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Author's reply

The effects of OipA on proinflammatory signalling, especially its ability to induce interleukin 8 (IL-8) in gastric epithelial cells, are controversial. Dossumbekova *et al* reported that the isogenic oipA knockout (Δ oipA) strain could induce IL-8 from KATO-III gastric epithelial cells, which is similar to its parental strain. In contrast, our previous studies showed that Δ oipA strains induced less IL-8 than their parental strains.^{1–3}

We have hypothesised that the ability to induce IL-8 by Δ oipA strains is strain dependent. There are many previous reports that CagA itself cannot induce IL-8; however, a recent report showed that CagA can induce IL-8 in a strain dependent manner.⁴

In our previous study, we constructed Δ oipA strains from 13 parental strains with a functional oipA gene and the cag pathogenicity island. Compared with their parental strains, all mutants induced intermediate amounts of IL-8 from three gastric epithelial cells.¹ Subsequently, we constructed additional Δ oipA strains from several parental strains, and discovered that some Δ oipA strains had the ability to induce levels of IL-8 similar to their parental strains (for example, multiple passaged 26695 strain). Originally, Δ oipA strains from 26695 strain induced intermediate amounts of IL-8¹ whereas Δ oipA strains from the multiply passaged 26695 strain induced IL-8 levels similar to their parental strain. To confirm this possibility, we used the JK51 strain that had been passaged more than 20 times in vitro, and its Δ oipA strain. We picked up to 20 clones for the Δ oipA strain and, importantly, a low percentage (10%) of Δ oipA strains induced IL-8 similar to their parental strain. We defined these strains as Δ oipA(IL+) strains. It is quite possible that other investigators may have selected such clones in their experiments. Luciferase reporter gene and electrophoretic mobility shift assays revealed that both low IL-8 producing Δ oipA strains as well as Δ oipA(IL+) strains failed to

activate the interferon stimulated responsive element (ISRE)-like element in the IL-8 promoter, which is the important regulator of IL-8 gene transcription. This finding suggests that OipA is directly involved in activating the ISRE-like element in the IL-8 promoter. Interestingly, activation of the IL-8 specific nuclear factor κ B site by the Δ oipA(IL+) strain was actually greater than that observed with the parental strains. This finding suggests that a mechanism in the Δ oipA(IL+) strain can compensate for the absence of a pathway that uses the ISRE-like element. Overall, we feel that we can determine the cause of the discrepant relationship between OipA and IL-8 induction; however, it currently appears that features of the Δ oipA(IL+) strain may largely be laboratory curiosities.

It will be necessary to perform in vivo studies to investigate the importance of virulence factors in *Helicobacter pylori*. However, Dossumbekova *et al* reported additional controversial IL-8 expression results when studying human gastric mucosa in vivo. We previously showed that mucosal IL-8 protein levels were higher in oipA “on” cases than in oipA “off” cases.² Our results differed from those of Dossumbekova *et al* however; they used a semiquantitative reverse-transcription polymerase chain reaction. In agreement with our study,² Dossumbekova *et al* showed that expression of cagA and oipA was closely linked (83% concordance). As they examined 53 patients, only nine patients are assumed to be infected with either cagA positive/oipA “off” strains or cagA negative/oipA “on” strains. Thus it is expected that one of the groups would contain fewer than five individuals, making it difficult to evaluate the data statistically and biologically. In addition, the mucosa contains many polymerase chain reaction inhibitors which makes it difficult to evaluate results using quantitative polymerase chain reaction. As such, further studies using a larger number of samples will be necessary to confirm the in vivo importance of OipA.

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Severe self limiting sclerosing cholangitis after pancreaticoduodenectomy due to autoimmune pancreatitis

Autoimmune pancreatitis is a chronic inflammatory disease of the pancreas that often mimics pancreatic malignancy. However, laboratory, radiological, and histological findings can be quite characteristic.^{1,2} Early clinical suspicion of this diagnosis is decisive. High titres of serum gamma globulins (especially immunoglobulin G4), autoimmune antibodies, and characteristic radiological and histological features strongly support the diagnosis.^{1,2} Steroid therapy usually substantially improves clinical, laboratory, and radiological parameters. Nevertheless, in some cases, surgical resection of a pancreatic mass lesion is still necessary, mainly to exclude pancreatic cancer and to treat low bile duct strictures.¹ Sclerosing cholangitis associated with autoimmune pancreatitis is part of a systemic fibroinflammatory response and can develop before, during, and after the development of autoimmune pancreatitis.^{1,2}

A 66 year old man was admitted for abdominal pain, weight loss, and a 10 day history of jaundice. Laboratory tests on admission showed a cholestatic obstructive pattern (bilirubin 142 μ mol/l) and endocrine and exocrine pancreatic insufficiency (with normal serum amylase). Treatment with insulin and pancreatic enzymes was begun. Ultrasound, abdominal computed tomography (CT) scan, and magnetic resonance (MR) imaging showed a 4.5 cm large tumour in the pancreatic head. Endoscopic retrograde cholangiopancreatography showed severe strictures of the main pancreatic duct and the lower bile duct (fig 1A, B). As pancreatic cancer was strongly suspected, pylorus sparing pancreaticoduodenectomy was performed. Histology of the resected specimen showed a diffuse fibrosing process with dense lymphoplasmacytic infiltration, predominantly in the periductal regions (fig 2A). Interestingly, the patient's serum showed specific immunoreactivity with normal pancreatic and biliary tissue (fig 2B, C) and autoimmune pancreatitis was diagnosed.

The patient was discharged 12 days post-operatively in good health. However, he was readmitted six weeks later for progressive jaundice. Laboratory analyses again showed an obstructive cholestatic pattern (bilirubin 184 μ mol/l) and increased serum titres of antinuclear and antilactoferrin antibodies; however, immunoglobulin G4 serum levels were normal. Abdominal CT scan and MR imaging showed extra- and intrahepatic bile duct strictures with strong periductular inflammation. Percutaneous transhepatic cholangiography was performed and the dilated bile ducts were drained (fig 1C). Thereafter, jaundice improved rapidly without steroid therapy and four weeks later cholangiography showed complete disappearance of the bile duct strictures, allowing for removal of the biliary drainage. Liver enzymes normalised and the patient became asymptomatic. Therapy for endocrine and exocrine pancreatic insufficiency was

Figure 1 (A, B) Preoperative endoscopic retrograde cholangiopancreatography showing an irregular stricture (arrow) of the pancreatic duct in the pancreatic head (A) and intrapancreatic biliary stenosis (arrow) with prestenotic dilatation of the intra- and extrahepatic bile ducts (B). (C) Postoperative right-sided percutaneous cholangiography showing a narrow common bile duct and multiple filiform strictures (arrow) of the bile ducts at the hepatic division with dilatation of the peripheral bile ducts.

continued. The patient remained in good health with normal liver values at regular follow up visits for three years.

In our exceptional case, postsurgical severe sclerosing cholangitis developed after pylorus sparing pancreaticoduodenectomy. In contrast

with other similar case reports in which steroids were used,³ complete remission of sclerosing cholangitis occurred in our patient without steroid therapy. This self limiting postoperative course is remarkable, suggesting that steroid therapy is not always necessary in this situation. Interestingly, immunoglobulin G of the patient's serum reacted both with the pancreas and biliary epithelia,⁴ supporting the diagnosis of autoimmune pancreatitis with associated sclerosing cholangitis. The pathogenetic role of this immunohistochemical finding needs to be clarified. In summary, it is important to recognise autoimmune pancreatitis and associated sclerosing cholangitis, which can suddenly occur after pancreatic resection.

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Figure 2 (A) The patient's pancreas, showing a pancreatic duct surrounded by a dense lymphoplasmacytic infiltrate. (B, C) Immunoglobulin G of the patient's serum bound to normal islets of Langerhans (*), and normal epithelia of the pancreatic ducts (arrow) and gall bladder (arrow in (C)). Bar 100 µm.

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Disappointing results of combination therapy for HCV?

Hepatitis C virus (HCV) infection is a common cause of liver disease in the UK. HCV can cause liver failure and liver cancer, and is a frequent indication for liver transplantation. HCV infection can be cured by antiviral therapy. Standard therapy includes the combination of pegylated interferon and ribavirin (PEG-IFN/RIBA) for 24 or 48 weeks, according to HCV genotype.^{1–3} A sustained virological response (SVR), defined as undetectable serum HCV RNA six months after cessation of therapy, indicates successful treatment, almost certainly cure. Published registration trials reported encouraging SVR rates of 42–52% for genotype 1 and 77–88% for genotypes 2/3.^{1–3}

However, analysis of the combined experience of six European and US centres reported significantly worse results.⁴ In that report, the response rate to treatment of genotype 1 infection with pegylated IFN alpha 2a and ribavirin was only 36%. Also, a large US based prospective randomised study reported response rates of 29–34%, depending on the dose of ribavirin used.⁵ In contrast, a Canadian study that prospectively tracked patients receiving HCV treatment reported SVR rates of 47.1% for patients with genotype 1 infection.⁶ Pretreatment counselling requires discussion with the patient of the likely response to treatment. Most physicians probably quote to their patients the success rates from the registration studies. It is important to be able to discuss the chance of cure as it stands before embarking on treatment, and also the chance of cure if the patient is able to tolerate and complete the proposed course of treatment.

We undertook a casenote and database review of consecutive patients at our centre treated with PEG-IFN/RIBA therapy between 2000 and 2005. We report an intention to treat (ITT) analysis of the results of treatment for this cohort. We also examined baseline clinical and laboratory characteristics of our treated cohort to identify those patients who would have been eligible for treatment according to the inclusion and exclusion criteria for one of those studies.¹ In practice, these criteria identify patients with more advanced liver disease, a difficult to treat (DTT) population. The results of treatment for the proportion of our cohort that would have been suitable for treatment in that registration study were examined. Finally, we examined the incidence and reasons for treatment intolerance or non-compliance.

A total of 243 patients were treated and had six months of follow up; 70% of patients were male and median age was 44 years (range 17–68). The genotype distribution was genotype 1–38%, genotype 2–10%, and genotype 3–49%.