The Journal of Rheumatology Volume 30, no. 9

# Therapeutic benefits of irsogladine maleate on aphthous stomatitis induced by methotrexate in rheumatoid arthritis.

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J Rheumatol 2003;30;2082-2083
http://www.jrheum.org/content/30/9/2082.citation


**INSTRUCTIONS FOR LETTERS TO THE EDITOR**

**Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.**

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## Aldolase Levels in Dermatomyositis and Polymyositis with Normal Creatine Kinase Levels

*To the Editor:*

We read with interest the recent letters by Carter, *et al*[1] and by Mercado[2], and would like to report our experience on the value of creatine kinase (CK), aldolase, aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) levels in diagnosing adult polymyositis (PM) or dermatomyositis (DM).

Since 1978, we have seen in our internal medicine and dermatology departments, 48 consecutive patients with either DM (35 patients) or other inflammatory muscle disorder (11 with polymyositis, one with overlap syndrome, and one with inclusion myositis). CK, aldolase, and AST were simultaneously measured before treatment in 46 patients, with additional measurement of LDH in 38. As shown in Table 1, there was discrepancy between CK and aldolase in 6 patients: 2 had elevated CK with a normal aldolase level, and 4 had a normal CK level with high aldolase level. Noteworthy, one patient had on several instances an 8-fold increase in aldolase level along with a very low CK level. This 70-year-old woman had a definite PM, including the finding of a high aldolase level[3] and 4 Bohan and Peter criteria[4], associated with blood eosinophilia and subclinical relapse of cancer of the breast[5]. The other 3 patients had clinical diagnosis of DM with 3 to 5 Bohan and Peter criteria, but no associated malignancy. Overall, 3 out of 6 patients with discordant data on muscle enzyme levels were found to have a malignancy associated with DM or PM. Although aldolase may become elevated in serum with malignant tumors, the only patient in our series who had an isolated high aldolase level and concurrent malignancy had polymyositis. Moreover, the aldolase quickly normalized when glucocorticoid treatment was introduced, thereby substantiating its muscle origin in this patient. Finally, no condition that can give rise to aldolase in the serum, such as myocardial infarction, acute hepatitis, obstructive jaundice, or hemolytic anemia, were apparent in any of these patients.

We found using the Spearman rank correlation a strong correlation in the 46 patients between CK and aldolase ($r = 0.69$, $p < 0.0001$), AST ($r = 0.79$, $p < 0.0001$), and LDH ($r = 0.66$, $p < 0.0001$). These results indicate that, in agreement with Dr. Carter's statement, when evaluating patients for DM or PM, the initial blood test should be a CK measurement. However, the finding of a high aldolase level as the sole blood marker of muscle damage in PM with or without dermatological signs may not be anecdotal, since we observed this scenario in 4 patients (9.5%) with the disorder. Similarly, Vignos, *et al* found that 4 out of 20 patients with PM had normal CK. Of these 4 patients, 2 had elevated aldolase levels[6]. Further, the AST and LDH levels may also be normal in this setting, as observed in 3 of 4 patients in our series. We therefore fully agree with Carter, *et al* and Dr. Mercado's opinion that, in the appropriate clinical setting, normal levels of both CK and AST do not preclude active PM. In patients, particularly (but not only) those with malignancy, whose clinical picture strongly suggests PM, but who are found to have normal CK levels, it may be useful to control aldolase levels. However, whether aldolase may accurately serve to follow the efficacy of treatment in patients with PM and a normal CK level deserves further study.

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*Table 1.* Clinical and laboratory findings in patients with polymyositis or dermatomyositis and discordant creatine kinase and aldolase levels.

| Patient | Age | Clinical Diagnosis | No. of Bohan Criteria | CK | Aldolase | AST | LDH |
|---|---|---|---|---|---|---|---|
| 1 | 46 F | DM and M | 5 | 440 (290) | 3.4 (4) | 14 (40) | 301 (500) |
| 2 | 75 F | PM and M | 4 | 412 (290) | 3.9 (4) | 48 (35) | NA |
| 3 | 70 F | PM and M | 4 | 31 (190) | 25 (3) | 35 (40) | 527 (500) |
| 4 | 33 M | DM | 5 | 120 (190) | 9 (3) | 68 (40) | 956 (800) |
| 5 | 53 M | DM | 3 | 181 (190) | 7 (3.5) | 21 (35) | 417 (500) |
| 6 | 65 F | DM | 3 | 140 (170) | 7.6 (3) | 25 (35) | 498 (800) |

DM: dermatomyositis; PM: polymyositis; M: malignancy (cancer of the breast in 2, breast and colon in one) CK: creatine kinase; AST: asparate aminotransferase; LDH: lactate dehydrogenase; NA: not available. Number in parentheses indicate the upper limit of normal values.

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## Dr. Carter, *et al* reply

*To the Editor:*

Dr. Liozon and his colleagues are to be commended on their data regarding inflammatory muscle disorders. To our knowledge, their cohort of 46 patients with adult polymyositis or dermatomyositis represents the largest series of patients in which creatine kinase (CK), aldolase, and aspartate aminotransferase (AST) were measured on all patients prior to treatment.

In their series of 46 patients, 4 (9.5%) had normal CK in the setting of elevated aldolase concentrations. In the series reported by Vignos, *et al*, 2 out of 20 patients (10%) had a normal CK with elevated aldolase[1]. Our group and Dr. Ulises Mercado described similar patients with definite dermatomyositis with elevated aldolase and normal CK levels in *The Journal*[2,3]. While the numbers are still rather small, these data suggest that perhaps as many as 10% of patients with active myositis can present with normal CK and elevated aldolase levels.

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## Dr. Mercado replies

*To the Editor:*

The interest in my report in *The Journal* is much appreciated. Three cases described by Dr. Liozon and colleagues are examples of idiopathic dermatomyositis (DM) with normal creatine kinase (CK) and elevated aldolase concentrations, while the other 3 cases are DM or polymyositis (PM) associated with malignancy.

As noted, the most useful enzymes in diagnosis and prognosis of inflammatory disorders of muscle are serum CK and aldolase. The aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH) enzymes may appear in increased amounts as well. These 3 enzymes share a site of origin in both muscle and liver. Aldolase, which catalyzes the breakdown of fructose 1,6-bisphosphate, is often thought to be a muscle-specific enzyme, but is also present in the liver. Therefore an increase of AST, ALT, and LDH enzymes obligates us to test for gammaglutamyl-transferase (GGT) to determine a liver origin, since this enzyme is not found in muscle[1].

Patients with myositis and malignancy who improved with therapy despite the presence of tumor have been described. In 1980, Perlman and Barth[2] reported a case of myositis, with elevated serum CK, breast cancer, and interstitial lung disease in a 47-year-old woman. She received corticosteroids and a cytotoxic agent. Despite the presence of tumor her CK level returned to normal. The tumor was then resected, but it recurred 4 months later. At that time muscle symptoms became more prominent, but her CK remained normal. She died of disseminated carcinomatosis. In their letter, Liozon, *et al* describe a 70-year-old woman with myositis, breast cancer, normal CK and elevated aldolase, and blood eosinophilia, who had relapse of the breast cancer. When she received corticosteroids, the aldolase rapidly normalized. While the blood eosinophilia could be explained by a hypersensitivity mechanism to tumor antigens, the high aldolase level may have been the result of involvement of both liver and muscle.

According to Pearson[3], metastatic tumors are rarely seen in skeletal muscle. However, they may be more common than is believed. In 1959, he found 6 cases of metastatic tumor out of 38 cases of malignant disease surveyed at autopsy.

Much has been learned about inflammatory disorders of muscle since the pioneer works by Carl M. Pearson. But what initiates muscle fiber destruction in idiopathic DM/PM? It continues to be a mystery.

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## Antineutrophil Cytoplasmic Antibodies in Patients with Systemic Sclerosis

*To the Editor:*

We read with interest the article of Ruffatti, *et al* concerning autoantibodies to proteinase 3 and myeloperoxidase in systemic sclerosis (SSc)[1]. In their study of 115 patients with SSc, they found that antibodies to proteinase 3 (PR3-antineutrophil cytoplasmic antibodies) as well as antibodies to myeloperoxidase (MPO-ANCA) might be detected in some SSc sera. Recently we also investigated SSc, and we now confirm this finding.

Sera from 11 patients with SSc were assayed by indirect immunofluorescence (IIF) on in-house ethanol-fixed normal human neutrophils and commercial formalin-fixed neutrophils, and on HEp-2 cells (The Binding Site, Birmingham, UK). All sera were tested by direct ELISA kits (The Binding Site) against PR3, MPO, bactericidal/permeability increasing protein (BPI). In-house ELISA against lactoferrin and human neutrophil elastase were also performed as described[2].

Table 1 gives the results. Three of the 11 sera produced perinuclear/nuclear staining pattern on ethanol-fixed neutrophils. When these sera were retested on formalin-fixed neutrophils granular cytoplasmic fluorescence was observed in 2 sera, and these sera were defined as p-ANCA positive. ELISA results revealed that 5 of the 11 sera contained ANCA directed specifically against the following neutrophil antigens: MPO (n = 2), PR3 (n = 2), BPI (n = 1), and human neutrophil elastase (n = 1). One serum contained ANCA against PR3 and BPI simultaneously. Only MPO-ANCA positive sera were p-ANCA positive by IIF.

Of note, the patient with PR3- and BPI-ANCA was repeatedly positive for these antibodies and clinically showed lung fibrosis and pulmonary

*Table 1.* ELISA and IIF results for ANCA testing in 11 patients with SSc. IIF used ethanol-fixed (EF) and formalin-fixed (FF) neutrophils as substrates for detection of ANCA and HEp-2 cells for detection of ANA.

| Patient | ELISA MPO-ANCA | ELISA PR3-ANCA | ELISA BPI-ANCA | ELISA LF-ANCA | ELISA HLE-ANCA | IIF EF Neutrophils | IIF FF Neutrophils | IIF HEp-2 Cells |
|---|---|---|---|---|---|---|---|---|
| 1 | – | + | + | – | – | P/N | Neg | Speckled + nucleolar |
| 2 | – | – | – | – | + | Neg | Neg | Nucleolar |
| 3 | – | – | – | – | – | Neg | Neg | Speckled + nucleolar |
| 4 | – | – | – | – | – | Neg | Neg | Nucleolar |
| 5 | – | + | – | – | – | Neg | Neg | Speckled + nucleolar |
| 6 | – | – | – | – | – | Neg | Neg | Speckled + nucleolar |
| 7 | – | – | – | – | – | Neg | Neg | Nucleolar |
| 8 | – | – | – | – | – | Neg | Neg | Nucleolar |
| 9 | – | – | – | – | – | Neg | Neg | Nucleolar |
| 10 | + | – | – | – | – | P/N | Cytoplasmic | Fine speckled |
| 11 | + | – | – | – | – | P/N | Cytoplasmic | Fine speckled |

P/N: perinuclear/nuclear. MPO: myeloperoxidase, BPI: bactericidal/permeability-increasing protein, LF: lactoferrin, HLE: human neutrophil elastase.

hypertension, but no renal involvement. No study patient had any symptom or sign of secondary renal disease.

Our small study indicates that the IIF results did not appear to predict the occurrence of specific ANCA in patients with SSc, in agreement with the findings of Ruffatti, *et al*[1]. Further studies are needed to determine whether autoantibodies to several neutrophil antigens are present in SSc and whether these antibodies are associated with some clinical features.

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## Dr. Ruffatti, *et al* reply

*To the Editor:*

We thank Dr. Manolova and Dr. Dancheva for their interest in our article[1]. The results they report confirm that proteinase 3 (PR3)-antineutrophil cytoplasmic antibodies (ANCA) as well as myeloperoxidase (MPO)-ANCA may be detected in some patients with systemic sclerosis (SSc). Moreover, the lack of correlation between their ELISA and indirect immunofluorescence (IIF) findings is in agreement with our data. Further, in addition to the classical p-ANCA pattern, a perinuclear/nuclear staining pattern on ethanol-fixed and negative staining on formalin-fixed neutrophils was found in their scleroderma sera. This too is in keeping with our findings when SSc sera were recently reexamined with IIF on ethanol- and formalin-fixed human neutrophils (Menarini, Inova Diagnostics, San Diego, CA, USA)[2,3]. Indeed, matched interpretations by 3 different observers resulted in the same ANCA pattern in 18 out of 115 SSc sera (15.65%). To our knowledge that particular ANCA staining, defined as an atypical p-ANCA pattern, has never been described in scleroderma sera. Its coarse perinuclear fluorescence on ethanol-fixed neutrophils was difficult to make out,

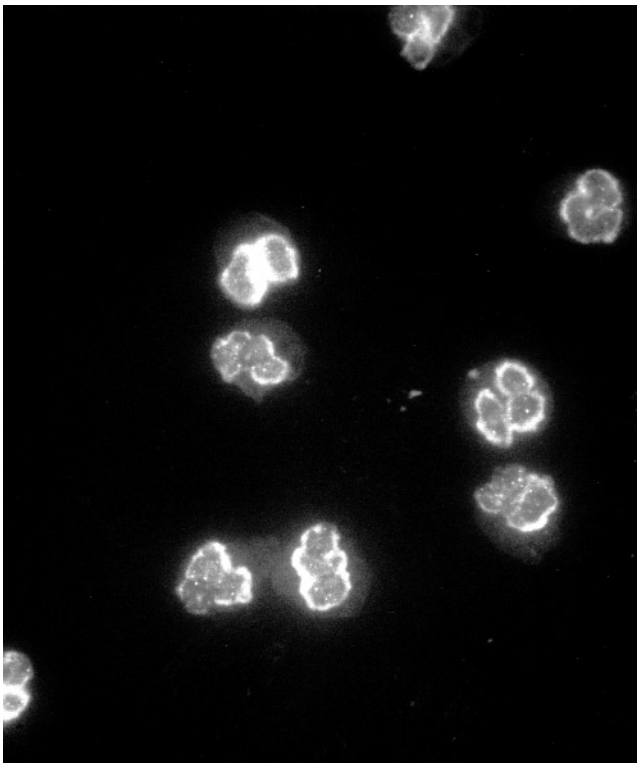

*Figure 1.* IIF test on ethanol-fixed neutrophils shows an atypical p-ANCA pattern, characterized by a coarse fluorescent ring confined to the perinuclear zone. Speckled nuclear fluorescence due to anticentromere antibodies is also evident (original magnification ×1000).

because it was always associated with nuclear fluorescence and in particular with a fine speckled pattern in 16 out of 18 positive sera (88.89%) and with a speckled staining in 2 (11.11%). The high titer of anti-topoisomerase I antibody causing a fine speckled pattern on ethanol-fixed neutrophils prevented our observing the perinuclear fluorescence of the atypical p-ANCA pattern, which was more evident in the diluted sera and when it was associated with speckled staining of anticentromere antibody (Figure 1).

Prevalences or mean values of some clinical and serological features of atypical p-ANCA positive patients were compared by Fisher's exact test and the Mann-Whitney U test with those of atypical p-ANCA negative patients, and no significant difference was found between the 2 groups (Table 1). In particular, no statistically significant association was observed between the atypical p-ANCA pattern and antibodies to PR3, MPO, and cathepsin G antigens. The relationship between atypical p-ANCA staining and antibodies to other neutrophil antigens and well defined clinical features in scleroderma patients needs further investigation if the significance of this particular ANCA fluorescence pattern is to be determined.

*Table 1.* Comparison of clinical and serological features of patients with an atypical p-ANCA positive pattern and those with atypical negative pattern.

| | Atypical p-ANCA Positive n = 18 | Atypical p-ANCA Negative n = 97 | p |
|---|---|---|---|
| Female, male | 15, 3 | 85, 12 | NS |
| Mean age, yrs | 54.11 | 54.31 | NS |
| Diffuse form (%) | 11 (61.11) | 44 (45.39) | NS |
| Limited form (%) | 7 (38.88) | 53 (54.63) | NS |
| Disease duration, mean of months | 77.6 | 86.32 | NS |
| Raynaud's phenomenon (%) | 18 (100) | 94 (96.90) | NS |
| Lung involvement (%) | 13 (72.22) | 62 (63.91) | NS |
| Heart involvement (%) | 5 (27.77) | 33 (34.02) | NS |
| Esophagus involvement* (%) | 11 (68.75) | 54 (72.97) | NS |
| Kidney involvement (%) | 6 (33.33) | 29 (29.89) | NS |
| Anti-topoisomerase I (%) | 6 (33.33) | 70 (72.16) | NS |
| Anticentromere (%) | 3 (16.66) | 35 (36.08) | NS |
| Anti-PR3 (%) | 1 (5.55) | 5 (5.15) | NS |
| Anti-MPO (%) | 0 (0) | 4 (4.12) | NS |
| Anti-cathepsin G (%) | 4 (22.22) | 12 (12.37) | NS |

* Esophagus involvement was studied in 16/18 positive and in 74/97 negative patients.

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## Effects of High Dose Intravenous Pamidronate on Disease Activity and Bone Metabolism in Patients with Active Rheumatoid Arthritis: A Randomized, Double-Blind, Placebo-Controlled Trial

*To the Editor:*

One single agent that decreases both disease activity and bone loss would be useful in the treatment of rheumatoid arthritis (RA). We assessed the effect of high dose intravenous pamidronate on disease activity and bone metabolism in patients with active RA.

Twenty six patients, recruited in outpatient rheumatology clinics between December 1999 and May 2002, were included in a randomized double-blind placebo-controlled trial and received a single intravenous infusion of 45 mg or 90 mg pamidronate or placebo as adjuvants to the conventional RA treatment. Patients with a recent change in disease modifying antirheumatic drugs (DMARD), unstable dosage of drugs known to interfere with bone metabolism (including glucocorticoids), intraarticular glucocorticoid injections, or bisphosphonate treatment before inclusion were excluded. Disease activity, markers of bone formation, and markers of bone and cartilage resorption were assessed at baseline and 1, 2, 4, and 6 weeks after infusion. To minimize the effects of changes in DMARD (allowed as of Day 14) on our results, Day 28 was chosen as endpoint. Data missing due to loss to followup were handled by a last-observation-put-forward approach. The changes in disease activity and markers of bone metabolism, expressed as area under the curve (AUC), between the 3 groups were compared by means of a test for linear trend across the groups within a one-way analysis of variance (ANOVA). Kruskal-Wallis tests, chi-square tests, or Fisher's exact tests were performed where appropriate. P values ≤ 0.05 (2 sided) were considered significant. The software used was SPSS for Windows v. 9.0 (Chicago, IL, USA).

Baseline characteristics of the 3 intervention groups were not significantly different (Tables 1 and 2). The disease variables and values of the markers of bone and cartilage metabolism at 4 weeks after infusion are shown in Table 2. The median [interquartile range (IQR)] AUC of change of Disease Activity Score from baseline to 4 weeks after infusion were –0.40 (–0.71 to –0.19), –0.30 (–0.62 to 0.16), and –0.46 (–0.73 to 0.28) in the 90 mg, the 45 mg, and the placebo group, respectively (nonsignificant in the intention-to-treat analyses). The per-protocol analyses did not change the significance of the results.

The bone and cartilage resorption markers decreased significantly in a dose-dependent way — p values of test for linear trend within ANOVA: 0.002 for urine ß-isomerized carboxy terminal telopeptide of type 1 collagen (ß-CTx), 0.002 for urine type 2 collagen C-telopeptide breakdown products (CTxII), and 0.01 for serum ß-CTx. Bone formation markers showed inconsistent results (p = 0.14 for serum N-terminal peptide of type 1 procollagen synthesis; and p = 0.03 for test for linear trend within ANOVA for serum osteocalcin). In the per-protocol analyses, only the AUC of change of urine ß-CTx consistently showed a significant dose-dependent difference between the 3 groups. In all patients but one, side effects con-

*Table 1.* Baseline demographic, disease, and therapy variables of the patients at randomization.

| | Group | | |
|---|---|---|---|
| | Placebo, n = 9 | 45 mg Pamidronate, n = 8 | 90 mg Pamidronate, n = 9 |
| Demographic variables | | | |
| Age, yrs | 66 (15) | 58 (13) | 56 (15) |
| Female/male (%) | 5 (56)/4 (44) | 5 (62)/3 (38) | 8 (89)/1 (11) |
| Disease variables | | | |
| Disease duration, yrs | 3.5 (0.8–16.6) | 9.6 (3.9–14.2) | 2.3 (0.3–12.2) |
| Rheumatoid factor positive (%) | 8/8 (100) | 6/8 (75) | 7/9 (78) |
| Erosive disease (%) | 5/8 (63) | 6/8 (75) | 6/9 (67) |
| Therapy variables | | | |
| Current medication influencing bone metabolism (%) | 5/8 (63) | 4/8 (50) | 6/9 (67) |
| Current corticosteroids (%) | 2/8 (25) | 3/8 (38) | 4/9 (44) |

Mean (SD) for continuous variables with normal distribution. Median (IQR) for continuous variables with non-normal distribution.

*Table 2.* Disease variables and markers of bone and cartilage at baseline and at 28 days after infusion with placebo (n = 8), 45 mg pamidronate (n = 8), or 90 mg pamidronate (n = 9). One patient out of 9 allocated to the placebo group was lost to followup after randomization.

| Outcome Measure | Baseline | | | Day 28 After Infusion | | |
|---|---|---|---|---|---|---|
| | Placebo | 45 mg Group | 90 mg Group | Placebo | 45 mg Group | 90 mg Group |
| Disease variables | | | | | | |
| Ritchie score | 23 (12) | 21 (14) | 23 (15) | 18 (9) | 20 (14) | 14 (9) |
| 44 swollen joint count | 19 (8) | 22 (12) | 19 (6) | 20 (8) | 18 (13) | 12 (7) |
| ESR, mm/h | 59.5 (29.5–98.4) | 52.0 (31.6–108.5) | 37.0 (13.3–81.5) | 73.0 (20.0 to 94.5) | 57.5 (20.5 to 98.0) | 32.0 (15.0 to 82.5) |
| CRP, mg/dl | 38.6 (24.2–65.8) | 24.4 (5.0–90.2) | 33.5 (4.8–50.8) | 22.7 (11.6 to 48.9) | 46.0 (3.9 to 104.7) | 27.1 (5.7 to 40.0) |
| Disease activity VAS | 6.3 (3.1) | 7.4 (2.3) | 6.2 (2.5) | 7.0 (1.5) | 6.1 (2.0) | 4.0 (2.7) |
| Pain VAS | 7.1 (2.8) | 7.5 (2.3) | 5.9 (2.2) | 6.4 (1.5) | 7.2 (2.1) | 3.7 (2.4) |
| Investigator's global assessment VAS | 6.8 (2.1) | 6.8 (1.9) | 7.1 (1.8) | 5.6 (2.0) | 4.8 (2.4) | 4.7 (2.6) |
| HAQ | 1.8 (0.5) | 2.3 (0.5) | 1.8 (0.7) | 1.9 (0.4) | 2.3 (0.6) | 1.6 (0.8) |
| DAS | 5.5 (1.3) | 5.5 (1.6) | 5.0 (1.2) | 5.3 (1.2) | 5.0 (2.0) | 4.3 (1.4) |
| Markers of bone and cartilage metabolism | | | | | | |
| Serum OC, ng/l | 28.6 (11.2) | 17.2 (6.2) | 26.5 (14.5) | 53.6 (26.9) | 33.8 (14.6) | 34.1 (20.3) |
| Serum PINP, µg/l | 56.2 (32.7) | 44.2 (15.5) | 55.5 (32.2) | 23.9 (8.6) | 13.9 (6.3) | 19.3 (12.4) |
| Serum ß-CTx, ng/l | 0.54 (0.41–0.71) | 0.40 (0.28–0.67) | 0.44 (0.20–0.61) | 0.50 (0.43 to 0.58) | 0.22 (0.10 to 0.31) | 0.10 (0.05 to 0.25) |
| Urine ß-CTx, µg/mmol | 364 (75) | 406 (264) | 349 (165) | 374 (136) | 147 (184) | 73 (96) |
| Urine CTxII, µg/mmol | 0.56 (0.39–1.76) | 1.00 (0.22–1.14) | 0.76 (0.26–1.07) | 0.52 (0.43 to 1.53) | 0.33 (0.07 to 1.00 ) | 0.28 (0.05 to 0.51) |

Mean (SD) for (changes in) continuous variables with normal distribution. Median (IQR) for (changes in) continuous variables with non-normal distribution. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale (0–100 mm); HAQ: Health Assessment Questionnaire; DAS: van der Heijde disease activity score; OC: osteocalcin; PINP: N-terminal peptide of type 1 procollagen; ß-CTx: ß-isomerized carboxy terminal telopeptide of type 1 collagen; CTxII: type 2 collagen C-telopeptide; bone and cartilage markers in urine per mmol creatinine.

sisting of fever and flu-like symptoms that occurred in some of the patients treated with pamidronate disappeared within 24 hours. Six patients in the placebo group, 3 in the 45 mg group, and 9 in the 90 mg group underwent a change in (dose of) DMARD at any time during the study [median Day 14 (IQR 11.5 to 20)].

In summary, intravenous administration of a single high dose of pamidronate did not result in a statistically significant beneficial effect on RA disease activity, while markers of bone and cartilage resorption were significantly suppressed in a linear dose-dependent way. In accord with our results, 3 out of 4 controlled studies that used intravenous bisphosphonates (maximum dose of 60 mg) showed no consistent advantageous effect on disease activity[1-3]. However, one study did find a significant decrease in tender and swollen joint counts as well as biochemical disease activity[4]. The apparent beneficial results of oral pamidronate in RA patients in one placebo-controlled study are difficult to interpret because of baseline disease activity differences in the groups[5]. Cantatore, *et al* found no favorable effect on clinical disease activity in their randomized controlled trial on the effects of oral alendronate in RA patients[6]. However, they did report a significant decrease in erythrocyte sedimentation rate and C-reactive protein in the active group in contrast to the placebo group after 3 months. The relatively small sample size of all studies, including our study, is likely to result in a lack of discriminatory power. Another explanation for the conflicting results remains a truly nonexistent effect of bisphosphonates on disease activity. However, ample evidence from *in vitro* studies as well as experimental animal models points toward a suppression of the inflammatory response by bisphosphonates[7,8].

In accord with our results, the controlled studies of the effects of bis-

phosphonates in RA showed a suppression of bone resorption markers[2-4,6]. Whether our findings on the suppression of the cartilage degradation marker CTxII confirm recent suggestions of a chondroprotective effect of bisphosphonates[9,10] or indicate a lack of specificity of the marker remains uncertain. Thus, whether and how bisphosphonates influence RA disease activity remains a question to be answered by studies of sufficient sample size and duration that investigate effects of highly potent bisphosphonates in patients with active RA.

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## Therapeutic Benefits of Irsogladine Maleate on Aphthous Stomatitis Induced by Methotrexate in Rheumatoid Arthritis

*To the Editor:*

Methotrexate (MTX) is a generally well tolerated drug that has become a first-line agent in the treatment of rheumatoid arthritis (RA)[1-3]. The development of aphthous stomatitis and/or oral ulcer will increase with high dose MTX treatment, as observed in 12% to 37% of patients followed in longterm studies[4]. This adverse effect is the most common cause of discontinuation of the treatment. Most examples of aphthous stomatitis are idiopathic, and effective treatment is limited. Some gastric mucosal protective agents have been reported to be effective for extragastric mucosal tissues, which promotes mucosal regeneration. Irsogladine maleate (Gaslon N, Nippon Shinyaku Co., Kyoto, Japan), which reinforces gap junctional intercellular communication *in vitro*, has been reported to be effective for treatment of aphthous stomatitis[5].

We examined the effects of irsogladine maleate on transient and relapsing aphthous stomatitis during treatment with MTX in RA. Subjects in this study were 24 patients with RA (20 women, 4 men; mean age 49.9 ± 11.3 yrs) diagnosed as having RA as defined by the American College of Rheumatology, and treated as outpatients between July 2000 and July 2002 at our university hospital. Each patient was randomly assigned to treatment with only irsogladine maleate (4 mg/day PO, BID) or only folic acid (5 mg/day) for 6 months. Clinical and laboratory features of each patient were investigated with their consent. Efficacy was evaluated according to patients' subjective assessment of symptoms and the macroscopic findings of oral lesions.

The incidence of transient aphthous stomatitis in the irsogladine-treated group was 7.7%, whereas that in non-irsogladine group was 45.5% ($p < 0.05$; Table 1). The incidence in the non-irsogladine group was higher than in the Japanese population as a whole who are generally treated with lower doses of MTX. No adverse events were observed during the study period and no new abnormal laboratory data were noted. In addition, 4 patients with RA, whose lesions recurred 10 or more times per year and who had discontinued the MTX treatment, were also treated with irsogladine (4 mg/day PO, BID) with concomitant use of MTX for 12 months. Two of the 4 patients with relapsing aphthous stomatitis manifested marked improvement in their complaints and oral lesions after 3 and 5 days of irsogladine maleate treatment, whereas the period to healing before administration of irsogladine maleate was 10 to 14 days. The other 2 patients had no additional development of their stomatitis. All patients were free of recurrence of stomatitis for 12 months.

MTX is a commonly prescribed disease-modifying antirheumatic drug (DMARD) for RA[1,2,6]. With increasing use of DMARD, gastrointestinal toxicity including aphthous stomatitis seems to increase. Although the aphthous stomatitis lesions may be transient, it tends to recur, and patients suffer eating disability induced by the mucosal pain. They may refrain from MTX treatment even when its antirheumatic efficacy is established. Management in such a situation includes dosage reduction, temporary withdrawal, or the addition of folic acid supplementation.

Irsogladine maleate has been shown to inhibit the formation of various experimental gastric ulcers produced by different agents without suppression of gastric secretion[7]. Hara, *et al* reported the presence of connexins 26 and 32 in human oral mucosa, and demonstrated that administration of irsogladine maleate was effective for transient or relapsing aphthous stomatitis of different causes[5]. Irsogladine maleate can reinforce the gap junction in the gastric mucosa to repair damaged epithelium in the stomach. Saitoh, *et al* experimentally confirmed that gap junction was associated with wound healing in cases such as glossitis, suggesting that such effect was not limited to the gastric mucosa only, and the wound healing seemed to be accelerated by intercellular communication through the gap junction[8]. It has been reported that irsogladine maleate reinforces the function of gap junction through phosphorylation of connexins mediated by increasing content of intercellular cAMP, maintaining intercellular pH mediated by Na+/H-exchange, stimulation of the M1 muscarinic acetylcholine receptor, and

*Table 1.* The effects of irsogladine maleate (IM) on transient aphthous stomatitis with methotrexate therapy in RA.

| Group | No. | Sex, F/M | Duration of RA, mo | Dosage of MTX, mg/week | Dosage of IM, mg/day | No. of Stomatitis |
|---|---|---|---|---|---|---|
| Irsogladine | 13 | 11/2 | 51.0 ± 9.8 | 8.8 ± 3.1 | 4 | 1 |
| No irsogladine | 11 | 9/2 | 56.9 ± 10.4 | 8.7 ± 3.9 | None | 5 |

Chi-square analysis: $p < 0.033$; Fisher's exact probability: $p < 0.048$.

suppressing Ca2+ mobilization[9,10]. It is difficult to separate the individual contributions of the factors contributing to aphthous stomatitis induced by MTX treatment. Because irsogladine maleate is effective in treatment of aphthous stomatitis and can reinforce the function of the gap junction, aphthous stomatitis might be partly induced by deteriorated intercellular communication through the gap junction.

Irsogladine maleate is a safe drug and seems effective to prevent the development of MTX-induced aphthous stomatitis in patients with RA.

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*Supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan.*

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