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LETTER TO THE EDITOR

Subcutaneous (SC) Methotrexate (MTX) is Better and Well-Tolerable than Oral MTX in Rheumatoid Arthritis Patients, Switched from Oral to SC Administration Due to Gastrointestinal Side Effects

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DEAR EDITOR,

Methotrexate (MTX) is an anchor drug in the treatment of patients with rheumatoid arthritis (RA) and is the preferred first line agent for this condition. It has a well established efficacy and safety profile but gastrointestinal (GI) side effects of oral route may restrict its use in most of the patients [1, 2]. Subcutaneous MTX is reported to be well tolerated and more effective even at higher doses than used orally [3, 4]. Subcutaneous form is suggested to be more expensive but it can impede the introduction of biologics and provide considerable savings [5, 6]. The aim of this study was to evaluate if subcutaneous MTX was more effective in our group of patients with RA, previously received oral MTX and switched to subcutaneous MTX, due to GI side effects.

We report a retrospective analysis of 80 patients with RA who were switched from oral to subcutaneous MTX recruited from the Rheumatology unit of a tertiary Education and Research Hospital. The ethics committee approved the study. We have included the switched patients due to GI side effects of oral MTX. The patients who were not only on MTX therapy as disease modifying agent, were excluded. Demographic data, including age, gender, disease duration, and disease activity parameters comprising DAS28, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), as well as rheumatoid factor (RF), and pain by visual analog scale (VAS) were recorded. Their disease control was reported for the last visit of oral MTX, and 1st and 3rd month visits after subcutaneous MTX.

Sixty-eight female and 12 male patients with a mean age of 54.06 ± 1.4 years were enrolled to the analysis. The mean disease duration and oral MTX duration were 122.5 ± 96.8 months and 52.01 ± 45.1 months respectively. The mean oral and subcutaneous dose were 15.1 ± 5.8 mg/week (7.5 mg-20 mg) and 16.5 ± 5.2 (10 mg-20 mg) respectively. RF positivity was present in 51 (64%) patients. The entire patients had GI side effects before starting subcutaneous MTX. Some of the patients were on low dose steroid (n=23) and/or NSAI drugs (n=42) in addition to MTX therapy. The most common GI side effects were nausea and/or vomiting (n=45), followed by disturbed liver function tests (n=18), budget taste and/or dyspeptic symptoms (n=10), diarrhea (n=9) and stomatitis (n=4). No patients had active ulceritis. All of the disease activity parameters including DAS28, ESR, CRP, pain by VAS were decreased at 1st and 3rd month visits after the subcutaneous therapy (Table **1**). The number of patients with GI side effects, were also decreased in the first (n=30, $p<0.05$) and third month visits (n=27, $p<0.05$). At 3rd month visit, there was no drop out with subcutaneous MTX.

A recent retrospective study indicated that the practice of switching from oral to SC MTX alleviated GI adverse effects in 57 RA patients [7]. We did not assess the quantitative intensity of GI side effects. The GI side effects of our patients do not disappear in the majority of patients but have been tolerable, as indicated with no drop-outs at the end of third month. The relatively small number of patients with attenuated GI adverse effects may be explained by the potential side effects of other drugs like corticosteroids and/or NSAIDs.

Previous placebo-controlled studies indicated that switching MTX from the oral to subcutaneous route improved responses over 24 weeks [4, 8]. Hameed and Jones reported significant improvements in disease activity of switched patients due to inefficacy or intolerability to oral forms of MTX. But this improvement was more significant when switching was applied due to intolerance to oral MTX [5]. The absence of placebo subcutaneous group and a relatively shorter study period could be considered as the limitations of our study. Therefore, we may not completely eliminate the natural amelioration of the disease in our patients who were switched from oral to subcutaneous MTX.

In conclusion our data indicates that the subcutaneous MTX may have better efficacy in regard to disease activity, and have better tolerability than in oral forms, if oral route is not endurable due to GIS side effects, in patients suffering

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Table 1. The disease activity parameters before switching from oral to subcutaneous MTX and at first and third months after switching.

	Last Visit of Oral MTX n=80	1st Month Visit After sc MTX n=80	3rd Month Visit After sc MTX n=80	p
DAS28	4.0±0.9	3.6±0.8	3.4±0.8	<0.01
ESR	42.5±21	33.8±17.4	29.7±15	<0.05
CRP	2.3±2.8	1.4±1.4	0.8±0.9	<0.05
pain by VAS	66.9±18.9	53.9±14.2	51.6±14.4	<0.05

from RA. We suggest a proper move to the subcutaneous form of MTX if there is intolerability to oral formulation, in order to allow its continuing use and sustain disease control.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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