Prescribing Trends in Disease Modifying Antirheumatic Drugs for Rheumatoid Arthritis: A Survey of Practicing Canadian Rheumatologists

JANET E. POPE, PAUL HONG, and BARRY E. KOEHLER

ABSTRACT. ***Objective.*** To determine the prescribing and monitoring practices of disease modifying antirheumatic drugs (DMARD) for Canadian rheumatologists in their treatment of rheumatoid arthritis (RA).

Methods. A survey questionnaire was mailed to 279 rheumatologists with a 70% response rate after 2 mailings.

Results. Antimalarials are prescribed commonly, with the preference being hydroxychloroquine (HCQ). For antimalarials, 78% do not routinely monitor laboratory results. There was wide variability in monitoring for ocular complications. Thirty-eight percent of rheumatologists never do a baseline eye examination and 39% always do. All rheumatologists frequently use methotrexate (MTX) in RA. The reported mean maximum dose for MTX was 25.1 mg/week (range 7.5–50), with 86% routinely using folate. Ninety-eight percent prescribe sulfasalazine (SSZ) for RA. Mean maximum dose prescribed for SSZ was 2.8 g/day. Most never used oral gold, while IM gold was used by 95%. Only 9% frequently use azathioprine in RA, to a mean maximum dose of 185 mg/day. Less commonly prescribed DMARD included cyclosporine (6% frequently; 25% never) and D-penicillamine (2% frequently; 53% never). There was a wide range of what exactly was monitored with respect to laboratory tests, and at what frequency, for many of the DMARD. Nearly all (99%) used combination DMARD, the most popular combination being MTX-HCQ. There were some significant differences in treatment trends when comparing year of fellowship completion, but no sex or type of practice differences were found. Those completing fellowships prior to 1984 were more likely to prescribe azathioprine ($p < 0.03$), chloroquine ($p < 0.01$) and chronic steroids ($p < 0.1$) in RA. There was, however, regional variability in the use of IM gold and newer DMARD — they were most prescribed in Western Canada and least in Quebec. Cyclosporine was prescribed most frequently in Quebec compared to Western Canada and least in Ontario and the Atlantic Provinces.

Conclusion. Canadian rheumatologists are fairly similar in their use of common DMARD and combination therapies in RA. There is variability in the use of some older medications including azathioprine and chloroquine, depending on when rheumatology training was completed, and use of some drugs varies by region. (J Rheumatol 2002;29:255–60)

Key Indexing Terms:
DISEASE MODIFYING ANTIRHEUMATIC DRUGS — PRESCRIBING PRACTICE
MONITORING PRACTICES — RHEUMATOID ARTHRITIS

Disease modifying antirheumatic drugs (DMARD) are standard treatment for rheumatoid arthritis (RA). Studies to determine the prescribing behavior of DMARD show wide variations in prescribing pattern, dose, and monitoring schedules[1-4]. As treatment for RA now involves introducing DMARD early in the course of the disease, it is important to assess and understand the current practice patterns for DMARD. Maetzel, *et al* found that methotrexate (MTX) was commonly prescribed for moderate and aggressive RA in Canada and the USA[5]. We are on the verge of more aggressive treatment strategies in RA, yet we live in a climate of constrained health care budgets. Thus, Canadian rheumatologists may need to define new guidelines for the use and monitoring practices of DMARD treatment in RA. We investigated (1) the frequency of use of various DMARD for RA by Canadian rheumatologists, including combination therapies; (2) the usual monitoring practices for each DMARD and if monitoring enabled detection of clinically significant adverse events; and (3) if any of the published guidelines were adhered to. Similar studies have been conducted in Europe[1,2] and the USA[3] and a brief survey exists for Canada[5].

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MATERIALS AND METHODS

A questionnaire to ascertain the prescribing, dosing, and laboratory monitoring habits of Canadian rheumatologists was devised. This questionnaire, with a covering letter, was sent to Canadian Rheumatology Association (CRA) members who are practicing rheumatologists in adult care (nonclinical, pediatric, retired, trainee, and CRA registrants practicing outside Canada were excluded). Mailings were repeated for those who failed to respond the first time.

The questionnaire began with a short demographics section and was followed by questions on specific DMARD [antimalarials, MTX, sulfasalazine (SSZ), gold, azathioprine, cyclosporin A, and D-penicillamine] and open questions about the use of other DMARD. For each DMARD, rheumatologists were asked about: (1) how frequently they use the particular DMARD; (2) their dose regimens; (3) their monitoring practices; (4) clinically significant/relevant abnormalities pertaining to the DMARD; and (5) their response to abnormal results. The range of maximum dose for a DMARD was reported as minimum reported maximum dose to highest reported. Data were entered into a spreadsheet and descriptive statistical analyses were performed. Trends in prescribing practices were studied on the entire population and by dividing the data by year of graduation (fellowship), sex, types of practice, and geographical region.

RESULTS

A total of 279 questionnaires were mailed and 195 responded (response rate 70%), of whom 60% were solely in clinical practice and 36% were in clinical and research practice. The remaining 4% reported involvement mostly in research. The mean year of completion of rheumatology fellowship was 1984 (range 1952–2000). Looking at prescribing trends, we divided year of fellowship completion at the mean (i.e., completion prior to 1984 compared to 1984 and after). Sixty-six percent of the respondents were male. For the proportion of patients with RA taking chronic steroids, the mean response was 23.3% with a range of 2–80%. In RA, all rheumatologists prescribe MTX and hydroxychloroquine (HCQ) and 98% prescribe SSZ. Figure 1 displays the patterns of prescription of other DMARD and nonsteroidal antiinflammatory drugs in RA.

Antimalarials. Chloroquine was less preferred than HCQ by our study population, as only 16% frequently prescribed chloroquine (45% occasionally, 39% never). Those graduating prior to 1984 were more likely to prescribe chloroquine in RA ($p < 0.01$). Most (78%) did not routinely monitor laboratory results when prescribing antimalarials. Complete blood count (CBC) results were monitored on average twice a year by 21% of rheumatologists, whereas only 10% monitored liver enzymes (Table 1). Despite the suggested guidelines for retinal monitoring in the *Compendium of Pharmaceuticals and Specialties* of the Canadian Pharmacists Association, 38% never performed baseline eye examinations prior to prescribing antimalarials (39% always, 24% occasionally). One-fifth did not dose

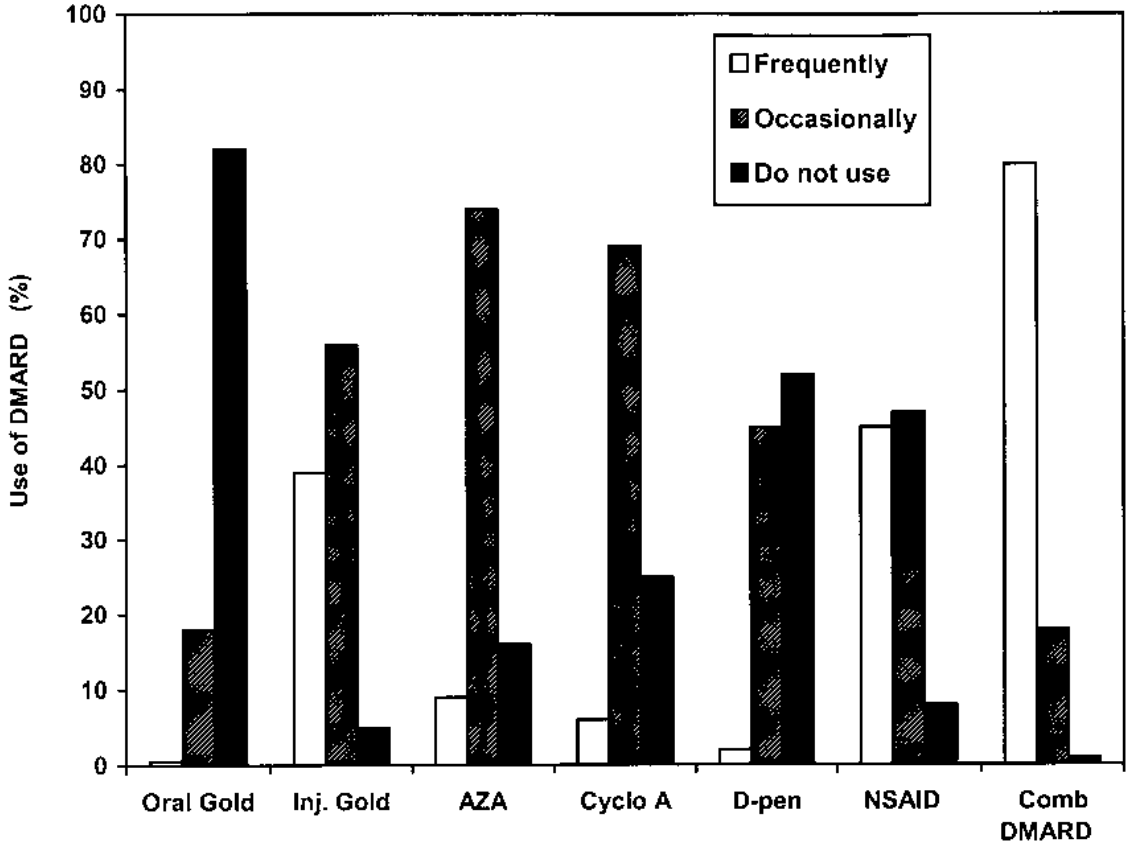

Figure 1. Frequency of use of DMARD by Canadian rheumatologists (shown as percentage of rheumatologists who reported using the DMARD). NSAID column refers to NSAID used in conjunction with cyclosporin A. All respondents reported using MTX and antimalarials. Four of 195 rheumatologists surveyed reported they prefer not to use sulfasalazine. AZA: azathioprine, Cyclo A: cyclosporin A, NSAID: nonsteroidal antiiflammatory drugs.

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Table 1. Percentage of physicians who monitor various tests with DMARD and the mean frequency that such tests are performed (q weekly). The denominator used to calculate the percentage was the number of physicians who prescribe that drug. The percentage groups are not mutually exclusive. Percentages are rounded to the nearest whole number.

	AST/ ALT	Bilirubin/ albumin/ ALP	GT	LDH	Creatinine/ urea	Electrolytes	Urine	CBC	ESR	Drug Levels	Frequency, Mean, weeks	Min, Max, weeks
Antimalarials	10	1	0	0	8	1	1	21	3	0	29	10, 65
MTX	97	68	5	2	59	1	8	99	8	0	7	2, 20
SSZ	78	30	1	1	31	2	11	98	4	0	10	1.5, 32
Gold*	5	1	0	0	12	0	93	98	8	0	6	1, 26
AZA	78	26	2	1	28	1	7	99	6	0	5	1, 15
Cyclo A	43	12	1	1	93	24	28	72	5	1	5	1, 18
D-pen	12	3	0	0	13	1	92	99	5	0	5	1, 27
NSAID	53	6	0	0	81	12	23	89	3	0	25	6, 52

* The frequency of monitoring for injectable gold is based on responses reported in terms of a time period, since 38% of physicians responded that they monitored laboratory results at the time of injection, and 8% monitored results every second injection or less frequently. MTX: methotrexate, SSZ: sulfasalazine, gold: injectable gold, AZA: azathioprine, Cyclo A: cyclosporin A, D-pen: D-penicillamine, ALP: alkaline phosphatase, GT: gamma glutamyltransferase, CBC: complete blood count, LDH: lactate dehydrogenase, ESR: erythrocyte sedimentation rate.

HCQ according to body weight; the rest used the 6.5 mg/kg/day guideline to dose accordingly. Regarding chloroquine usage, 61% reported using it at least occasionally. Forty percent of rheumatologists have never seen a significant ocular complication within their RA population using antimalarials. Although chloroquine was less frequently used than HCQ, among ocular complications that were reported, they were more likely to occur with chloroquine (43% chloroquine, 37% HCQ, and the rest, 21%, with both drugs).

Methotrexate. All rheumatologists prescribed MTX in RA at a mean maximum dose of 25.1 mg/week (PO, SC, or IM) with a reported maximum dose range of 7.5 to 50 mg/week. Most (85%) indicated that they would diminish the MTX dose with abnormal laboratory results (AST > 1.5 times normal). Two-thirds indicated permanently stopping MTX for persistently elevated liver enzymes in at least one patient with RA. Liver biopsy was routinely ordered for patients with no risk factors for liver disease by only 4% of the respondents. Nearly all used folate, 86% using it routinely and 13% occasionally. The laboratory monitoring practices were widely variable with respect to what was monitored and at what frequency (Table 1). Virtually everyone monitored CBC and AST/ALT. However, 59% in addition monitored renal function. For patients with stable RA taking longterm MTX, 66% stated they decrease the frequency of laboratory monitoring. For stable users of MTX, laboratory monitoring was done every 7 weeks (ranging from 2 to 20 weeks).

Sulfasalazine. Mean maximum dose prescribed for SSZ was 2.8 g/day, with a reported maximum range of 1–8 g/day. Variable laboratory results were monitored at inconsistent frequencies (Table 1). Nearly everyone monitored CBC, 78% monitored transaminases, and urinalyses, renal function and other liver tests were monitored by 11 to 30% of rheumatologists. Eighty-seven percent of the time, regular monitoring detected the very significant clinically relevant abnormal laboratory results.

Gold. Oral gold was rarely used (82% never use), whereas IM gold was frequently used by 40%, and occasionally by 56%. There was great consistency with respect to monitoring for gold: CBC (98%) and urinalysis or urine dip (94%). The mean maximum dose for oral gold was 6.7 mg/day (n = 35, range 3–9 mg/day). For IM gold, 53% said they decrease monitoring for patients with stable RA taking longterm gold. Laboratory monitoring usually detected excessive toxicity (90% of the time).

Azathioprine. Most respondents prescribed azathioprine at least occasionally in RA (9% frequently and 74% occasionally), of whom 81% dosed according to the patient's body weight. Mean maximum dose was 185 mg/day, with a maximum range of 100–500 mg/day. There were differences in what was monitored. All respondents monitored CBC, 78% transaminases, and 28% renal function. Regular monitoring detected the clinically relevant abnormal laboratory tests most (94%) of the time. Azathioprine was more likely to be used by rheumatologists obtaining their fellowship prior to 1984 ($p < 0.03$).

Cyclosporin A. Very few (6%) reported using cyclosporine frequently, while 69% used it on occasion. One-third said they do not prescribe this particular DMARD for the following reasons: (1) toxicity, (2) inefficacy, and (3) cost. All respondents that prescribed cyclosporine routinely monitored laboratory results (Table 1).

D-penicillamine. Only 2% reported frequently using D-penicillamine (45% occasionally, 53% never). Urinalysis and CBC were commonly monitored and usually nothing else (Table 1).

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Table 2. Adherence to guidelines of DMARD prescribing/monitoring.

	Recommended[6,17,21]	Actual
Antimalarials		
Baseline eye examination	No (unless age > 40 or eye disease)	Yes, 39% Occasionally, 23% No, 38%
Frequency of eye examinations	q 6–12 mo	Yes, 81% Leave up to ophthalmologist, 19% No eye exam, < 1%
Dose/body weight	≤ 6–6.5 mg/kg	Adjustment for weight Yes, 74% No, 26%
Methotrexate		
Baseline hepatitis B and C serology	Yes	Did not ask
Routine baseline liver biopsy	No, unless risk factors	96%
Monitor: AST, ALT, albumin	q 4–8 weeks	Yes, 97% (intervals varied) Yes, 68% (intervals varied)
Monitoring liver biopsy	Not routinely, but Yes if: 1. 5/9 or 6/12 abnormal AST 2. Decreased albumin in well controlled RA	Not routinely, 96% Every 1 g, 0.5% Every 3–4 g, 1% q 5 yrs, 0.5% q 10–20 yrs, 1% With significant abnormalities, 1%
Monitor: CBC	q 4–8 weeks	Yes, 99% (intervals varied)
creatinine	q 4–8 weeks	59%
Cyclosporine		
Dose	2.5–4 mg/kg/day	< 2 mg/kg/day, 0.5% 1–5 mg/kg/day, 99% 10 mg/kg/day, 0.5%
Monitor BP	Yes	Did not ask
Monitor lab results	Creatinine Occult urinalysis Occult K^+ (lytes) Occult CBC	Yes, 93% Yes, 28% Yes, 24% Yes, 12%
Use with NSAID	Use cautiously	Yes, 45% Occasionally, 47% No, 8%
Gold		
Monitor lab results	CBC, platelet count, urine dip for protein (prior to each injection, and after 20 weeks, q every or every other week)	For stable gold injection: CBC, 98% (intervals varied) Urinalysis, 93% (intervals varied)
Sulfasalazine		
Baseline monitor	Baseline G6PD Stable, q3 monthly CBC	Did not ask CBC, 98% AST/ALT, 78% Creat, 31% (intervals varied)

Combination DMARD. The majority of respondents used combination therapy in RA — 80% frequently and 19% occasionally. The most popular combination consisted of MTX and HCQ — used by 61%. Distant second (15%) and third (8%) combinations were MTX-HCQ-SSZ and MTX-SSZ, respectively. For the proportion of patients with RA taking combination DMARD, mean response was 40% with a range of 1 to 100%.

Other DMARD. Open-ended questions were asked about other DMARD [the questionnaire was mailed initially to CRA members before the release of leflunomide (Arava) and anti-tumor necrosis factor-α drugs]. Fifty-four percent used tetracyclines or minocycline, 33% used leflunomide, and 13% used anti-TNF-α therapies (Remicade and Enbrel).

Steroids. Rheumatologists reported that about one-quarter of their patients with RA were taking chronic steroids, with 25% of the respondents having obtained their fellowships before 1984 and 19% after ($p < 0.1$).

Additional analyses. We divided the respondents into regions consisting of Ontario (n = 82), Quebec (37), and eastern (13) and western (58) provinces to analyze regional variability in prescribing and monitoring practices. The only

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statistically significant differences we found were that newer DMARD (in Canada) such as leflunomide and minocycline were more commonly used in Western Canada and least of all in Quebec ($p < 0.005$). In addition, the use of IM gold and cyclosporin A showed significant differences across the various regions, with the Western provinces using IM gold more frequently ($p = 0.03$) and Quebec prescribing far more cyclosporin A than other regions ($p = 0.02$), followed by Western Canada. When other variables such as sex and type of practice (whether solely clinical, both clinical and research, or mostly research) were compared with respect to prescribing and monitoring practices, no other statistically significant differences were found.

Table 2 compares published guidelines for specific DMARD and compares them to the practices of the CRA members. Most rheumatologists chose HCQ as stated in guidelines; many did not monitor laboratory results, and there was variability on whether a baseline eye examination was done. We inquired about indications for and use of routine liver biopsies with MTX therapy. It appears that in Canada we do not order routine liver biopsies even after reaching specific doses (96% never did liver biopsies routinely).

We did not ask about blood pressure monitoring for cyclosporine therapy. Recent guidelines have suggested doses of 2.5 mg/kg/day, increasing to 4 mg/kg/day[18]. Only 2 rheumatologists who stated they used cyclosporine reported either underdosing (< 2 mg/kg/day) or increased dosing at 10 mg/kg/day. All followed laboratory tests such as creatinine.

DISCUSSION

This study has several limitations. The respondents may have different prescribing practices from nonrespondents. In addition, we asked about frequency of use and adverse events, yet did not validate the impressions of the rheumatologists with chart audits. Adverse events could very well have been over- or underestimated. We did not specifically ask about all published guidelines for specific DMARD use and monitoring, so adherence or failure to adhere to certain parts of specific guidelines may not be fully interpretable. For instance, we did not ask if hepatitis B and C serology testing was routinely performed prior to prescribing MTX. Many respondents were similar in practice to the American College of Rheumatology (ACR) guidelines for monitoring liver toxicity[6,7]. We found that Canadian rheumatologists are aggressive in the maximum doses of DMARD they use (well beyond the doses used in published trials such as 25 mg/wk MTX), likely due to their comfort level with respect to safety and perceived efficacy at higher doses. The 1994 Canadian survey on the prescribing practices for MTX showed the mean maximum dose was 15 mg/week, so over the last 5 years the maximum dose for MTX has almost doubled[8]. The longterm hepatoxicity at these doses is unknown. Other studies have documented the well known trend of using MTX more frequently in RA and often as an initial DMARD[1,8]. The use of double and triple therapy has been widely adopted. Over half of respondents (61%) reported MTX-HCQ was their primary combination. This was not unanticipated, since there are several studies that show the superior nature of this combination compared to monotherapy[9-13]. A study of 25 Canadian rheumatologists in 1998 also indicated that the MTX-HCQ combination was the most commonly prescribed in 246 patients with RA who experienced inadequate response to monotherapy[14]. Despite rigorous attention to laboratory results in patients taking DMARD, clinically significant side effects do occur that are not detected (such as 10% with IM gold). This would make one wonder if all the laboratory tests and rigorous monitoring practices should be reassessed (and perhaps done even less often — but others may argue for more frequent testing). Comer, *et al* surveyed rheumatologists in London, UK, finding that most DMARD were monitored with monthly CBC and that it was quite expensive[15]. The cost in 1995 to detect one adverse reaction was £32,000, and the cytopenias detected were generally mild. However, others have found guidelines to be cost effective[16]. Comparing the ACR guidelines for liver biopsies[7] with MTX therapy to older guidelines resulted in fewer liver biopsies being performed and cost savings of more than $1400 US per patient who would otherwise have undergone biopsy. However, the ACR guidelines had roughly 80% sensitivity and specificity, so cases of more serious liver disease could occasionally be missed.

Guidelines have been published to monitor cyclosporin A use in RA[17,18]. They recommend monitoring blood pressure[17] and creatinine[18] and adjusting the dose downward if elevations are detected. Nearly all the Canadian rheumatologists (93%) monitored creatinine when using cyclosporin A. Although not identical, the monitoring of laboratory results and their frequencies were mostly comparable to the ACR guidelines for DMARD monitoring[6].

Although chloroquine is used far less than HCQ, a disproportionate number of retinal side effects have been found with chloroquine. With the low number of reported cases of retinal toxicity in appropriate doses of HCQ (< 6.5 mg/kg/day of lean body weight)[19], and the wide variation in ophthalmologic monitoring found in our study, with toxicity being rarely detected, one wonders if we should monitor for HCQ toxicity at all, except in higher risk patients (where dose of 6.5 mg/kg of lean body weight is exceeded, or possibly in people with renal or hepatic insufficiency).

We anticipate widespread use of new DMARD for RA as they become available in Canada, largely due to increased efficacy, especially after treatment failure of other commonly used DMARD, yet the cost and possible side effects may prohibit these agents as a first-line treatment option for many patients. As our data show, leflunomide and anti-TNF-α drugs such as Enbrel (etanercept) and Remicade

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(infliximab) are already being prescribed in Canada. The wide use of these agents may be restricted by limited access on provincial drug formularies.

The regional variation (comparing the Western provinces to Quebec) in prescribing tetracyclines and leflunomide cannot be accounted for by rheumatologists' characteristics (sex, year of completion of fellowship, and type of practice). Another study has examined the variability of DMARD prescription in RA, and found that some of the variability can be accounted for by the characteristics of the rheumatologists, such as practice setting, demographics, payment method, and training location, and less so by patients' clinical features[20]. We did not ask where the respondents were trained, and in Canada the payment method is via the respective provincial ministry of health, so we still cannot account for the variability that we observed. However, we observed only minimal variability on most questions we asked.

Virtually all Canadian rheumatologists use MTX, HCQ, and SSZ in RA, and MTX in combination treatment, which accounts for an average of 40% of RA patients treated. However, due to the high morbidity and work disability in RA and diminished treatment response for most of our DMARD by 5 years of treatment, we are in need of safe, effective, widely available agents for treatment of RA to halt the disease progression over time. We conclude that rheumatologists in Canada treat RA with DMARD most of the time, but that there is no agreement with respect to monitoring practices. Comparing surveys in other countries, Canadian rheumatologists use combination DMARD more frequently, and use higher doses than in the past. We anticipate these practices may change when biologic therapies are more widely available.

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