

PostScript

LETTERS

If you have a burning desire to respond to a paper published in *Gut*, why not make use of our "rapid response" option?

Log onto our website (www.gutjnl.com), find the paper that interests you, and send your response via email by clicking on the "eLetters" option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on "read eLetters" on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines

We were interested to read the report by Ransford and Langman of their analysis of yellow card reports of suspected adverse drug reactions for sulphasalazine and mesalazine (*Gut* 2002;51:536-9). These reports, submitted to the Committee on Safety of Medicines, may provide useful flags to signal unrecognised hazards of drugs. However, as adverse reactions are not always recognised or reported to the regulatory authorities by physicians, these reports usually underestimate the frequency of any adverse drug reaction. Of greater importance, underreporting is usually not random but selective, which may introduce serious bias when comparing different drugs.¹ Various examples have been described previously of drugs that showed substantive differences in reporting rates, which were not substantiated after further research.¹ For this reason, it is recommended that, once there is a signal for a suspected adverse drug reaction, other sources of data are investigated.²

We recently initiated a study to quantify the risk of renal toxicity in patients taking aminosalicilate (5-ASA) drugs in the UK.

The General Practice Research Database (GPRD) was used for this study, with data collected as part of routine medical practice. The GPRD has previously been demonstrated to be a representative sample of the general population of England and Wales, and the completeness and validity of the GPRD recording of medically significant events is well established. Its data have been used frequently to quantify the risk of adverse drug reactions.³ Our study population included almost 40 000 patients. We found that the overall incidence of renal damage (which included interstitial nephritis) was rare in patients taking 5-ASA drugs, but was increased relative to control patients (table 1). The risk of renal toxicity in patients taking mesalazine and sulphasalazine was comparable. Interestingly, we found that the risk of renal disease was related to indicators of severity of inflammatory bowel disease and to concomitant disease and drug treatment. A recent report also suggested that the kidney can be an extraintestinal target in Crohn's disease.⁴ We presented the results of this study at the recent British Society of Gastroenterology meeting.

Our findings also highlight the substantive underreporting of the data used by Ransford *et al* (table 1). Given the selected and incomplete nature of the reports of suspected adverse drug reactions, one needs to establish whether physicians reported cases of interstitial nephritis equally for users of different 5-ASA drugs. The authors did not provide any data for the comparability of the users of the various 5-ASA drugs in the UK.

In conclusion, while we agree that renal function should be evaluated and monitored in patients taking 5-ASAs, the results of our large epidemiological study show no difference in renal toxicity between mesalazine and sulphasalazine and that confounding factors can also significantly affect the overall risk. A statistical analysis of suspected adverse drug reaction reports may generate signals but does not provide conclusive evidence of differences in safety between drugs.

R F Logan

Clinical Epidemiology, University Hospital, Nottingham, UK

T P van Staa

Procter & Gamble Pharmaceuticals, Egham, UK

Correspondence to: Professor RFA Logan, Division of Public Health and Epidemiology, School of Community Health Sciences, University of Nottingham Medical School, Nottingham NG7 2UH, UK; Richard.Logan@nottingham.ac.uk

References

- 1 **Wiholm B-E**, Olsson S, Moore N, *et al*. Spontaneous reporting systems outside the United States. In: Strom BL, ed. , eds. *Pharmacoepidemiology*. Chichester: John Wiley and Sons, 1994:139-55.
- 2 **Evans SJW**, Waller PC, Davis S. Use of proportional reporting ratios (PPRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drg Safety* 2001;10:483-6.
- 3 **Walley T**, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350:1097-9.
- 4 **Izzedine H**, Simon J, Piette A-M, *et al*. Primary chronic interstitial nephritis in Crohn's disease. *Gastroenterology* 2002;123:1436-40.
- 5 **van Staa**, Travis SPL, Leafkens HG, *et al*. 5-Aminosalicylic acids and the risk of renal toxicity: a large British epidemiological study. *Gut* 2003;52(suppl 1):A14.

Author's reply

We do of course recognise that making deductions from examination of spontaneous adverse reaction reports poses problems from the incomplete nature of the data, and the limited knowledge of biases. Thus we say "spontaneous reporting...cannot be used to determine true rates of reaction". We also speculate that reporting rates of interstitial nephritis with mesalazine may be high "because a specific warning of possible renal toxicity had been issued".

The comparatively equal values quoted by Logan and van Staa of 1.2 (mesalazine) and 1.7 (sulphasalazine) cases of interstitial nephritis per 1000 patient years are very different from the 29 cases reported spontaneously on yellow cards for mesalazine with none for sulphasalazine in the time period assessed (there are a total of 47 for mesalazine and two for sulphasalazine, a fairly large difference).

Being aware of the problems of judging true rates of reaction from spontaneous reports, and knowing that there was (as for interstitial nephritis) a relative paucity of reports for pancreatitis with sulphasalazine, we have recently analysed data from the General Practice Research Database (GPRD) on prior drug exposure in cases of acute pancreatitis. This clearly shows raised odds ratios for mesalazine, but not for sulphasalazine, and with the odds ratio for mesalazine being particularly high in those with first exposure in the prior three months.¹ The finding is consonant with the spontaneous adverse drug reaction data presented by us.

Rates from GPRD for interstitial nephritis, as presented by Logan and van Staa per 1000 patient years, are difficult to relate to individual patient exposures. It would be valuable to have such information. Given that sulphasalazine is the older drug, one would expect longer exposure in each such taker (particularly if it was for inflammatory bowel disease). It would also be valuable to know if the cases of renal damage in sulphasalazine takers identified by Logan and van Staa were in patients with inflam-

Table 1 Rates of renal events in the General Practice Research Database (GPRD)³ study and in the study of Ransford *et al*

| | | | Rate per 1000 person years |
|-----------------------|------------------|------------------|----------------------------|
| GPRD | Renal toxicity | During 5-ASA use | 1.2 |
| | | Mesalazine | 1.2 |
| | | Sulphasalazine | 1.7 |
| | Control cohort | 0.6 | |
| Ransford <i>et al</i> | During 5-ASA use | | |
| | Mesalazine | | 0.1 |
| | Sulphasalazine | | 0 |

matory bowel disease rather than in those with rheumatoid disease, where confounding by use of other agents, notably penicillamine and gold, and by complicating renal amyloid, would need to be borne in mind. Differences between our findings may be resolved in due course by current surveillance studies being conducted by the British Society of Gastroenterology.

M J S Langman, R A J Ransford
Queen Elizabeth Medical Centre, Birmingham, UK

Correspondence to: Professor M J S Langman, Department of Medicine, University of Birmingham, Edgbaston, Birmingham B15 2TH, UK; m.j.s.langman@bham.ac.uk

Reference

- 1 **Lancashire RJ**, Cheng K, Langman MJS. *Alimentary Pharmacol Ther* 2003;17:887–91.

Worsening of steatosis and fibrosis progression in hepatitis C

We thank Ratziu *et al* for their interest in our work.¹ To grade steatosis, we used the Metavir scoring system, shown by their group to be accurate and reproducible.^{2,3} Worsening was characterised by an increase in the amount of lipids in hepatocytes, as defined in this grading system. As emphasised in our paper, our main finding was that worsening of steatosis was the only independent factor associated with fibrosis progression in multivariate analysis. This study was observational and not aimed at establishing causal links, a goal that requires a combination of prospective clinical studies and careful in vitro experiments. Ratziu's discussion of our data is interesting but remains purely speculative.¹ The issues raised by our results and their discussion in both our paper and Ratziu's letter are currently being addressed through appropriate studies in our centre.

L Castéra, J-M Pawlowsky, D Dhumeaux
Hopitalier Universitaire Henri Monor, Creteil, France

Correspondence to: Dr L Castéra, Service de Virologie (EA 3489) Centre, Hopitalier Universitaire Henri Monor, Creteil 94010, France; laurent.castera@chu-bordeaux.fr

References

- 1 **Ratziu VD**, Saboury M, Poynard T. Worsening of steatosis and fibrosis progression in hepatitis C. *Gut* 2003;52:1386.
- 2 **The French METAVIR Cooperative Study Group**. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994;20:15–20.
- 3 **Groupe METAVIR**. Which classification for chronic hepatitis? Lessons from the hepatitis C virus. *Gastroenterol Clin Biol* 1994;18:403–6.

Complete regression of advanced HCC with long acting octreotide

Various therapeutic approaches for unresectable hepatocellular carcinoma (HCC) have been suggested in recent years. However, major advances concerning tumour regression or patient survival were not achieved. A few trials have assessed the effect of the somatostatin analogue octreotide in advanced HCC with divergent results.^{1,2} The latter might be due to expression of somatostatin receptor type 2 (SSTR2) in some but not all patients with HCC.^{3,4} Herein we describe a patient with advanced HCC who was treated with long acting octreotide,

which resulted in complete and prolonged regression of the tumour.

The patient was diagnosed with HCC after a suspect nodule was detected in the abdominal ultrasound. Laboratory testing revealed a highly increased alpha fetoprotein (AFP) level and positive hepatitis C virus antibodies. Computed tomography (CT) of the liver displayed multiple tumours (maximum diameter 5 cm) in segment seven and two smaller nodules in segments six and one. Histology of an ultrasound guided biopsy revealed HCC. Due to the advanced stage of the tumour, surgical resection was not feasible. As the patient refused local ablative therapies, treatment with octreotide was initiated (initially 250 µg twice daily followed by long acting octreotide (Sandostatin LAR) 10 mg monthly). Four months later a 50–70% reduction in the size of the multifocal tumours was demonstrated by CT. Furthermore, complete regression of the formerly described tumours was noted 10 months after initiation of octreotide therapy. This was paralleled by normalisation of the formerly elevated AFP values (33.1 ng/ml v 7615.3 ng/ml). Octreotide receptor scintigraphy performed after 12 months and 19 months of therapy did not reveal any suspicious enhancement. However, after 13 and 19 months a gradual increase in AFP levels from 37 to 223 ng/ml and a new suspicious liver nodule by CT scan was observed. To date, the patient has not experienced any tumour associated symptoms or drug related side effects and has been in excellent condition during the 22 months of treatment.

The survival improving treatment effects of octreotide described by Kouroumalis and colleagues¹ were not confirmed in a subsequent randomised placebo controlled trial.² Of the octreotide receptors expressed in the liver, octreotide has the highest affinity for SSTR2 compared with the four other isoforms of the somatostatin receptors.³ SSTR2 is expressed in HCC^{3,4} and has been shown to play a major role in mediating cell cycle arrest.⁵ Although we were not able to prove SSTR expression in our patient due to tissue preparation in another hospital, high SSTR2 expression in our patient might be the reason for the unusual beneficial clinical course. The recent increase in AFP levels could reflect the ability of the tumour cells to escape somatostatin receptor treatment, possibly by downregulation or mutation of the respective receptor.

To the best of our knowledge, complete and prolonged regression of advanced HCC with normalised AFP levels during octreotide treatment has not been described previously. Based on our observation and the divergent results of recent studies, forthcoming trials evaluating the effect of octreotide in advanced HCC might additionally stratify patients according to the respective somatostatin receptor expression profile of tumour cells.

J T Siveke

Department of Internal Medicine II, Technical University of Munich, Munich, Germany

C Folwaczny

Medizinische Klinik und Poliklinik, Klinikum der Universität, Munich, Germany

C Herberhold

Department of Surgery Innenstadt, Munich, Germany

Correspondence to: C Folwaczny, Medizinische Klinik und Poliklinik, Klinikum der Universität, Numbbaumstr. 20, 80336 München, Germany; Christian.Folwaczny@medinn.med.uni-muenchen.de

References

- 1 **Kouroumalis E**, Skordilis P, Thermos K, *et al*. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998;42:442–7.
- 2 **Yuen MF**, Poon RT, Lai CL, *et al*. A randomized placebo-controlled study of long-acting octreotide for the treatment of advanced hepatocellular carcinoma. *Hepatology* 2002;36:687–91.
- 3 **Reubi JC**, Waser B, Schaer JC, *et al*. Somatostatin receptor sst1- sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. *Eur J Nucl Med* 2001;28:836–46.
- 4 **Reubi JC**, Zimmermann A, Jonas S, *et al*. Regulatory peptide receptors in human hepatocellular carcinomas. *Gut* 1999;45:766–74.
- 5 **Benali N**, Cordelier P, Calise D, *et al*. Inhibition of growth and metastatic progression of pancreatic carcinoma in hamster after somatostatin receptor subtype 2 (sst2) gene expression and administration of cytotoxic somatostatin analog AN-238. *Proc Natl Acad Sci USA* 2000;97:9180–5.

Diagnosing small bowel Crohn's disease with wireless capsule endoscopy

We read the article by Fireman *et al* (*Gut* 2003;52:390–2) with great interest. We agree that full visualisation and imaging of the entire length of the small bowel is unsatisfactory at present and that capsule endoscopy (CE) is a novel technique and can be considered as a promising new approach for the diagnosis of obscure disease located in the small bowel.

The authors diagnosed Crohn's disease (CD) in 12 of 17 patients with clinically suspected CD according to the findings of CE. The authors state that the majority of diagnostic lesions were located in the distal ileum. At least one colonoscopy had been performed prior to CE in 15 of 17 patients. Unfortunately, the investigators do not report whether or not they were able to explore the terminal ileum in all of these patients. Hence the important question arises of which endoscopic and histological findings had been observed in the terminal ileum of these 15 study patients prior to CE, and whether this clinical information may have affected the interpretation of the CE findings in this investigational setting. Furthermore, the authors did not compare their non-diagnostic x ray findings with the CE results.

To date, we have performed a total of 130 capsule endoscopy procedures. In 50 patients with obscure gastrointestinal bleeding, we were able to disclose CD as the most probable underlying cause of bleeding in four patients. In addition, one patient suffering from Peutz-Jegher's syndrome was diagnosed as also having CD of the small bowel. We also performed CE in eight patients in whom the diagnosis of CD had been established prior to CE to "stage" the small bowel for additional lesions that could influence treatment decisions. In the majority of our patients we found that the main pathological lesions were located in the terminal ileum. We were however able to confirm most CD lesions histologically by applying a second ileocolonoscopy with special emphasis on the small bowel biopsies in most of these patients, which allows for a greater diagnosis validity

as small bowel ulcerations obtained with CE may also be caused by non-steroidal anti-inflammatory drug abuse, ulcerative ileitis, or coeliac disease. Hence from our experience we strongly recommend that patients with suspected CD should initially undergo careful ileocolonoscopy with close inspection of as much as the ileum as possible, and acquisition of multiple ileal biopsies to histologically establish CD prior to therapy.

We believe that at present CE is only clinically indicated in patients with signs and symptoms suggestive of small bowel CD in whom:

- a stenosis/stricture has clearly been excluded,
- the terminal ileum looks unremarkable on endoscopy, or
- the ileum cannot be intubated for technical reasons.

The present study does not elucidate whether CE is really superior to conventional endoscopy plus histological assessment, which must still be considered the gold standard for the diagnosis of CD. As there is a substantial risk of capsule retention in the gastrointestinal tract in patients with stenosing CD, it should be determined if the benefits of CE findings outweigh the risks of this otherwise remarkable novel technique in individual patients.

K Schulmann, S Hollerbach, W Schmiegel
Ruhr University, Bochum, Germany

Correspondence to: Dr K Schulmann, Ruhr University, In der Schornau, 23–25, Bochum, Germany; karsten.schulmann@ruhr-uni-bochum.de

Authors' reply

We thank Drs Schulmann, Hollerbach, and Schmiegel for their interest in our paper on the subject of diagnosing small bowel Crohn's disease with wireless capsule endoscopy.¹ Regarding colonoscopy,¹ please note that in the materials and methods section, under study population, it is clearly stated that all underwent colonoscopies elsewhere, at most six months prior to entering the study, and this statement is repeated in the first paragraph of the results section. As these patients came to us from other medical centres with the results of their previous colonoscopies, we sent the results of capsule endoscopy (CE) to their own physicians (Re: exploration of the terminal ileum). In the results section, we state that six patients underwent ileoscopy which was normal.

We appreciate the experience of your group and agree with your indications and contra-indications regarding the CE study.

Z Fireman, Y Kopelman
Gastroenterology Department, Hillel Yaffe Medical Center, Hadera 38100, Israel

Correspondence to: Dr Z Fireman; fireman@hillel-yaffe.health.gov.il

Reference

- 1 Schulmann K, Hollerbach S, Schmiegel W. Yield of capsule endoscopy in Crohn's disease may depend on the quality of prior ileo-colonoscopy (electronic response to Fireman Z *et al.* Diagnosing small bowel Crohn's disease with wireless capsule endoscopy). *gutjnl.com* 2003. <http://gut.bmjournals.com/cgi/letters/52/3/390#49>.

Cost effectiveness of pegylated interferon alpha 2b and ribavirin combination in chronic hepatitis C

I read with great interest the excellent cost effectiveness analysis of pegylated interferon alpha 2b and ribavirin combination in patients with chronic hepatitis C (*Gut* 2003;**52**:425–32). I was surprised by the relatively low cost of treatment initiation in Germany (table 3). The cost estimate of pre-therapeutic diagnostics, at 473, included a pregnancy test, quantitative hepatitis C virus-RNA, thyroid stimulating hormone, thyroxine, liver biopsy, and partial inpatient cost for initiation of treatment. Do you exclude the genotype assessment in these baseline tests? In a previous US cost effectiveness study¹ and in our hospital, the same pre-therapeutic diagnostics seems more expensive (>1000). How do you estimate the cost of a liver biopsy? Even without taking into account the complications of liver biopsy (three severe complications out of 1000 and three deaths out of 10 000), the cost of the baseline diagnostics could be decreased by using non-invasive biochemical markers of liver features, such as the Fibrotest-Actitest, which costs only 90 euros.^{2,3}

T Poynard

Service d'Hepato-gastroenterologie Groupe Hospitalier, Pitie-Salpetriere 75651, Paris, France; tpoynard@teaser.fr

Conflict of interest: T Poynard has participated in clinical trials for viral hepatitis and as an advisor with the following companies: BMS, Boehringer, Gilead Science, GlaxoSmithKline, Idenix, Roche, and Schering Plough. He is a consultant and has financial participation in the capital of Biopredictive (start up company from Bioincubator ParisBiotech, University Paris 5), which is marketing Fibrotest and Actitest.

References

- 1 Wong JB, Bennett WG, Koff RS, *et al.* Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. *JAMA* 1998;**280**:2088–93.
- 2 Imbert-Bismut F, Ratziu V, Pileri L, *et al.* Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001;**357**:1069–75.
- 3 Halfon P, Imbert-Bismut F, Messous D, *et al.* A prospective assessment of the inter-laboratory variability of biochemical markers of fibrosis (FibroTest) and activity (ActiTest) in patients with chronic liver disease. *Comparative Hepatology* 2002;**2**:3.

Risk of fracture in coeliac disease

We agree that the risk of fracture in coeliac disease needs to be estimated more precisely and that judicious use of DEXA scanning is appropriate in this group, as it is in the general population. However, as Walters and colleagues (*Gut* 2003;**52**:1229–30) and others have clearly shown, bone mineral density does improve following treatment with a gluten free diet, so recommendations to screen all newly diagnosed patients with coeliac disease at diagnosis do not seem judicious.¹

Larger studies are needed and one such is in progress. Nevertheless, the small increases in risk which we found are similar to those found in the only other population based study of fracture risk in patients with coeliac disease.² In the absence of robust data showing a marked increase in the risk of fracture in patients with coeliac disease, perhaps the onus should be on those making such recommendations¹ to provide

evidence supporting their efficacy and cost effectiveness.

R Logan, J West

Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK

Correspondence to: Professor R Logan, School of Community Health Sciences, Division of Public Health Sciences, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, UK; richard.logan@nottingham.ac.uk

References

- 1 Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. *British Society of Gastroenterology. Gut* 2000;**46**:i11–8.
- 2 Vestergaard P, Mosekilde L. Fracture risk in patients with celiac disease, Crohn's disease, and ulcerative colitis: a nationwide follow-up study of 16,416 patients in Denmark. *Am J Epidemiol* 2002;**156**:1–10.

NOTICES

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2004

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years old or less on 31 December 2004 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

British Society of Gastroenterology Hopkins Endoscopy Prize 2004

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to the Council the recipient of the 2004 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TEN COPIES) should be made to the Endoscopy Section Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.