In September 2004, the safety committee of the Adenomatous Polyposis Prevention on Vioxx® (APPROVe) study discovered a two-fold increase in cardiovascular events in patients taking rofecoxib vs. placebo. The study was stopped. Rofecoxib was pulled from the market. Within two weeks, a similar investigation, the Adenoma Prevention with Celebrex® (APC) trial, reported a dose-related increase in cardiovascular events in patients taking celecoxib vs. placebo. By November, valdecoxib was shown to increase predefined cardiovascular events post coronary artery bypass graft (CABG) surgery. Between February 16-18, 2005, there was a public enquiry before an expert advisory panel hosted by the Food and Drug Administration (FDA). In response to a request from the FDA, valdecoxib was also eventually removed from the market.

Confronted with demand by patients with arthritis, industry and other interested parties, Health Canada decided to hold a similar public review in front of an expert advisory panel.

A panel of 13 members was selected by the Ministry of Health, chaired by Andreas Laupacis, the Director of the Institute for Clinical Evaluative Sciences (ICES). This author was one of three rheumatologists on the panel, along with Michel Zummer and Peter Tugwell. Other panel members represented family practice, cardiology, gastroenterology, internal medicine, biostatistics and people with arthritis.

The expert panel met in Ottawa, Ontario between June 9-10, 2005. The first day of the meeting included presentations from Health Canada and several manufacturers of the products and there was also a time set aside for panel members to hear directly from Canadians. The second day was held in camera for panel members to deliberate on what they heard and to prepare advice based on the questions posed to them by Heath Canada. The questions related to the safety and efficacy of the products being discussed.

CONCLUSIONS
The panel was convinced that all COX-2 inhibitors increase the risk of clinically important cardiovascular events (a constellation of vascular death, heart attack and stroke) compared with placebo. This conclusion was based upon the results of numerous individual randomized trials, and a systematic review of 138 randomized trials of at least four weeks duration involving 144,296 patients, which was presented to the panel by Dr. Colin Baigent (not yet available for public release because it is being considered for peer-reviewed publication). The review demonstrated a statistically significant 41% relative increase in clinically important cardiovascular events in patients allocated to COX-2 inhibitors vs. placebo.

The panel felt that the increase in clinically important cardiovascular events was associated with both short-term and long-term use of COX-2 inhibitors. The absolute magnitude of the increased risk depends upon the length of use (greater absolute risk with longer use), the patient’s underlying risk of cardiovascular disease (greater absolute risk in those with a history of, or risk factors for, cardiovascular disease) and perhaps the dosage used.

Colin Baigent’s study found a statistically insignificant relative 12% decrease in clinically important cardiovascular events in patients treated with COX-2 inhibitors compared with non-naproxen nonsteroidal anti-inflammatory drugs (NSAIDs). He also found a statistically significant 57% relative increase in clinically important cardiovascular events in patients treated with COX-2 inhibitors compared with naproxen. The panel believes that, as a group, selective COX-2 inhibitors are associated with an increased risk of clinically important cardiovascular events compared with placebo, and that this increased risk is similar to the risk associated with most NSAIDs. This increased risk is present for all patients taking anti-inflammatory agents (with the possible exception of naproxen), but the absolute risk likely increases with longer-term use and in the presence of risk factors for, or a history of, cardiovascular disease. Naproxen may be associated with a lower risk than other anti-inflammatory agents.

Available evidence, based upon systematic reviews of randomized trials, suggests that the risk of peptic ulcer disease in patients who take both a COX-2 inhibitor and aspirin is similar to the risk of patients taking NSAIDs. Thus,
the addition of aspirin markedly reduces or eliminates the decreased incidence of gastrointestinal side effects demonstrated with COX-2 inhibitors compared with NSAIDs.

**RECOMMENDATIONS**

It was the panel’s opinion that the available information justifies marketing celecoxib in Canada (Vote: 13 in favour, 0 against).

It was the panel’s opinion that the available information justifies marketing rofecoxib in Canada (Vote: 12 in favour, 1 against).

It was the panel’s opinion that the available information did not justify marketing valdecoxib in Canada (Vote: 8 in favour, 5 against). The majority who voted that valdecoxib should not be marketed in Canada at the present time felt that there is very little information about the long-term cardiovascular risk of the agent. There is concern about the possible increased risk of severe adverse skin reactions (although the absolute frequency of these reactions appears small).

The panel felt that Health Canada should consider ibuprofen only being sold to individuals after discussion with a pharmacist and ensure that the risks of cardiovascular events are prominently displayed in material that individuals receive at the time they purchase the drug, as well as any package inserts.

The panel supports ensuring that appropriate warnings about the risks of COX-2 inhibitors are added to the product monograph and material given to the patient (including adding a “black box” warning).

The panel strongly recommended that when a drug is being considered for marketing by Health Canada, pharmaceutical manufacturers must publicly release all data (published and unpublished) from completed randomized trials and other studies of relevance to the safety and efficacy of their drugs, and register all ongoing trials publicly. The panel also strongly recommended that Canadian regulations should be modified to ensure that all material submitted to Health Canada in support of a request to license a drug (as well as Health Canada’s assessment of that drug) is made publicly available.

The panel felt that future studies of COX-2 inhibitors should be of similar size to the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) with lumiracoxib (a recently published efficacy trial comparing lumiracoxib—not yet licensed in Canada—to both diclofenac and naproxen), and powered to identify small but clinically important increases in cardiovascular events, so that gastrointestinal safety and cardiovascular risk can be examined at the same time.

For a more complete review of the Health Canada advisory panel report and a list of the members, visit the Health Canada website (www.hc-sc.gc.ca).

– Arthur A. M. Bookman, MD, FRCPC

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**Fickle Finger of Fame Award**

Don’t forget to send your nomination for this year’s Fickle Finger of Fame Awardee! The CRAJ wants to find Canadian rheumatologists who do more than just count joints, draw graphs, pipette cells and write long diatribes. The CRAJ is searching for rheumatologists with the most interesting pastimes, hobbies, locations, aspirations, vacations, facial hair, tattoos, children, you name it, etc., to be featured in our Holiday 2005 issue. Tell us about yourself or nominate a colleague in a brief note (photos are a bonus!). The CRAJ Editorial Board will then decide on this year’s most interesting arthritis specialist. The usual evanescent paraphernalia for such a prestigious and fleeting accomplishment will be presented at an appropriately effervescent time.

Please send your message and/or nomination today to stephc@sta.ca.
An Inflammatory Issue

modern medicine is driven by best evidence. Sometimes the science is not as robust as we would like and the conclusions are subject to interpretation. The issue of safety regarding anti-inflammatories, coxibs and traditional nonspecific nonsteroidal anti-inflammatory drugs (NSAIDs) has occupied physicians, the public and the media for the past year. The Canadian Rheumatology Association (CRAJ) Interim Guidelines provided a basis for rational prescribing during this tumult.

In the preceding article, Dr. Arthur Bookman reported and reviewed the recent Health Canada recommendations for this important set of medications. When the coxibs were first introduced there was a general consensus with regard to their appropriate use for individuals with a high risk for gastrointestinal complications. Physicians demonstrated their compliance with guidelines for the use of anti-inflammatories (Thomson G et al. J Rheum 2004; 31:1433.). What is needed now is a consensus as to the way forward with the identification of cardiovascular risk for anti-inflammatories. The CRAJ has asked some of your expert colleagues for their opinions as to whether the new Health Canada recommendations represent this consensus and will alter their prescribing habits. Their responses are provided below.

– Glen Thomson, MD, FRCPC

Will the proposed recommendations from the expert panel advising Health Canada on the use of anti-inflammatories alter the way in which you prescribe these drugs?

Response from S. Edworthy, MD, FRCPC
Calgary, Alberta

Dr. Bookman has summarized the results of a 13-member expert panel convened by Health Canada. The panel voted overwhelmingly in favour of allowing rofecoxib to return to the Canadian market place, as well as continuing the market presence of celecoxib. Not so for valdecoxib, which they felt needed more studies.

Presumably, despite the evidence for an increased rate of cardiovascular events, such as vascular-related death, heart attacks and strokes, it was felt that the benefits of the COX-2 agents outweighed the risks. If rofecoxib were to be returned to the Canadian market (which is still a company decision) some of my patients could safely and happily return to its use.

But will these proposed recommendations alter my prescribing?

Part 1 – My clinical response:
Not in a “clinically meaningful way.” In part, this is because I had not altered my prescribing habits to a great degree when the COX-2 agents were released. I have always found naproxen and diclofenac very satisfactory agents for any patient not at increased risk of serious gastrointestinal (GI) complications. Misoprostil, with or without diclofenac, was a good agent to ameliorate risk in those who were on anticoagulants or who had a previous GI bleed. Moreover, my cardiology colleagues have told me for years to avoid NSAIDs in their cardiac patients since they block the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors, leading to hospitalizations for congestive heart failure or hypertensive crisis. In the tough decision involving a rheumatoid patient with a known GI risk factor plus a cardiac risk factor and who needs an anti-inflammatory agent, I would probably prescribe naproxen along with misoprostil. But that wasn’t in the recommendations.

Part 2 – My epidemiological response:
Personally, I am pleased with the panel’s decisions, but perhaps for different reasons than outlined by Dr. Bookman. For example, I’m still uncertain what constitutes a clinically relevant rate for the cardiovascular events we are concerned with. Yes, 41% sounds like a big increase, but if there are only 20 events out of 1,000 patient years’ experience, then the increase to 28 (eight more events is roughly the 41% increase anticipated) has to be weighed against the benefit obtained (i.e., presumably a lower number of GI bleeds).
Furthermore, what are those eight events related to? Evidence from trials of nonspecific agents, such as diclofenac, indicate that some events will be due to mechanisms quite unrelated to specific COX-2 effects. Moreover, are these “events” more meaningful than a “joint flare,” or an incapacity to engage in daily activities? Epidemiological analysis of benefits and risks may be in the eye of the beholder, depending on what subspecialty he/she holds.

Response from H. Tannenbaum, MD, FACP, FRCP
Chair, Third Canadian Conference on NSAIDs
Montreal, Quebec

The third Canadian Consensus Conference on the use of NSAIDs met in January 2005. Its recommendations, supplemented by the findings of the Food and Drug Administration (FDA) advisory (February 16-18, 2005) and the Health Canada advisory (June 9-10, 2005), will appear shortly in the Journal of Rheumatology.1 I had declined to sit on the Health Canada expert panel due to a conflict of interest, but attended this meeting and presented our conference recommendations. Unlike the three-day FDA meeting, where all discussion, debate and voting was open to public scrutiny, the Health Canada meeting was relatively poorly attended and its major discussions and voting were held in camera. Nevertheless, the conclusions of all three groups were similar:

• All coxibs and NSAIDs have cardiovascular risk relative to placebo (with the possible exception of naproxen);
• Acetylsalicylic acid (ASA) plus a coxib carries the same gastrointestinal risk as a nonselective NSAID;
• Regarding drug availability, celecoxib should remain on the market; valdecoxib should be delisted (at least eight deaths now reported due to an exfoliative dermatitis-type reaction); consider new drug application for rofecoxib if requested by Merck.

I believe the Health Canada expert panel went too far by recommending that ibuprofen only be sold to individuals after discussion with a pharmacist. The drug has been available over the counter for about 20 years, is used primarily for pain and is marketed at a low dose. We are witnessing a knee-jerk reaction without evidence to support this recommendation. More importantly, the Health Canada advisory gives us no practical direction on what to do with our cardiovascular patients who are on low-dose ASA. There has not been an appropriate meta-analysis or a randomized controlled trial comparing ASA plus coxib versus ASA plus nonselective NSAID on either cardiovascular or gastrointestinal (GI) outcomes. Observational studies have demonstrated fewer hospitalizations due to GI events in patients receiving ASA plus coxib versus ASA plus nonselective NSAID, but this data needs confirmation. It was our recommendation that when any anti-inflammatory drug is given to a patient already on ASA, then consideration be given to adding a proton pump inhibitor.

Reference:

Response from M. Khraishi, MB, BCh, FRCP
St. John’s, Newfoundland

I felt that the recommendations were appropriate and well researched. Over the last year, my practice regarding coxibs was driven by many factors: the scientific data available from randomized controlled trials was definitely a significant element in my decision making, as well as pressure from the patients and, frankly, an element of uncertainty about the future of the available coxibs also played a role in my prescription of NSAIDs.

Like most Canadian rheumatologists, I was also aware of the Food and Drug Administration recommendations in February and tried to incorporate these into my practice. However, I feel that the new Canadian recommendations enable me to use them as a credible background in my discussions with my patients and colleagues in other specialties. I also now feel that I have an additional tool to defend myself in the rare possibility of complaints. Although I’ve always looked at the risk/benefit aspects of each patient to whom I’ve considered prescribing an NSAID, I tend to now document these risk factors in my notes.

Response from S. Huang, MD, FRCP
Vancouver, British Columbia

NSAIDs and coxibs have been prescribed at the lowest effective dose, as required, for the shortest duration
because of NSAID-induced upper gastrointestinal toxicities, as well as the emerging data on cardiovascular toxicities with both NSAIDs and coxibs. The Health Canada Expert Panel’s recommendation will not alter the above, as the recommendations affirm that coxibs and NSAIDs are both associated with increased cardiovascular events. Therefore, coxibs will remain the anti-inflammatory of choice for those who require such drugs, especially for those with gastrointestinal risks. Individuals at risk of cardiovascular events will require low-dose acetylsalicylic acid and possibly a concomitant gastro-protective agent.

Response from C. Patterson, MD, FRCPC
Vancouver, British Columbia

The old “see-saw” of balancing risk and benefit will continue to drive my prescription of anti-inflammatories. Anti-inflammatories are but one item on the menu of treatments for arthritis; if a patient with arthritis cannot cope without it, I will prescribe the NSAID that provides the best efficacy/tolerability/safety ratio, in the lowest dose necessary to relieve symptoms, for the shortest possible time. I will continue to use this approach, modified as usual by patient preference. Risk is inherent in medical practice and it is in the management of that risk that our challenge lies.

Response from J. Thomson, MD, FRCPC
Ottawa, Ontario

The expert panel’s conclusions and recommendations suggest that all NSAIDs and coxibs (with the possible exception of naproxen) should be considered to possibly increase the risk of cardiovascular events. At a clinical level, therefore, I am informing all patients that NSAIDs and coxibs may increase the risk of cardiovascular events (e.g., myocardial infarction, stroke). I continue to avoid the use of these drugs in patients with a history (especially recent) of an acute cardiovascular event and other patients with a predictably increased risk of a cardiovascular event. I remain cautious with the use of these drugs in patients, especially elderly, with a history of hypertension, weighing the risks versus the benefits. I am prescribing celecoxib somewhat more often than in the recent past, believing that it is likely safer from a gastrointestinal toxicity standpoint and probably no worse from a cardiovascular toxicity standpoint than a traditional NSAID.

I remain uncertain about the mechanism of the increased cardiovascular events. Could this be related to fluid retention and hypertension rather than prostacyclin/thromboxane?

Response from W. Bensen, MD, FRCPC
Hamilton, Ontario

“Time’s glory is to calm contending kings, 
To unmask falsehood and bring truth to light.”
- William Shakespeare

The first Canadian advisory panel on coxibs and NSAIDs is a positive first step—but only the first step towards a modern, progressive and responsive drug program. In a time of rapid change, the old, slow drug approval process is not adequate to meet the crushing need for better treatments as soon as possible.

Arthur Bookman, one of the panelists, has described the process and the recommendations. I will limit myself to additional comments.

I heard much of Colin Baigent’s speech at the panel meeting but have not seen the results in detail. My main objection was that he lumped all of the coxibs together, including rofecoxib and its cousin etoracoxib, as well as celecoxib, valdecoxib and lumiracoxib. My impression was that celecoxib, valdecoxib and lumiracoxib were relatively benign and that rofecoxib and etoracoxib were relatively toxic in terms of cardiovascular disease. Coxibs are chemically different compounds and lumping them together, I believe, may distort the truth.

Real-world experience by Graham et al at the Food and Drug Administration and published in the Lancet1 suggested that celecoxib and placebo are both relatively benign; all NSAIDs have some additional toxicity, and more so with rofecoxib, especially at higher doses. By looking at Figure 1 in the Lancet article, it is easy to see that lumping placebo with rofecoxib would make placebo appear more toxic than NSAIDs also. We will
have to wait and see the systemic review of 138 trials involving nearly 145,000 patients to know whether the statistically significant 41% relative increase relates to all or just some of the coxibs.

An analogy would suffice. If you were to compare safety between foreign-made and North American-made cars and lumped the Yugo and Lada in with BMW, Mercedes and Audi, you might easily be able to show that foreign cars were unsafe in many categories as compared to North American cars. The truth however might be that Yugo and Lada have safety issues but it would be much less likely for BMW, Mercedes and Audi. They are all cars but they are all different.

In terms of cardiovascular disease in high-risk patients, all anti-inflammatories are of concern. It appears that long-term use at high doses in high-risk patients may increase cardiovascular disease above placebo. Clearly, in this group of patients judicious use of any NSAID has to be carefully considered, with the benefits and risks balanced.

One of the weaknesses of the advisory panel process was too little time for too much information and debate. The time spent on valdecoxib was 10 minutes. As a result, what I and many colleagues feel is an important drug was easily dismissed. No one argues that the post-marketing surveillance stresses that valdecoxib has slightly more dermatologic toxicity but the increase is relatively small compared to the need in the marketplace.

Valdecoxib’s cardiac toxicity relates at a dose of four to eight times in patients undergoing coronary bypass, many who receive the drug intravenously. Can you imagine acetaminophen prescribed in the same way? The difference in toxicity would not be 1%-2%; it might be universal fatality.

Was the 8:5 vote on valdecoxib the statisticians versus the clinicians? I hope not. The number of our patients who have had to stop work and start taking disease-modifying drugs and even biologics because of valdecoxib’s withdrawal easily negates any potential savings that have been made. Many patients find they have no other options.

I also was surprised that the presentation made by Novartis on lumiracoxib, which has the largest study of anti-inflammatory safety in history (including gastrointestinal and cardiac) did not get a response from the panel. Was it the lack of real-world applicability or the urge not to discuss a drug that has not been approved? Lumiracoxib has many positive qualities and an exemplary research record; in any situation prior to September 2004, it would already be on the marketplace.

Our patients need more choices. No single drug works in every patient and some drugs seem to lose their power over time. During the last 50 years we have always had alternatives, but now in Canada we have only one remaining coxib.

There are hundreds of thousands of patients in Canada who have acute and chronic arthritis with inadequate control. These patients suffer daily, have their quality of life diminished and are disabled. They need newer, safer drugs as soon as possible. Many are now forced to take much more dangerous drugs because of the public negativity on anti-inflammatories as a class. Their need must dictate a change in national response and policy. The current inertia is not good enough. His Excellency John Ralston Saul, in the first LaFontaine-Baldwin lecture referring to the homelessness of Toronto, got under the skin of our complacency:

“These numbers have become our modern form of gossip; they are the People magazine of public policy. Somehow, the lives that lie behind the drama cannot be integrated into our consciousness in a long-term way. Instead there is a sense of immobility. ‘That’s the way things are.’ ‘There isn’t the money.’ It is as if, seen from within the complexity of our systems, it is impossible to identify the relationship between responsibility and action. Curiously enough, these same surging waves of numbers also create an impression of urgency – almost a mental state of siege. And yet this is an unusual urgency because it is not attached to any practical sense of the obligation to deal with the cause. It is as if we are addicted to the emotion of urgency for its own sake, and so rush on, from fast emotion to fast emotion, in a directionless manner.”

Our task is to reconnect responsibility and action, remove the sense of immobility and frustration in dealing with musculoskeletal disease and get off the roller coaster of urgency to a meaningful, progressive solution.

Reference:
In the spring of this year, a number of rheumatologists from across Canada engaged in a review of their practice, looking specifically at the way they manage rheumatoid arthritis. Personal digital assistants (PDAs) were selected to collect data in an electronic format. Surprisingly, in the space of a four-week practice audit, 837 consecutive patients—including 56 newly diagnosed rheumatoid arthritis (RA) patients—were identified by the 45 participants. This audit, called the Assessment In Rheumatology (AIR) program, was developed by a core group of nine rheumatologists who created the questionnaires through a facilitated teleconference. This data will provide those individuals with comparators of their practice at both the regional and national level. It will also help inform policy makers, educators, and administrators.

Participation was voluntary and rheumatologists did not collect any personally identifying information on the patients in their practice. Only patients who had previously been identified with RA or who had been referred for a diagnostic workup for inflammatory polyarthritis were to be included.

**PATIENTS AND METHODS**

Practice characteristics, including duration of practice, academic affiliation, size of practice community, solo or group association, and other aspects of the practice were collected at the time of initial sign-on. This generally took less than 20 minutes to complete. Following the initial overview of their practice, the rheumatologists were then able to start entering their consecutive RA patients. All rheumatologists were provided with an Identification and Password to allow entry to the national website so that they could assess their own personal data compared to regional and national averages. Credits for Section 5 of the Royal College of Physicians and Surgeons were available for any rheumatologist participating, based on the standard measures of two credits per hour of audit and reflection of one’s own personal practice.

Based on referral from various sources (see Table 1), 56 new patients with inflammatory polyarthritis were seen, 34 of whom had definite RA and the balance being probable RA. The identification of new patients provides insight into how long it takes to see a rheumatologist after the onset of persistent symptoms, and what the initial approaches to therapy are.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>REFERRAL SOURCES</th>
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<tbody>
<tr>
<td>Family practice</td>
<td>81.5%</td>
</tr>
<tr>
<td>Emergency room</td>
<td>7.4%</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>7.4%</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>3.7%</td>
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</table>

The duration of persistent symptoms prior to the referral was less than three months in 52% of cases, but over a year in 26% of cases. The time from referral request to actual consultation was less than one month in 81% of cases; all were seen in less than 12 weeks. The quality of a small number (14%) of referrals was deemed “excellent,” however, referral information was inadequate or only fair in 52%, largely due to incomplete data. The consultation request was missing information on current comorbidities (78%), date of onset (70%), current medications (70%), inflammatory signs (63%), and inflammatory symptoms (52%).

The initial consultation always included a history, general physical, and detailed joint exam. The Health Assessment Questionnaire (HAQ) was used 37% of the time, while the MD Global Pain and Patient Global Pain were used 63% and 70% of the time, respectively. Sedimentation rates were requested 95% of the time and 85% of patients were sent for radiographs.

Treatment with disease-modifying antirheumatic drugs (DMARDs) was initiated in 54 of 56 cases. Nonsteroidal anti-inflammatory drugs (NSAIDs) were used in 30 patients, intramuscular or intra-articular steroids in 16, while oral steroids (5 mg to 10 mg) were started in six patients.
Follow-up patients (N=781) with RA were an average of 58.5 years of age; 74.6% were females. The last visit was within two months in 35.7% of patients, three to four months in 31.6% and the balance (30.1%) was seen between five to 12 months previously. Of the 21% of patients with disease duration of greater than 15 years, 4% were followed by the same rheumatologist. Seventeen percent of follow-up patients were felt to be in remission, 25.7% were ‘smoldering’ with mild disease activity, while 22.4% had active disease. Of the 331 patients with either smoldering or active disease, 65% were seen at an interval less than four months from their previous visit, with only 32% seen in less than two months.

Table 2 shows which drug treatments were prescribed to patients. The majority (491/781; 63%) was prescribed either oral or intramuscular methotrexate, alone or in combination with other agents. Biologic agents were prescribed in 143 patients (18%).

<table>
<thead>
<tr>
<th>Drug</th>
<th># of Patients (N=781)</th>
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<tbody>
<tr>
<td><strong>DMARDs</strong></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>491 (63%)</td>
</tr>
<tr>
<td>- Oral</td>
<td>369 (47%)</td>
</tr>
<tr>
<td>- Intramuscular</td>
<td>122 (16%)</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>278 (36%)</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>76 (10%)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>74 (9%)</td>
</tr>
<tr>
<td>Intramuscular gold</td>
<td>30 (4%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

| **Biologics**      |                       |
| Infliximab         | 38 (5%)               |
| Etanercept         | 81 (10%)              |
| Adalimumab         | 19 (2%)               |
| Anakinra           | 2 (0.2%)              |
| Investigational agents | 3 (0.3%)        |

| Prednisone         | 219 (28%)             |

| **NSAIDs**         |                       |
| - Traditional      | 292 (37%)             |
| - Coxibs           | 171 (22%)             |

Prednisone was used in 219 patients (28%), mainly at a dose of less than 10 mg. Intra-articular injections were provided to seven patients and intramuscular to five patients. NSAIDs were prescribed for 463 patients (59%).

The rheumatologists did not change their patient’s rheumatic disease therapy in 465 cases (59% of total follow-up assessments). Out of these 465 patients, 46% were felt to have their disease activity acceptably controlled while 29.9% had no evidence of activity, and 6.6% were improving on existing therapy. About 6% did not have enough time to determine benefit. All options were exhausted in 3.9% while 1% had reached maximum tolerable therapy. Patient preference influenced the decision not to change therapy in 10.2% of cases. Management decisions in the remaining 41% of total follow-up patients included dose adjustments (both up and down), adding new medications, and stopping agents. A total of 2252 medication change decisions were made in the remaining 316 patients.

Treatment for comorbidities was noted in 58.8% (459/781) of patients, with hypertension, osteoporosis, osteoarthritis, depression and heart disease being the most common (see Table 3). Documentation of treatment of these conditions included a long list of medications, with the principle ones being for cardiac, gastric, endocrine and respiratory management.

Following their appointment, 72% (562/781) of patients required further attention/follow-up (e.g., reviewing labs, evaluating x-rays, further tests; see Table 4). Referrals were made for 52 patients (i.e., 20 to orthopedic surgeons, seven to either physiotherapy [PT] or occupational therapy [OT], five to neurology, three to pulmonary and others to dermatology, endocrinology, oncology and podiatry). Of note, joint replacements had been undertaken in 12.6% of the follow-up patients and 3.5% were waiting for joint replacement surgery at the time of their assessment. A wait of greater than four months was evident for 60% of patients and 9.5% had been waiting for more than a year.

**CONCLUDING REMARKS**

The quality of referral information could be improved by having the referring doctor (i.e., the GP in 81.5% of cases) record the date of onset of symptoms, inflammatory signs and symptoms, concurrent medications, comorbidities and level of functional impairment. The vast majority of these
patients were seen within two months of the referral request, and all were evaluated by 12 weeks. Almost all were started on DMARDs right away; only one was started on a biologic. Some were “cooled down” with low doses of prednisone and a small number required steroid injections. Many of these patients had cardiac and gastric comorbidities, which may account in part for the observation that not all were placed on NSAIDs. Of the 463/781 follow-up patients who were on NSAIDs, approximately 2/3 (63%) were on traditional NSAIDs while the remainder was on COX-2 agents. Questions regarding the use of COX-2 agents in light of recent cardiovascular concerns, as well as the negative effect that NSAIDs (except perhaps naprosyn) have, in general, on cardiovascular outcomes, might be addressed through this network of interested rheumatologists.

The interval between visits for follow-up patients with and without disease activity is instructive. This may help to establish standardized expectations across the country. The participating rheumatologists initially had the perception that they would see active RA patients within a two-month window in 65% of the cases and 100% by three to four months. However, in actuality, they only saw 32% of their patients within a two-month window and only 64% of their active patients within four months. Determining the best method of triaging patients for follow-up appointments is a challenge, as is finding the time to see them in a busy practice. New approaches to this task need to be worked out.

The overall impression of disease activity was that 17% were in remission, 35% were controlled, 25.7% were “smoldering,” and 22.4% were active. A discussion area for Canadian rheumatologists is the treatment of patients who have “acceptably controlled disease activity,” of which there were 212 patients of the 465 who did not have changes to their therapeutic management. This may be a fruitful area for further investigations, or the development of new approaches to disease measurement. Another area that may require more understanding is the 10% of patients who did not want their medications changed, despite evidence for uncontrolled disease activity. As a testimony to the complexity of RA medicinal management is the observation that a total of 2252 medication changes were made on the 316 patients whose health status needed refinement. The degree of pharmaceutical management is extensive, and perhaps would benefit from more systematic methods of coordination with other healthcare providers.

In conclusion, the AIR program has laid a solid foundation for Canadian rheumatologists to undertake their own practice audit, in conformance with recommendations from the Royal College of Physicians and Surgeons. Baseline data on how RA patients are seen and managed will provide policy makers, educators, and others interested in the maintenance of competence with reasonable practice measures. Hopefully, new approaches to developing best practices, particularly for the follow-up of active RA patients, can be developed through discussion of the findings in this audit.

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