, version 15.0 for Windows). All quantitative variables including age, duration of the symptoms and age of onset were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). Means were compared using Student’s t test for two groups. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using the $\chi^2$ or Fisher’s exact test whichever was applicable. All statistical tests were two-sided and were performed at a significance level of $\alpha = 0.05$.

**Results**

In this study, 52 patients with a clinical diagnosis of active spreading vitiligo were included. One patient in group 1 discontinued MTX because of severe nausea, and one patient in the OMP group was lost to follow-up. Fifty patients, 25 in each group, completed the study and were included in the final analysis. The youngest patient was 14 years of age and the oldest 62 years. The mean age in group 1 and group 2 was 38.60 ± 12.52 and 32.68 ± 15.48 years, respectively. Twenty-four patients were females and 26 males. There was no statistically significant difference between the two groups in comparison to age, gender, duration of disease and age of onset as shown in the online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000433424).

Precipitating factors like trauma in 11 (22%) patients (6 in group 1, 5 in group 2), drugs in 3 (6%) patients in group 1 and pregnancy in 1 (2%) patient (group 1) were observed. Associated autoimmune disease was noted in 6/50 patients (hypothyroidism, diabetes mellitus and lichen planus were seen in 4, 1 and 1 patient, respectively), 15 (30%) patients, i.e. 7/25 patients in group 1 and 8/25 in group 2, had a family history of vitiligo in first degree relatives.

**Disease Activity**

In group 1, among 25 patients, during the course of treatment for 24 weeks, overall 6 patients developed new vitiliginous lesions, i.e. 2 patients each at weeks 2, 12 and 20, respectively. Similarly in group 2, 7/25 patients developed new lesions, i.e 1 patient each at weeks 4, 6, 8, 16 and 20, and 2 patients at week 12, respectively. Statistical correlation between the two groups showed no significance in the number of patients who developed new lesions (increasing disease activity) in either of the groups. Similarly on using intention to treat analysis, the two groups were comparable without any statistical significance.

At the end of study, it was demonstrated that patients in both groups had a similar reduction in the VIDA score as shown in online supplementary figure 1. Assessment of repigmentation in the observed lesions of the patients in both groups revealed that 11 and 15 patients in groups 1 and 2, respectively, had attained repigmentation to a variable extent (online suppl. fig. 2), and the same was demonstrable by IgA evaluation also (online suppl. fig. 3).

Diffuse repigmentation was the commonest pattern noted in 16 (64%) patients overall (6 in group 1 and 10 in group 2), followed by a perifollicular one in 5 (20%) patients (1 in group 1 and 4 in group 2). Two (8%) patients in group 1 showed combined repigmentation, and 1 (4%) patient in group 2 showed marginal repigmentation. Patients in both groups demonstrated reduction in the VASI at the end of 24 weeks of follow-up as shown in online supplementary figure 4.

**Adverse Effects**

Apart from 1 patient who discontinued MTX because of severe nausea, only 4 (16%, nausea) patients in group 1 and 5 (20%, weight gain and acneiform eruption) in group 2 developed adverse effects, which was mild and did not warrant the discontinuation of drugs in either group.

**Discussion**

Although vitiligo has been documented since times immemorial under various terminologies, the exact course of disease is unpredictable with nearly half presenting before 20 years of age. Generalized vitiligo is the commonest presentation often involving the face and acral regions. Although few may itch or have a propensity to sunburn most of them are asymptomatic. In active vitiligo there is either appearance of new lesions or increase in size of previously present lesions with or without the presence of Koebner’s phenomenon. As vitiligo is associated with psychosocial stigma affecting the individual’s quality of life, it needs to be controlled religiously. Response to treatment depends upon multiple factors; cases with recent disease onset, darker skin types, lesions on the face, neck and trunk respond better to treatment than those with longer disease duration, mucosal and acral lesions. As most patients seek treatment when the disease is active, for treatment to be effective, arrest of disease activity is equally important as it is to induce repigmentation.
Although the etiology of vitiligo is unknown, substantial data from clinical research has supported the ‘autoimmune theory’ which is further supported by the frequent association of vitiligo with other autoimmune disorders like Hashimoto’s thyroiditis, Graves’ disease, type 1 insulin-dependent diabetes mellitus and Addison’s disease. An increase in the production of proinflammatory cytokines like interleukin (IL)-6 and IL-2 in vitiligo patients may play an important role in melanocytic cytotoxicity [14].

Parameters which recognize disease activity and severity are the VASI and VIDA. Oral corticosteroids given systemically have been shown to be effective in controlling disease activity in various studies [10]. OMP with corticosteroids is the simplest of all the treatment modalities available, given only 2 days a week with a better side effect profile, improved patient compliance and lesser steroid phobia over daily corticosteroids.

The disease activity control by corticosteroids varies from 44 to 89%. Pasricha and Khaitan [10] studied 40 vitiligo patients of whom 36 had actively spreading disease; disease activity was arrested in 89% of patients within 1–3 months of treatment initiation. In another study by Kanwar et al. [11] on 32 patients, stability of disease activity was seen in 14 (44%) patients, and they also noted mild to moderate repigmentation. No side effects were observed in patients. In a retrospective study on patients with progressive unstable vitiligo, who were administered oral dexamethasone 2.5 mg/day on 2 consecutive days weekly, 91.8% of patients showed arrest of disease activity within 13.2 ± 3.1 weeks [15].

In our study group 2 (OMP), 72% of patients showed arrest of disease activity, which coincides with the previously reported figures of 44 and 89% [11, 16]. Lesional repigmentation of the observed lesions in our group 2 patients was noted in 60% of patients in comparison to the 80% of Pasricha and Khaitan [10], 76% of Banerjee et al. [17] and 17.2% of Radakovic-Fijan et al. [16]. Adverse reactions like weight gain or acneiform eruptions were observed in only 20% in our study patients, in comparison to the studies by Kanwar et al. [15] (9.2%), Pasricha and Khaitan [10] (22.5%) and Radakovic-Fijan et al. [16] (69%).

MTX is a time-tested effective drug extensively used in various autoimmune disorders. In autoimmune disease, MTX inhibits the oxidative burst in neutrophils and monocytes, prevents leukocyte chemotaxis and inhibits monocyte and macrophage secretion of multiple cytokines, e.g. tumor necrosis factor (TNF)-α, IL-6, IL-10 and IL-12. MTX selectively induces apoptosis in activated, proliferating CD4 T cells rather than in resting T cells.

Based on our experience of treating vitiligo as well as successful treatment with half the standard dose of OMP (total dose of 5 mg/week as compared to 10 mg/week) [15], we used a low dose of MTX in this study.

Singh et al. [14] observed an increase in the production of proinflammatory cytokines such as IL-6 and IL-2 in vitiligo patients, which may play an important role in melanocytic cytotoxicity. Rudwaleit et al. [18] showed that MTX treatment results in a decreased number of T cells capable of TNF-α production, whereas the number of T cells producing IL-10 after polyclonal activation increased. MTX possibly suppresses TNF-α-induced nuclear factor-κB activation through the release of adenosine, which may contribute to the role of MTX in anti-inflammatory, immunomodulatory and antiproliferative effects [19]. Modulations of IL-6 synthesis and reactive oxygen species production may contribute to the therapeutic effects of MTX [12].

Recently Al Ghamdi and Khurrum [20] studied the effect of MTX on 6 vitiligo patients with an average age of 29 years with more than 6% of the body surface area affected; in total, they underwent 6 months of MTX treatment (25 mg/week) with folic acid 5 mg daily except the day on which they took MTX. Clinical and photographic assessments revealed no change in their vitiligo lesions. The MTX therapy was well tolerated, and no side effect was noted. In another case report by Sandra et al. [21], a patient with long-standing rheumatoid arthritis with recently developed progressive vitiligo lesions responded well to a weekly oral dose of MTX 7.5 mg with improvement of arthritis and arrest of vitiligo activity along with considerable repigmentation at 3 months of follow-up. We observed that among 25 patients in group 1 who received MTX, stabilization of disease activity was achieved in 19 (76%); only a few (6 patients) had breakouts of disease activity in the treatment period who stabilized on continuing MTX therapy. Six (24%) developed new lesions during 24 weeks, in the remaining 19 (76%) the drug was successful in stabilizing the disease activity. In group 2 (OMP), 7 (28%) patients developed new lesions, and the remaining 18 (72%) did not show any new lesions in the follow-up period; however, the difference was not statistically significant (p = 0.75). Disease-related psychological and emotional stress was observed as the reason for exacerbation in most of the patients.

The VIDA was used to assess the disease activity of vitiligo. Patients in both groups showed similar reductions in the VIDA score. At 0 week, both groups had VIDA +4, that means new lesions had appeared during the last 6 weeks or less, and after 24 weeks of treatment the mean
VIDA in group 1 was 1.72, and in group 2 it was 1.76; the difference was not statistically significant (p = 0.352).

In our study repigmentation of vitiliginous lesions in each topographical area was assessed using a standard protocol of digital photography and VASI; 15 (60%) patients in group 2 showed mild to moderate pigmentation at response sites which was more when compared to only 9 (36%) patients in group 1. Patients in both groups demonstrated a reduction in the VASI at the end of 24 weeks of follow-up, the commonest form of repigmentation being the diffuse pattern.

The side effects observed in our study were minor and did not warrant discontinuation of either treatment modality in any of the patients.

Our study exemplifies that both drugs are equally effective in controlling the disease activity of vitiligo. Results were comparable in both groups, and the difference observed was not statistically significant. MTX can be used in patients with active vitiligo, wherever corticosteroids are contraindicated like in diabetes mellitus, hypertension, cataract, glaucoma patients, etc. As there is only 1 previous study of MTX use in 6 patients with vitiligo and no studies comparing MTX and OMP, further studies are required to corroborate our results. Also our study used 24 weeks of follow-up; long-term controlled studies with blinded assessment of a larger cohort are required to augment the findings of our study [22–25].

Disclosure Statement

No conflict of interests and no financial support to disclose.

References