

patients exposed) and worldwide (more than 20 million) has been extensive, and with this degree of exposure one would expect significant adverse event patterns to emerge. Reference to the Adverse Drug Reactions Advisory Committee and FDA database does not indicate a prothrombotic tendency of celecoxib. Further, we at Pharmacia do not consider that the four case studies presented by Cleland et al provide strong support for a prothrombotic tendency for celecoxib, especially as all patients described had diseases with high risk for thrombosis.

On the basis of a large body of controlled trial data (including CLASS) and extensive community exposure, the evidence does not show any more thrombosis with celecoxib than with NSAIDs.

Results of the CLASS and VIGOR studies clearly differ. It is clinically unjustified and scientifically unsound to suggest that rates of MI seen with rofecoxib can be ascribed to celecoxib and described as a "class effect".

1. Cleland LG, James MJ, Stamp LK, Penglis PS. COX-2 inhibition and thrombotic tendency: a need for surveillance. *Med J Aust* 2001; 175: 214-217.
2. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study*. *JAMA* 2000; 284: 1247-1255.
3. Throckmorton DC. FDA Center for Drug Evaluation and Research memorandum. Comparative safety of celecoxib, diclofenac and ibuprofen. Rockville, MD: FDA, 1 May 2001. <[http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1\\_07.pdf](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_07.pdf)>
4. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343: 1520-1528. □

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**IN REPLY:** The response from the Medical Director of Pharmacia to our article highlights some problems for all clinicians and independent scientists seeking to evaluate the balance of risks and benefits of pharmaceuticals and to validate the marketing messages of pharmaceutical companies. On the one hand, we lack the time and statistical resources to trawl through all data related to all trials with a test drug. On the other, our efforts to evaluate data are confounded by the publication and reporting biases associated with company-sponsored studies. In this regard, it is notable that the definitive results of CLASS<sup>1</sup> have not been published, although the Food and Drug Administration (FDA) review of the data is available through an FDA website,<sup>2</sup> as indicated by Fenn. While this document places data in the public domain, its location is neither within the pathway of MEDLINE search engines, nor is it known to the general body of clinicians.

As reported in the FDA presentation, CLASS was a very large, double-blind safety study of at least six months' treatment that failed to achieve its primary endpoint of reduced complicated upper gastrointestinal events with celecoxib relative to the comparator, non-steroidal anti-inflammatory drugs (NSAIDs). While an interim analysis at six months was published, with extrapolation of event rates to 12 months,<sup>3</sup> failure to publish the final results has withheld important results from wider scrutiny. In essence, the FDA document shows no overall long-term safety advantage of celecoxib over standard NSAIDs.<sup>2</sup>

The FDA analysis<sup>4</sup> of the VIGOR study<sup>5</sup> also shows no overall safety advantage for rofecoxib compared with NSAID, with fewer complicated upper gastrointestinal events being offset by a highly statistically significant ( $P = 0.0016$ ) increase in serious thrombotic cardiovascular events.

Collectively, these FDA analyses invalidate the promotion of selective cyclooxygenase-2 (COX-2) inhibitors as a safe alternative to NSAIDs, notwithstanding encouraging results from short-term trials. Further, although an increase in serious cardiovascular events was not seen in the CLASS study, its design was not optimal for detecting increased cardiovascular risk, and it is unlikely that CLASS was sufficiently powered to detect the degree of increased risk seen with rofecoxib in VIGOR. As explained in our article,<sup>6</sup> unbalanced prothrombotic eicosanoid production associated with selective COX-2 inhibition (ie, a class effect) appears the most likely explanation for the increased cardiovascular events seen in VIGOR.

Finally, we wish to reassert that, for effective postmarketing surveillance, it is essential that prescribers be adequately informed about safety concerns associated with new drugs, particularly when they involve events that are common and not usually seen as unwanted drug effects.

1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study*. *JAMA* 2000; 284: 1247-1255.
2. US Food and Drug Authority. NDA 20-998/S-009. Celebrex capsules (Celecoxib). Medical Officer Review. Sept 2001 <[http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1\\_03\\_med.doc](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.doc)>
3. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study*. *JAMA* 2000; 284: 1247-1255.
4. FDA Advisory Committee Briefing Document, NDA 21-042, s007, VIOXX Gastrointestinal Safety <[http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2\\_03\\_med.pdf](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.pdf)>
5. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343: 1520-1528.
6. Cleland LG, James MJ, Stamp LK, Penglis PS. COX-2 inhibition and thrombotic tendency: a need for surveillance. *Med J Aust* 2001; 175: 214-217. □

## Liver biopsy in hepatitis C: reassessing its role in 2001

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**TO THE EDITOR:** Chronic hepatitis C (HCV) infection affects more than 200 000 Australians.<sup>1</sup> As the degree of hepatic fibrosis is the best predictor of morbidity, liver biopsy has a central role in management. Biopsy is also carried out to exclude additional pathology. However, because liver biopsy carries real risks and is expensive,<sup>2,3</sup> debate exists as to whether liver biopsy should be performed routinely.<sup>3,4</sup> Despite controversy surrounding the need to treat patients with minor histological changes,<sup>4</sup> our impression is that many informed patients request treatment irrespective of liver histology. In Australia, liver biopsy is a prerequisite for antiviral therapy under the Pharmaceutical Benefits Scheme Highly Specialised Drugs Program (Box).<sup>5</sup>

To assess the impact of liver biopsy on management, we performed a retrospective study of patients with chronic HCV infection who underwent liver biopsy from March 1998 to December 2000. We identified 76 patients (51 men, 25 women), with a mean age of 29 years (range, 20-52 years). The biopsy was performed to stage and grade hepatitis C in all patients, and additionally to investigate a second pathology in seven patients. No alternative diagnoses were raised. Additional diagnoses (all suspected before biopsy) were confirmed in three patients and refuted in four patients. Biopsy findings were all consistent with chronic HCV infection, with some degree of fibrosis in 69 patients. There were five patients with histologically confirmed cirrhosis (including incomplete cirrhosis in three), and this was clinically evident in two patients. When S100 criteria at the time of biopsy were applied, after exclusions on clinical grounds, only one patient would have been ineligible for interferon monotherapy based on liver histology. Under current S100 criteria, nine patients would be ineligible for combination therapy, but all nine would remain eligible for monotherapy. Of our patients who attended follow-up and were HCV RNA positive, 62 of 64 patients received or are awaiting therapy.

Our results confirm the finding that liver biopsy in patients with chronic HCV infection rarely identifies alternative diagnoses.<sup>3</sup> These data reflect the fact that

### Section 100<sup>5</sup> criteria for use of combination therapy with interferon alfa 2b and ribavirin

Patients with chronic hepatitis C who satisfy the following criteria are eligible for interferon alfa 2b and ribavirin:

- On liver biopsy, are staged as METAVIR stage 2 or greater, or METAVIR stage 1 with grade A2 or A3 inflammation (except patients with coagulation disorders);
- Have abnormal alanine aminotransferase levels in conjunction with demonstration of viral infection (HCV RNA positive);\*
- Do not have other liver disease;\*
- Are not pregnant, not lactating, and are using two reliable methods of contraception;\*
- Have no history of significant psychiatric illness;
- Would be likely to attend regularly for treatment and follow-up; and
- Take no more than seven standard alcoholic drinks a week.

Genotype of virus should be assessed before treatment

Treatment course is 24 weeks except:

- With Genotype 1 and patients with cirrhosis or bridging fibrosis (regardless of genotype), where treatment course is 48 weeks; and
- Treatment will be continued for 48 weeks only if HCV RNA qualitative assay is negative at 24 weeks.

OR

- Patients who have relapsed after treatment with interferon 2a/2b monotherapy supplied as a Section 100 medication. This course is limited to 24 weeks.

### Section 100<sup>5</sup> criteria for use of monotherapy with interferon alfa 2b

Patients with chronic hepatitis C confirmed on liver biopsy (except patients with coagulation disorders) are eligible for interferon alfa 2b monotherapy if they satisfy the criteria marked with asterisks above. (*When monotherapy fails, patients become eligible for combination therapy.*)

Treatment is to cease if plasma HCV RNA remains detectable by HCV RNA qualitative assay after 12 weeks of treatment.

The course must be continuous and excludes retreatment of non-responders or patients who relapse.

most chronic liver diseases can be diagnosed before biopsy. Biopsy remains an important tool for histological diagnosis of cirrhosis. However, as unexpected findings are uncommon and some patients will be treated irrespective of liver histology, there is an emerging argument not to perform liver biopsy routinely. This argument will strengthen if valid biochemical markers of fibrosis are confirmed.<sup>6</sup> We believe each patient should be assessed individually, and treatment could be offered without biopsy to patients who:

- meet all criteria for treatment under current guidelines other than known liver histology;
- have no alternative or additional diagnoses after thorough work-up;
- strongly desire treatment regardless of histology, and there is sound indication for treatment (eg, extrahepatic symptoms, concerns of vertical or occupational transmission);
- have a high chance of sustained viral response (eg, favourable genotype);
- have no clinical, biochemical or haematological suggestion of cirrhosis; and
- with the physician, accept the implications of treatment without biopsy.

An alternative strategy could be to consider a biopsy in patients who do not have a sustained virological response, to allow prognostication. Clearly, such

changes would greatly affect biopsy practices in Australia.

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### Changes in serum folate concentrations following voluntary food fortification in Australia

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**TO THE EDITOR:** With the recognition that supplements of folate given early in pregnancy can reduce the incidence of neural tube defects,<sup>1,2</sup> Australian manufacturers were allowed voluntary food fortification with folate from 1995, and these foods subsequently became available from August 1996. We assessed the impact of this fortification by comparing the results of assays of serum folate, a sensitive index of folate intake, before and after the introduction of folate-fortified foods.

Data were available for serum folate samples assayed by the chemiluminescence method (Chiron Healthcare Pty Ltd, Scoresby, Victoria) at our laboratory in Melbourne. Quality assurance data indicated no analytical drift, and external proficiency testing yielded satisfactory results throughout the period under study.

A total of 20 506 samples from women aged 14–45 years, the target group for supplementation, and 5528 samples from men of the same age group were assayed during 1993–2000. The results for the years 1993–1996, before fortification, where sample numbers were relatively small, were pooled. The results were analysed by Bhattacharya plot, eliminating the effect of outlier values,<sup>3</sup> mindful of the limitations of extrapolating data derived from clinical

### Serum folate concentrations in Victorian women and men aged 15–45 years before (1993–1996) and after (1997–2000) the introduction of voluntary food folate fortification

	Year				
	1993 to 1996	1997	1998	1999	2000
<b>Women</b>					
Number	3865	2989	4168	4385	5099
Mean folate concentration (nmol/L)*	14.0	14.5	15.3	16.4	16.7
95% confidence limits	6.7–28.3	5.0–38.6	5.7–38.1	5.7–41.0	5.6–45.5
% Low values <sup>†</sup>	8.5	7.1	5.7	4.3	4.1
<b>Men</b>					
Number	1077	849	1130	1117	1355
Mean folate concentration (nmol/L)*	14.0	14.9	15.7	16.5	16.2
95% confidence limits	6.4–28.7	4.7–31.0	5.5–35.6	6.2–41.6	5.9–42.1
% Low values <sup>†</sup>	7.9	8.1	6.5	4.1	5.1

\* Derived from log normal distribution of community values by Bhattacharya method. <sup>†</sup> 8.0 nmol/L.