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Relapse of rheumatoid arthritis after substitution of oral for parenteral administration of methotrexate

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We read with interest the letters: "Is parenteral methotrexate worth trying?" by Osman and Mulherin[1] and "Intramuscular methotrexate in inflammatory rheumatic disease" by Burbage, Gupta, and Lim.[2] We would like to present our findings, which indicate that parenteral methotrexate (MTX) may be more efficient than oral MTX at the same dose and in the same patients with inflammatory joint disease.

During the second half of 2000 we were faced with an unexpected shortage of parenteral MTX (ABIC, Israel) which lasted for more than five months, and patients were switched to oral MTX (Lederle, Germany). This gave us the opportunity to evaluate the difference in efficacy of parenteral versus oral administration of low dose MTX.

CASE REPORTS

Eight patients (seven female) with a mean age of 55 (38–70) years, who fulfilled the following criteria, were analysed retrospectively: (*a*) all had inflammatory joint diseases (four seropositive rheumatoid arthritis (RA), two seronegative RA (revised American Rheumatism Association criteria for RA), and two RA-like psoriatic arthropathy); (*b*) all were receiving parenteral MTX and were in complete clinical remission (fulfilling at least five of six criteria for complete clinical remission in RA); (*c*) all had an exacerbation of their disease when switched from parenteral to oral MTX at the same weekly dose and without any interval between the two treatments.

Ninety seven patients with inflammatory joint diseases were treated with parenteral MTX. Eighty one of them were faced with the drug supply shortage. Four patients remained in clinical remission for five months without MTX treatment. Eighteen who were not advised to switch immediately had an exacerbation of their disease within three weeks. The other 59 patients were switched to oral MTX without any treatment interval. Ten of the 59 patients received an oral dose more than 2.5–5 mg higher than the parenteral dose; no exacerbation occurred. Forty nine patients were switched to the same oral dose. Eight of them (16%) deteriorated and became the subject of our investigation.

The following variables were investigated: duration of the disease and of the remission period, *x* ray imaging (joint erosions), concurrent treatment, MTX weekly dose, EULAR disease activity score (DAS28 with three variables[3]) at the time of relapse and two months after renewing the parenteral MTX treatment, compared with remission period.

Table 1 summarises the patients' details. These patients did not differ from the patients who did not have an exacerbation after switching. All eight patients were in stable remission which had lasted for three years on average. Relapse occurred quite rapidly: 3–10 (mean 6) weeks after switching. The mean (SD) DAS28 activity index rose from 1.8 (0.4) to 4.9 (0.4).Within two months after reinstitution of the previous parenteral MTX marked improvement was noted from DAS28 4.9 (0.4) to DAS28 3.4 (0.6).

DISCUSSION

After oral administration MTX is rapidly but incompletely absorbed. Its bioavailability is about 70% at low doses ($\leqslant$10 mg/m^2), approximately 15–20% lower than that of intramuscular (IM) or intravenous (IV) MTX.[4 5] In addition, there is a marked interindividual and a moderate intraindividual variability in the extent of absorption of oral MTX.[6] Oral administration in doses above 25 mg/day is associated with lower bioavailability due to the saturation of the absorption mechanism. Thus in high doses the parenteral administration is mandatory.[7] IM MTX showed higher bioavailability than oral MTX either as tablets or as solution.[8] However, other studies have shown a similar MTX concentration after oral, IM, or IV administration.[5 9]

To compare the relative bioavailability of oral versus intramuscular administration in patients with RA, the pharmacokinetics of MTX at both the usual starting dose of 7.5 mg and at established higher maintenance doses was examined in 21 patients.[10] Pharmacokinetics measurements were repeated six and 18 months after baseline while patients were receiving maintenance doses of MTX (17.0 (3.8) mg). The relative bioavailability of the maintenance dose was reduced by 13.5% as compared with the initial dose of 7.5 mg. The area under the curve of the serum concentration versus time curve

Table 1 Patients with relapse of polyarthritis after exchange of parenteral to equal dose of oral methotrexate (MTX)

Patient No	Diagnosis	Age	Disease duration/period of remission (years)	MTX dose per week during substitution of PO for IM (mg)	Period of oral MTX therapy up to relapse (weeks)	Concurrent treatment	Joint erosions (x ray)	Activity index (DAS28)[2] during remission/relapse	Activity index (DAS28) 2 months after renewal of IM MTX	Improvement in DAS28 (EULAR good response: >1.2)
1	RA sero(+)ve	63	10/3	12.5	3	Pred 5 mg/d	+	1.6/4.4	3.1	1.3
2	RA sero(+)ve	47	12/2	15	4	–	+	2.2/5.3	3.8	1.5
3	RA sero(+)ve	62	8/4	20	8	Pred 5 mg/d SSZ	–	1.7/4.7	2.9	1.8
4	RA sero(+)ve	38	1/0.5	12.5	3	–	–	1.9/5.1	3.6	1.5
5	RA sero(–)ve	70	5/2.5	17.5	4	Pred 5 mg/d Plq	–	1.2/4.5	2.8	1.7
6	RA sero(–)ve	53	15/4	12.5	8	Plq, SSZ	+	2.5/5.5	4.4	1.1
7	PsA	49	3/2	12.5	8	Pred 5 mg/ 7.5 mg/d	+	2.1/4.9	3.7	1.2
8	PsA	55	7/6	20	10	–	–	1.4/4.7	3.0	1.7
Average (SD)		55 (10)	8 (5)/3 (1.7)	15 (3.4)	6 (2.8)			1.8 (0.4)/4.9 (0.4)	3.4 (0.6)	1.5 (p<0.001)

RA, rheumatoid arthritis; PsA, psoriatic arthropathy; IM, intramuscular; PO, oral; Pred, prednisone; SSZ, sulfasalazine; Plq, Plaquenil.

was significantly lower for oral than for IM administration at usual maintenance doses, but similar at an MTX dose of 7.5 mg a week. The authors concluded that clinicians using MTX should not assume constant and complete bioavailability across the dose range. The findings explained the benefit which follows the switching from oral to parenteral administration in patients receiving maintenance doses of MTX as well as the failure of the inverse switching reported here. It should be mentioned that all our patients were treated with MTX in doses higher than 7.5 mg/week and from the study of Hamilton and Kremer[10] it seems that it is only safe to switch from IM to oral administration at a dose of 7.5 mg/week. Two other recent studies also supported a switch to parenteral MTX in patients previously intolerant of, or who have failed to respond to, oral MTX.[1 2]

Various drugs currently used in RA may interact with MTX. It is known that corticosteroids do not interfere with the pharmacokinetics of MTX, whereas chloroquine may reduce gastrointestinal absorption of the drug. This might be relevant to two of our patients (Nos 5 and 6, table 1).

In conclusion, polyarthritis may be exacerbated owing to switching from parenteral to oral MTX using the same dosage. Reinstitution of IM MTX usually suppresses the disease activity.

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