An Australian survey of current prescribing practices of methotrexate in rheumatoid arthritis

A 15-item questionnaire was distributed by Australia Post between October-December 1992, to Australian rheumatologists. The sample was ascertained from the Australian Rheumatology Association (ARA) Directory. Any ARA registrant whose practice was limited strictly to paediatrics or non-clinical research, e.g. immunology, was excluded. A total of 180 eligible practising rheumatologists was identified. Second and third mailings of the questionnaire were made to non-respondents at intervals of about one month. The analysis was based mainly on descriptive statistics.

Responses were obtained from 137 rheumatologists (response rate – 76%). The mean year of graduation from medical school of respondents was 1973 (range – 1951-1985) (non-respondents: mean – 1972, range – 1952-1986, p = ns) and the mean year of starting practice in rheumatology of respondents was 1980 (range = 1958-1992). Thirty per cent of respondents were in private practice, 42% in private practice with academic centre affiliation, and 28% were based in an academic centre.

The majority of respondents preferred to use oral routinely (99%) rather than intramuscular (1%) methotrexate (MTX), and all but two had initiated treatment with MTX in the preceding year.

Respondents were presented with three clinical scenarios representing progressively higher levels of severity. They were instructed that a) the patient had not been on slow acting anti-rheumatic drug (SAARD) therapy previously; b) there were no contraindications to any SAARD, and c) impending pregnancy was not an issue. Respondents were asked to list their initial choice, i.e. the drug or drugs which they might first prescribe in the treatment of the various scenarios. The results of this exercise are shown in Table 1. Twenty-six per cent of respondents selected the same SAARD of first choice for Scenario A (RF +), Scenario B (age 30) and Scenario C, while 14% selected the same SAARD of first choice for all five clinical situations.

The usual starting dose was 7.5 mg/wk (37%) although some respondents preferred lower or higher doses: 5 mg/wk (34%), 2.5 mg/wk (10%), 10 mg/wk (18%) or 12.5 mg/wk (1%). The range of maximum doses prescribed ranged from 7.5 mg/wk to 50 mg/wk, most respondents limiting the dose to 20 mg/wk (33%), 25 mg/wk (31%) or 15 mg/wk (24%). The average dose of MTX prescribed, once a stable dose had been established, was usually 10-12.5 mg/wk (59%), although doses of 5-7.5 mg/wk (26%), 7.5-10 mg/wk (6%), 15-17.5 mg/wk (7%) or 20-22.5 mg/wk (1%) were also prescribed by some respondents. The majority of rheumatologists routinely continued non-steroidal anti-inflammatory drugs (NSAIDs) when prescribing MTX (Table 2, see (a)). Having achieved a significant therapeutic response, most rheumatologists either attempted to determine the minimum effective dose or maintained the minimum effective dose (Table 2, see (b)).

Almost all rheumatologists routinely performed liver function tests on a regular basis (Table 3). A minority required pre-MTX on interval liver biopsies after a certain time or cumulative dose, although most rheumatologists would consider the procedure if liver function test abnormalities persisted (Table 3). Of the 6% of rheumatologists who routinely performed pulmonary function tests, all used them pre-MTX (Table 3). The mode and range of risk estimates for MTX related side effects as judged by responding rheumatologists was as follows: anaemia 5% (range – 0-15), neutropenia 5% (range = 0.5-50), thrombocytopenia 5% (range = 0.5-20), pancytopenia 0.5% (range = 0.1-15), cirrhosis 0.5% (range = 0-20), nausea/vomiting 10% (range – 1-85), neurologic 5% (range = 0-10), oral ulcers 5% (range = 1-50), acute pulmonary toxicity 1% (range = 0.1-10), chronic pulmonary toxicity 1% (range – 0-10), rash 5% (range = 0-20), renal 0.5% (range = 0-10), infertility 0% (range – 0-90), and teratogenicity 100% (range = 0-100).

Given an elevation in AST and/or ALT and/or alkaline phosphatase, the threshold above the upper limit of the normal range at which respondents would alter, i.e. reduce or withdraw, MTX therapy varied as follows: 1.5 × normal (16%), 2 × (45%), 2.5 × (15%), 3 × (24%). Given the need to alter MTX therapy, 36% elected to suspend therapy until enzymes returned to baseline, while 59% preferred to reduce the dose and follow the enzymes.

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TABLE 1
First Choice SSARD selection

DMARD of first choice	Scenario A[a]		Scenario B[b]		Scenario C[c]
	RF +	RF –	30 yr.	65 yr.	
Single drug therapy*					
Antimalarial (ANTI)	9†	17	6	4	—
Auranofin (AURA)	2	1	1	2	1
D-penicillamine (DPEN)	1	—	1	1	1
Intramuscular gold (IMG)	15	10	15	13	21
Methotrexate (MTX)	25	17	29	30	61
Sulfasalazine (SULF)	45	53	44	47	5
Combination drug therapy*					
ANTI/IMG		—	1	*	—
ANTI/MTX	1	—	1	1	4
ANTI/SULF	1	2	1		—
IGM/MTX	1	—	1	1	3
IGM/SULF	—	—		—	1
MTX/SULF	—		—	—	1
ANTI/IMG/MTX	—	-	—	—	1
Azathioprine/IMG/MTX		—	—	—	1

[a]Scenario A: Your patient is a 24 year old mother of two with a 6 month history of symmetrical polyarthritis primarily involving the MCPs, PIPs, wrists, knees and feet with moderate functional impairment, responding poorly to non-steroidal anti-inflammatory drugs (NSAIDs), having periarticular osteopenia without erosions on plain films of hands and feet.
[b]Scenario B: Your patient is a woman in a busy law practice who has had seropositive rheumatoid arthritis (RA) non-steroidal anti-inflammatory drugs for 5 years, treated with various NSAIDs, developing early deformities with a low grade constant synovitis and slowly progressive erosive disease with mild-to-moderate functional limitations not strictly interfering with home or business activities.
[c]Scenario C: Your 30 year old patient has rapidly progressive, seropositive, erosive, destructive RA with major functional impairment.
*No respondent selected azathioprine, cyclophosphamide or cyclosporine as drug of first choice.
†The numbers in the table represent the percentage of respondents choosing the given drug(s).

Finally, there was variability in the use of folic acid both for prophylaxis and to treat MTX side effects as well as in the dose and dose schedule selected (see Table 2(c), (d)).

Eighty-five per cent of rheumatologists noted that 1.70% (mode – 5%) of their patients refused to accept their recommendation to start MTX usually for fear of side effects (Table 3).

In interpreting survey data, it should be noted that the techniques used probed the opinions of respondents, and made no attempt to audit prescribing practices directly. Response rates of >60% are generally regarded as adequate in surveys of this type, a figure far exceeded in the current study (76%). It has been demonstrated that year of graduation is one of the determinants of prescribing practice.[4] We noted no statistically significant difference between respondents and non-respondents in their year of graduation from medical school, and, therefore, have increased confidence that the survey characterises the prescribing habits of the majority of Australian rheumatologists.

While there is significant variability in the approach of MTX utilisation in rheumatoid arthritis (RA) (i.e. minimum, maximum, maintenance doses, etc), there is a high level of compliance to traditional standards in those areas where the corpus of knowledge is adequate to dictate a norm. As the severity or apparent aggressiveness of RA increased in the scenarios, the

TABLE 2
Methotrexate Prescribing Practices in Rheumatoid Arthritis Patients

Prescribing practice	%
(a) Policy regarding the co-administration of NSAIDs and MTX	
routinely continue NSAID when initiating MTX	87
stop certain NSAIDs	9
stop all NSAIDs	1
switch NSAIDs	4
(b) MTX dose adjustment following achievement of a significant response	
determine minimum effective dose	62
continue initial dose as long as response maintained	31
lower the dose or stop drug entirely after certain time	7
(c) Policy regarding folic acid prophylaxis	
routine use as prophylaxis during MTX treatment	33
majority prescribed — 1 or 5 mg/day (range = 0.5-10)	79
dosing schedule	
every day	49
once per week	27
on some, but not all, days	24
(d) Policy regarding the use of folic acid to treat MTX side effects	78
mouth ulcers	36
nausea/vomiting	32
haematologic	11

Abbreviations: NSAIDS = non-steroidal anti-inflammatory drugs MTX = methotrexate.

TABLE 3
Methotrexate Related Toxicity Issues

Toxicity issues	%
Routine monitoring of liver function tests	99
AST (SGOT)	97
alkaline phosphatase	76
ALT (SGPT)	75
gamma GT	74
total bilirubin	38
lactate dehydrogenase	23
albumin	7
prothrombin time	*
total protein or other	1
Frequency of LFT monitoring in first 6 months	
every week	4
every 2 weeks	18
every 4 weeks	60
every 6 weeks	8
every 12 weeks	4
Utilisation of predrug liver biopsy	
on all patients	1
on patients with history of alcohol abuse	42
on patients with liver function abnormalities predrug	6
Utilisation of liver biopsy while on MTX therapy	
after a given time period	11
after a certain cumulative dose	20
after a significant increase in liver enzymes	19
if persistent liver enzyme abnormalities despite altering or stopping therapy	87
Routine use of pulmonary function tests	6
pre-MTX	6
after a certain time period	2
Reason for refusing treatment	
fear of side effects	80
fear of taking a 'cancer drug'	11
necessity to restrict alcohol intake	4
miscellaneous	18

Abbreviations: AST (SGOT) = aspartate aminotransferase
ALT (SGPT) = alanine aminotransferase
LFT = liver function tests
MTX = methotrexate

proportional utilisation of MTX as drug of first choice increased from 25% in the first scenario to 61% in the third scenario. This may suggest a trend towards favouring MTX for more severe or aggressive RA. Also, the more severe the portrayed RA disease the greater was the inclination for using combination drug therapy. Rheumatoid factors status affected the prescribing pattern with a proportional increase in antimalarial use if the RA patient was seronegative. Age appeared to play no role in drug of first choice being not significantly different whether the patient was 30 or 65 years of age. Overall these data suggest that the majority of Australian rheumatologists are selective in their use of SAARDs and that MTX has not yet become established as the invariable drug of first choice even for severe or aggressive RA.

Given a paucity of information regarding clinically important interactions and the frequent necessity to co-prescribe MTX and NSAIDs in order to control the disease, it is not surprising that the majority of respondents routinely used these drugs in combination.

While the majority of rheumatologists routinely monitor 'liver function tests', there is diversity in the perceived necessity for liver biopsy during MTX therapy. This conflict of opinion is likely to continue given Walker *et al.*'s[2] recent report of documented cases of cirrhosis in RA patients in MTX.[4,5] There is also invariability in the use of supplementary folic acid and the role of pulmonary function testing. The use of folic acid, both in prophylaxis and in the treatment of side effects, is likely to increase in the future given a number of recent favourable studies.[6,7] Although most rheumatologists rated the risk of MTX side effects as being low, the range was extremely broad, and might, in part, explain the significant refusal rate by patients to accept MTX therapy. Despite potential toxicity, the majority of respondents used MTX in the treatment of RA in adults. ■

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