PostScript

LETTERS

Cyclosporin A treatment of steroid-refractory ulcerative colitis during pregnancy: report of two cases

Treatment of fulminant, steroid-resistant ulcerative colitis during pregnancy is extremely challenging. Calcineurin antagonists like cyclosporin A (CyA) have been used in the past in fulminant colitis; yet, the experience using CyA during pregnancy is limited, as are the data on the long-term course after the initial treatment phase.

Case reports

The first patient is a 31-year-old woman with a 7-year history of ulcerative colitis. During her first pregnancy, she developed an acute flare of ulcerative colitis confirmed using endoscopy. Despite taking intravenous steroids, disease activity remained high, necessitating the transfusion of packed red blood cells. Within 7 days after initiating intravenous CyA the blood loss and abdominal pain subsided, and the frequency of bowel movements was reduced to 5 per day. The patient was discharged home on oral CyA. As a side effect, she developed hirsutism, which subsided after CyA was discontinued. The patient refused treatment with azathioprine, so we began oral mesalazine for maintenance of remission. In the 36th week of her pregnancy, she gave spontaneous birth to a healthy child. During the 7-year follow-up period, the child developed normally, the patient had four more flares of colitis, yet only one was severe enough to warrant inpatient treatment. She is now in remission using mesalazine.

The second patient is a 34-year-old woman with a 13-year history of ulcerative colitis presenting with an acute flare of ulcerative colitis in the 13th week of her first pregnancy. She failed to respond to conventional treatment with mesalazine, oral and intravenous steroids. After confirming the diagnosis by sigmoidoscopy, we began treatment with intravenous CyA. Within 1 week, the patient improved significantly. After 21 days of treatment with intravenous CyA, the treatment was changed to oral CyA for five more weeks. During CyA treatment, the patient had one self-limiting episode of second-degree arteriovenous block and developed hypertrichosis. In the 25+5 week of pregnancy, she underwent an emergency caesarean section for suspected placental insufficiency. The child suffered a femur fracture, a third-degree intracerebral haemorrhage and respiratory distress syndrome of the neonate. Yet, follow-up after discharge showed normal intellectual development and no impairment of motor skills. In the following 10 years, the patient herself had two more flares of ulcerative colitis, which were treated with oral and intravenous steroids, respectively. She is now in remission under mesalazine treatment.

Conclusions

The main goal of CyA treatment in pregnant patients with ulcerative colitis is to avoid

emergency colectomy, because of its high risk for the mother and for the unborn child, with a mortality of 22% and 49%, respectively.¹ CyA has been proven to induce remission in patients with fulminant ulcerative colitis rapidly and effectively² in patients who did not respond to 7 days of intravenous steroids. Our results once again show that CyA is highly potent (fig 1) in inducing remission in patients with ulcerative colitis, and seems to be safe when used at lower dosage, aiming for blood levels of 200 ng/ml. In addition, our follow-up data also suggest that the long-term prognosis in pregnant patients might be different from the prognosis in non-pregnant patients with severe or fulminant ulcerative colitis, regarding the need for later colectomy. Yet recent encouraging results in the treatment of fulminant colitis using infliximab,³ and the fact that infliximab is rated risk category B during pregnancy by the Food and Drug Administration whereas CyA is rated as category C, indicate that the question as to what drug to recommend is not yet solved.

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Informed consent has been obtained from the patients for publication of their details in this letter.

doi: 10.1136/gut.2006.105288

Competing interests: None declared.

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Proton pump inhibitors and gastric neoplasia

We read the leading article by Kuipers (*Gut* 2006;55:1217–21) with great interest. The conclusion that proton pump inhibitor (PPI) treatment does not increase the risk of gastric neoplasia is reassuring. The overview by Kuipers, however, lacks a few important points:

1. *Hypergastrinaemia.* The maximal trophic effect of gastrin is reached at concentrations lower than that realised by most clinicians, both in rats and in humans.¹ A concentration of 400 ng/ml or 200 pM induces nearly maximal effect.
2. *Hypergastrinaemia and gastric carcinoids.* Kuipers claims that prolonged hypergastrinaemia leads to enterochromaffin-like (ECL) cell carcinoids only in rats.² This is not correct. Mice also develop gastric carcinoids when treated with insurmountable histamine 2 antagonists.³ PPIs have low potency in this species, which is the cause of the widespread misunderstanding that hypergastrinaemia in mice does not induce ECL cell carcinoids. Moreover, long term treatment of dogs with PPI was reported not to induce any changes in the gastric mucosa.⁴ Unfortunately, the dose used was not sufficient to induce hypoauidity and accompanying hypergastrinaemia. Even in humans gastric endocrine tumours have been described after PPI treatment,¹ although, surprisingly, a more detailed report on these patients does not

Figure 1 Rachmilewitz Index at admission to the intensive care unit (ICU) and after 7 days of treatment with intravenous cyclosporin A (CyA).

exist. It is, therefore, likely that not only rats, but every species, including humans, exposed to long-term hypergastrinaemia is at risk of developing ECL cell carcinoids.

3. **Role of the ECL cell in gastric cancer.** Kuipers does not discuss the role of the ECL cell in gastric carcinogenesis. It is now apparent that a higher proportion of gastric carcinomas than previously realised are probably neuroendocrine carcinomas.¹⁻⁵ Moreover, most of these neuroendocrine carcinomas develop from the predominant neuroendocrine cell in the stomach, the ECL cell.¹ In addition, gastric ECL cell carcinoids secondary to hypergastrinaemia may progress to neuroendocrine carcinomas.¹ The gastric carcinomas developing in patients with pernicious anaemia most often originate in the oxyntic area, indicating that the lack of acidity is not the most important factor in gastric carcinogenesis in these patients, and that the ECL cell is probably the cell of origin in these carcinomas.¹ It should also be recalled that the carcinogenic effect of *Helicobacter pylori* infection may be related to hypergastrinaemia.¹

To conclude, PPI treatment induces hypergastrinaemia. Long-term hypergastrinaemia predisposes to ECL cell tumours, such as ECL cell carcinoids and ECL cell neuroendocrine carcinomas. Long-term PPI treatment might, therefore, increase the risk of gastric cancer. It should be remembered that carcinogenesis is a long-term process often taking decades.

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Competing interests: None.

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Author's response

In theory, profound acid suppression can promote the development of gastric neoplasia via various pathways, including the trophic effect of hypergastrinaemia on the epithelial lining, stimulation of enterochromaffin-like (ECL) cells leading to formation of carcinoids and neuroendocrine carcinomas, promotion of bacterial overgrowth and induction of a chronic active *Helicobacter pylori* pan-gastritis pattern. Waldum *et al* focus on the theoretical implications of hypergastrinaemia and ECL cell

stimulation, a relevant hypothesis that has often been discussed but remains speculative. Indeed, as Waldum points out, data suggest that the incidence of gastric carcinoids has been rising. This has been noted over the past 50 years, in particular since the early 1970s. This primarily correlates with the increase in gastric diagnostic procedures, firstly using x rays and later endoscopy with biopsy sampling, rather than the more recent introduction of proton pump inhibitors (PPIs).¹ Nevertheless, gastric carcinoids remain rare, with an incidence of 0.1–0.2 per 100 000 population per year,² without an obvious association with PPI use. I mentioned previously that carcinoids have never been described in long-term PPI users, but I was mistaken. Dr Manson from the UK had reported a patient who was diagnosed with a primary gastric carcinoid after having taken 40 mg omeprazole for 4 years for reflux disease.³ Waldum refers to another case; this was, however, not a long-term PPI user, but a patient with recurrent peptic ulcer who was diagnosed with a gastric carcinoid after intermittently having been treated with famotidine, omeprazole and lansoprazole for a total of 5 months over a 5-year period (ie, <10% of the time).⁴

ECL cells may also play a role in the formation of gastric adenocarcinoma. In fact, it has been suggested that about 10% of gastric adenocarcinomas, in particular of the diffuse type, may have a neuroendocrine component.⁵ In the US, a rise in the incidence of the diffuse type of gastric cancer between 1973 and 2000 has been noted, from 0.3 to 1.8 per 100 000 per annum.⁶ It is unknown whether acid-suppressive drugs have made any contribution to this process. As pointed out previously, data on gastric cancer formation in long-term PPI users have not shown any increased incidence of gastric cancer (diffuse and intestinal) at all within the first 18 years after the introduction of PPI.⁷

In conclusion, in contrast with the statement of Waldum *et al*, there is, at present, no evidence that promotion of ECL cell growth is a clinically important issue in long-term PPI users, for the formation of either gastric carcinoids or neuroendocrine adenocarcinomas. I fully agree though with the implicit proposition that monitoring of large cohorts of long-term PPI users as well as reporting of any specific cases such as that by Dawson *et al*³ remains relevant, because only in that way can we eventually settle issues such as raised in this discussion.

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Competing interests: In the past 5 years, EJK has received research funding from Altana Pharma, AstraZeneca and Janssen Pharmaceuticals, and consulting fees from AstraZeneca.

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Dissemination of evidence-based clinical practice guidelines for hepatocellular carcinoma among Japanese hepatologists, liver surgeons and primary care physicians

Supported by the Japanese Ministry of Health, Labour and Welfare, the first *Clinical practice guidelines for hepatocellular carcinoma* (the JHCC guidelines) were compiled in Japan, using an evidence-based methodology. Covering six major research fields for hepatocellular carcinoma (HCC), this set of guidelines consists of 58 pairs of research questions and recommendations, and practical algorithms for the surveillance and treatment of HCC (fig 1).¹⁻² A complete English translation of the main body of the guidelines has recently been uploaded on the website of The Japanese Society of Hepatology (<http://www.jsh.or.jp/>). The JHCC guidelines are primarily intended to support both physicians and patients in their decision making on the management of HCC.

In March 2006, approximately a year after the publication of the JHCC guidelines book, a questionnaire survey was conducted to investigate the level of awareness and influence of the guidelines among 2279 members of the Liver Cancer Study Group of Japan. Of the 843 (37.0%) responders, 467 (55.4%) were hepatologists and 320 (38.0%) were liver surgeons. More than 70% were working at university hospitals or designated teaching hospitals. Over the previous 3 months, 533 (63.2%) and 357 (42.3%) of the responders had treated ≥10 HCC patients at outpatient and inpatient bases, respectively.

The same questionnaire was sent out to 689 primary care physicians in Osaka and Hyogo prefectures, and 332 (48.2%) responded; 159 (48%) were internists, 146 (44%) were surgeons and 209 (63%) were working at clinics. The majority (86.4%) had treated <10 patients with HCC in the previous 3 months.

The JHCC guidelines have been acknowledged by 71.9% of hepatologists, 75.6% of liver surgeons and 61.0% of primary care physicians. Answers obtained regarding the possible actions taken for clinical questions on HCC are shown in fig 2A. Medical magazines, literature search, the JHCC guidelines and colleagues' opinions were the main sources of information, both for hepatologists and for liver surgeons, whereas specialists' or colleagues' opinions were the major sources of information for primary care physicians. After the introduction of the JHCC guidelines, only 19–21% of hepatologists or liver surgeons changed their practice pattern (fig 2B); 50–52% did not change their practice pattern, and were convinced that their choice of treatment was similar to the recommendations in the guidelines. In total, 43% of primary care physicians changed their practice pattern as per the recommendations in the guidelines, or by paying more attention to patients' preferences.