Oral events related to low-dose methotrexate in rheumatoid arthritis patients

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Abstract: Low-dose methotrexate (MTX) is frequently used for patients with rheumatoid arthritis (RA). High doses of MTX frequently produce side effects. The aim of this study was to explore oral complications of low-dose MTX therapy in a population of RA patients. This is a cross-sectional study in which oral examination was performed on a population of RA patients. Patients undergoing MTX therapy (5-20 mg weekly) for at least six months were included in the study group, and RA patients being treated under another regimen were used as controls. The frequency of oral lesions was compared between groups. The chi-square test was used to compare frequencies. Relative risk (RR) and its confidence interval (CI) were established. Significance level was set at 0.05. Twenty-eight RA patients on a low-dose MTX regimen and 21 controls were enrolled in the study. Oral lesions were found in 22 patients (78.6%) undergoing MTX therapy, and in 5 patients (23.8%) undergoing other therapies ($p < 0.001$). There were no significant differences regarding age, gender or dosage. The most common oral events observed in patients in the MTX group were ulcerative/erosive lesions (60.7%) and candidiasis (10.7%). Patients in the control group presented lower prevalence of the same lesions ($p < 0.001$). The RR for developing oral lesions was 11.73 (CI 2.57 – 58.98), with low-dose MTX therapy. In conclusion, the prevalence of oral mucosa lesions in RA patients receiving low doses of MTX therapy is higher than in RA patients not receiving the drug.

Descriptors: Methotrexate; Arthritis, rheumatoid; Oral manifestations; Mucositis.

Introduction

Rheumatoid arthritis (RA) is the most common rheumatic disease, and low-dose methotrexate (MTX) is used extensively as a second line therapy in the treatment of RA. High doses of MTX are used for treating hematological malignant neoplasms, and may produce many adverse events such as hepatotoxicity, pneumonitis, opportunistic infections, and the development of certain types of malignancies.[1-3] Oral mucosa may be frequently affected by high doses of MTX, but few clinical trials have reported oral mucosa impairments in patients taking low doses of MTX.[2,4-8]

Methotrexate has been studied for the management of rheumatic diseases over the past twenty years, but most knowledge about MTX comes

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from oncology studies.[9] This drug is used in low doses in the treatment of rheumatic diseases, but it still may produce side effects such as dizziness, nausea, diarrhea, cough, headache, skin rash, malaise and mouth ulcers.[2,8]

Oral and intestinal epithelial cells are sensitive to the effects of MTX and may be frequently affected by mucositis.[1,10] Erythematous, erosive and ulcerative oral lesions may be a consequence of MTX therapy.[2,4-8] The aim of this cross-sectional study was to compare the findings regarding oral events of RA patients taking a low-dose MTX regimen with those of RA patients not taking MTX.

Material and Methods

Patient population

All patients assigned to this transversal study were being treated at the Rheumatology Clinic of the University Hospital, Federal University of Rio de Janeiro. Men and woman, at least 18 years old and with active RA, were eligible for the study. Patients were diagnosed with RA as defined under the revised criteria of the American Rheumatism Association.[11] To be included in the study group, patients must have been undergoing low-dose methotrexate therapy (5 to 20 mg weekly) for least 6 months, without interruption. Patients being treated under another RA therapy regimen were included in the control group. Patients who did not meet the RA criteria definition, and those undergoing MTX therapy for less than six months, were excluded from the present study. The study was approved by the institutional ethics committee. Fully informed consent was obtained from each patient.

Clinical assessment

From April to June 2005, an oral examination was performed on each subject at the Rheumatology Clinic by a stomatologist using a halogen light source. Demographic status and clinical data were obtained from medical records.

Statistical analysis

Sample size was calculated using Epi-Info 6.0® (Centers for Disease Control and Prevention, Atlanta, GA, USA), based on a pilot study. The chi-square test was used to compare frequencies. Student's t-test was used to compare measured data. Statistical analysis was performed with SPSS 10.0® (SPSS Inc., Chicago, IL, USA). Alpha error level was set at 0.05. Additionally, relative risk for developing oral events to MTX was calculated using Epi-Info 6.0®, and its confidence intervals were expressed with limits of 95%.

Results

Sixty-five RA patients were examined. Sixteen patients were excluded for using MTX for less than six months, twenty-eight RA patients taking low doses of MTX (5-20 mg/week) were included in the study group, and twenty-one patients with RA being treated with drugs other than MTX were used as controls. The demographic and clinical data of RA patients from the two groups are shown in Table 1.

Two patients using MTX experienced nausea and headache. Oral lesions were observed in 22 patients (78.6%) in the MTX group and in 5 patients (23.8%) undergoing regimens involving other therapies ($p < 0.001$) (Table 2). Moreover, the relative risk for developing oral lesions as an adverse effect with low-dose MTX therapy was 11.73 (confidence interval: 2.57-58.98).

The most common oral lesions in both groups were ulcerative/erosive lesions (60.7% in patients undergoing MTX therapy and 19.1% in patients undergoing other therapies). The most frequent sites were the alveolar mucosa (35.1%) and the tongue (21.6%), followed by the palate (18.9%), buccal mucosa (13.5%), gingival mucosa (8.1%) and the floor of the mouth (2.7%). Erythematous candidiasis occurred in 10.7% of patients taking MTX, while one patient (4.8%) not taking MTX presented pseudomembranous candidiasis. The patient with parotid enlargement did not show other clinical or laboratorial evidence for Sjögren's syndrome.

As far as the dose of MTX was concerned, no significant correlation to oral lesions was found ($p = 0.32$). Moreover, oral ulcerative/erosive lesions were not correlated to either age ($p = 0.07$) or gender ($p = 0.30$). There were three patients (10.7%) in the MTX group with no folic acid therapy. All of them presented oral ulcerative/erosive lesions, and

Table 1 - Demographic and clinical characteristics of the 49 patients with rheumatoid arthritis in the study.

	Patients undergoing MTX therapy n = 28	Patients undergoing other therapies n = 21	*p* value*
Gender			
• Male	3 (10.7%)	5 (23.8%)	0.220
• Female	25 (89.3%)	16 (76.2%)	
Age			
• Mean ± Standard Deviation	53 ± 11	55 ± 14	0.295
• Range	33 – 78	32 – 81	
Ethnicity			
• White	9 (32.1%)	9 (42.9%)	0.446
• Non-white	19 (67.9%)	12 (57.1%)	0.213
Comorbidities			
• Hypertension	10 (35.7%)	4 (19.0%)	0.206
• Sjögren's syndrome	1 (3.5%)	-	0.386
• Other comorbidities	8 (28.6%)	8 (38.1%)	0.486
Medications			
• Corticoid	26 (92.8%)	17 (80.9%)	0.213
• NSAID	13 (46.4%)	9 (42.9%)	0.806
• DMARD (other than MTX)	9 (32.1%)	8 (38.1%)	0.668
• Folic acid	25 (89.3%)	2 (9.5%)	< 0.001
• Other medications	25 (89.3%)	16 (76.2%)	0.414

NSAID = nonsteroidal anti-inflammatory drug; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate.
*Student's t-test was performed for evaluation of age, and the chi-square test for the other variables.

Table 2 - Prevalence of oral and perioral conditions of the 49 patients with rheumatoid arthritis in the study.

	Patients undergoing MTX therapy n = 28		Patients undergoing other therapies n = 21	
	Male n = 3 (10.7%)	Female n = 25 (89.3%)	Male n = 5 (23.8%)	Female n = 16 (76.2%)
No lesions	2 (7.1%)	4 (14.3%)	4 (19.0%)	12 (57.1%)
Ulcerative/erosive lesions	1 (3.6%)	16 (57.1%)	-	4 (19.1%)
Candidiasis	-	3 (10.7%)	1 (4.8%)	-
Gingival hyperplasia	-	1 (3.6%)		
Parotid enlargement	-	1 (3.6%)		
p value		0.736		0.953

The result of the chi-square test for the difference in the frequency of lesion development between groups was $p < 0.0001$.

one of them presented erythematous candidiasis.

Discussion

The population of patients with rheumatic arthritis and undergoing low-dose MTX therapy, who participated in this study, presented high relative risk (11.73; CI: 2.57-58.98) for developing oral events. The RA patients under MTX therapy presented significantly higher prevalence of oral lesions than RA patients using other drugs. These data may suggest

that low-dose MTX therapy induces impairments in oral mucosa, and are consistent with other studies that have also reported higher prevalence of oral events in RA patients undergoing MTX therapy.[2,4-8]

Rheumatoid arthritis patients not being treated with MTX also presented oral lesions. However, the prevalence of oral lesions in the control group (23.9%) is consistent with the prevalence of oral lesions in the Brazilian population.[12] The oral candidiasis found in patients of both groups may be due to the use of imunossupressive drugs[13] or to lower salivary flow rates that usually affect RA patients.[14,15]

Regarding some peculiarities observed in some of the patients, there was a parotid enlargement found in one RA patient taking MTX, which might be a marker of salivary gland dysfunction and/or an early sign of secondary Sjögren's syndrome. This patient did not show evidence for Sjögren's syndrome in laboratory tests. The gingival hyperplasia found in one patient may be due to cyclosporin therapy.[16]

The present study did not find correlation of oral lesions with age or with MTX dosage, in RA patients taking low-dose MTX. These findings are in agreement with those of Hoekstra *et al.*,[6] who studied 411 RA patients in a randomized placebo-controlled trial. However, they did find a correlation between gender and side effects, which was not found in the present study. In a review study of MTX intolerance in the elderly, Drosos[17] reported that aging does not seem to predispose RA patients undergoing low-dose MTX treatment to adverse events.

Kremer *et al.*[2] described MTX dose-related oral ulcers in RA patients in a double blind, randomized, placebo-controlled study for further evaluation of treatment with etanercept and MTX. However, Ruperto *et al.*[3] studied the safety and efficacy of different low doses of parenteral MTX, and reported no relationship between the prevalence of oral lesions and the different doses.

It is noticeable that side effects from low-dose MTX treatment may occur also in the gastrointestinal mucosa. The sensitivity of the gastrointestinal epithelium may be due to greater accumulation and persistence of MTX in the cells of the intestinal mucosa.[9,17] The scope of the present study was limited to oral mucosa alterations.

In an effort to explain the appearance of oral lesions related to MTX use, the mechanism of action was researched. The methotrexate mechanism involves many pathways, resulting in inhibition of inflammatory markers;[18] also, in an increase of adenosine, which is associated with several anti-inflammatory and immunosuppressive effects.[19] A potential mechanism by which MTX may diminish inflammation of the joint is by reducing cytokine production. It reduces the levels of polyamines accumulated in the synovium of RA patients, and of the antigen-stimulated T-cell proliferation. However, the most important mechanism may be related to an increase in the adenosine A_{2A} receptor, a potent inhibitor of neutrophil leukotriene synthesis,[19,20] which acts by inhibiting interleukin (IL) 12 and tumor necrosis factor alpha (TNF-α).[21] Low-dose MTX used by RA patients mimics non-steroidal anti-inflammatory drugs or cyclo-oxygenase-2-selective drugs. However, there is no clear explanation for the development of the oral lesions with low-dose MTX.[22] Oral toxicity produced by high doses of chemotherapy drugs involves a complex mechanism with gene up-regulation and liberation of nuclear factor-$\kappa\beta$, TNF-α, IL-1β, IL-6, among other mediators, with consequent apoptosis and tissue damage.[23]

Studies have reported that folic acid may play a protective role when associated with MTX therapy.[2,6,17,24] In fact, the three patients in the present study that were not taking folic acid as a complement to MTX therapy presented oral ulcerative/erosive lesions. The administration of folic acid, in doses of 1 to 5 mg per day, helped to prevent the toxicity of MTX without interfering with the anti-inflammatory efficacy of the drug.[19,20] MTX acts as a folate antagonist, and most of the adverse effects of MTX are related to the antifolate activity which may mimic symptoms of folate deficiency.[17] Folates are involved in the synthesis of purines, and disruption of purine metabolism leads to an increase in extracellular adenosine by the increase of adenosine receptors.[24] It is possible that high concentrations of adenosine and related compounds may be directly toxic.[24]

Interestingly, some patients do not develop oral mucositis under a high-dose MTX regimen. Genetic

polymorphism has been implicated as a predictive factor for MTX toxicity.[25] Hematopoietic cell transplant recipient patients, carrying some genotypes, should be considered to be at greater risk for developing oral mucositis.[26,27] Further studies are needed to clarify the role of the genetic polymorphism theory.

Studies analyzing oral lesions, related to different doses and routes of administration of MTX, must be performed in order to understand the natural history of the oral manifestations related to the use of MTX. Furthermore, laboratory findings must be considered to exclude haematinic deficiencies such as eosinophil counts, vitamin B12, iron and folate levels in the blood. In addition, clinical trials focusing on the prophylaxis of oral events resulting from MTX must be conducted. In practice, healthcare professionals must be aware of monitoring for oral events in RA patients taking MTX.

Conclusion

The prevalence of oral mucosa lesions in RA patients being treated with low-dose MTX therapy is higher than in RA patients not taking the drug. Clinicians must be aware not to misdiagnose the oral lesions caused by low-dose MTX use.

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