measurements with biomarkers may increase the diagnostic accuracy of both tests.^{7,8}

In conclusion, repeated stiffness assessment appears to be a good and safe alternative method of indicating antiviral combination therapy in PN-ALT patients reluctant to undergo liver biopsy.

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Supported by grant ISC III 03/02.

Conflict of interest: None declared.

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Fatal aseptic meningoencephalitis following infliximab treatment for inflammatory bowel disease

Tumour necrosis factor α (TNF- α) plays a pivotal role in the pathogenesis of Crohn's disease. Infliximab, a chimeric monoclonal antibody against TNF- α , has been shown to be highly effective in the treatment of Crohn's disease.¹ However, treatment with infliximab may give rise to serious adverse events, including autoimmune disorders.² We report a case of fatal aseptic meningitis associated with infliximab therapy.

A 53 year old Caucasian man was admitted to a regional hospital with progressive bloody diarrhoea. His medical history revealed a myocardial infarction in 1993. Endoscopy and histology established a diagnosis inflammatory bowel disease (IBD) but could not distinguish between ulcerative colitis and Crohn's disease. Because his symptoms did not improve following steroid and azathioprine treatment, infliximab therapy was initiated. Six days after the initial infliximab

infusion, temporary numbness of the right arm and the right perioral area developed, followed four days later by dysarthria and left sided weakness and sensory loss. Cerebral computed tomography imaging revealed no abnormalities. All neurological symptoms resolved spontaneously within a few days.

Because of ongoing complaints consistent with luminal disease activity, a second dose of infliximab was administered two weeks after the initial dose. Complaints related to IBD gradually diminished with this regimen. After three days, however, neurological symptoms recurred. Over the course of three weeks he developed a dysarthria, left sided hemianopia, and motor aphasia. His level of consciousness decreased gradually and generalised seizures occurred. At that time, cerebrospinal fluid analysis showed a mild pleiocytosis and meningoencephalitis was suspected. He was treated with acyclovir, but analysis of blood and cerebrospinal fluid cultures as well as polymerase chain reaction (PCR) did not reveal any infectious agent.

Seven months after the onset of gastrointestinal symptoms and 3.5 months after the first dose of infliximab, the patient was referred to our hospital. He had a normal blood pressure and was afebrile. On neurological examination he had reduced consciousness (Glasgow coma scale E2M4V2), no meningism, intact light and corneal reflexes, and a right hemiparesis. Magnetic resonance imaging of the brain revealed bilateral hyperintense cortical and subcortical lesions on T2 weighted imaging that showed enhancement with gadolinium. There were no signs of cerebral sinus thrombosis. Cerebral angiography showed focal narrowing of branches of the middle cerebral arteries, suggestive of vasculitis. Because repeated cultures and PCR of cerebral tissue (obtained on biopsy), blood, and cerebrospinal fluid remained negative (including for JC and BK virus) it was decided to start treatment with cyclophosphamide and prednisone for a suspected cerebral vasculitis. Despite this treatment, the patient's condition deteriorated gradually and he died approximately one month later. An autopsy was performed.

Histopathological examination revealed necrosis of the cerebral cortex (fig 1) and mononuclear infiltration with macrophages and giant cells. As no causative infectious agent or evidence for cerebral vasculitis was found, the diagnosis aseptic meningoencephalitis was made.

Neurological complications related to infliximab are uncommon.² It has been suggested that treatment with infliximab may give rise to inflammatory demyelinating

Figure 1 Cross section of the cerebral frontal cortex with multiple yellowish lesions (arrowheads) in the grey matter compatible with inflammatory infiltrate and tissue necrosis.

disease of the central nervous system.^{3,4} Aseptic meningitis related to infliximab, as in our patient, has been reported twice,^{5,6} but this is the first case of meningoencephalitis with a fatal outcome. In our patient, involvement of a broad range of infectious agents, including tuberculosis, was excluded.

The pathogenesis of infliximab related aseptic meningitis is unknown, and in the first case reported⁵ generation of antibodies to neurones or to infliximab was excluded. Presumably, the inability of infliximab to pass the blood-brain barrier results in a failure to downregulate proinflammatory pathways in the brain while effectively blocking peripheral TNF- α . Based on the present case and the currently available literature, we conclude that infliximab therapy should be withdrawn permanently when (even transient) neurological symptoms occur.

Acknowledgements

We thank RHWMDerksen, MD PhD, Department of Rheumatology and Immunology, UMC Utrecht, for critically reviewing our manuscript.

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doi: 10.1136/gut.2006.093294

Conflict of interest: None declared.

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Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts

Fat maldigestion with steatorrhoea is the main problem in the management of exocrine pancreatic insufficiency (EPI).¹ When

uncoated pancreatic enzyme extracts are used for therapy, inhibition of gastric acid secretion is frequently needed to avoid acid mediated lipase inactivation.³⁻⁴ Modern pancreatic enzyme preparations in the form of enteric coated mini-microspheres were developed to avoid this problem but fat maldigestion still persists in a relevant proportion of patients with this therapy. Patients with EPI frequently have low pancreatic bicarbonate secretion which may become insufficient to neutralise the acidity of the chyme emptied from the stomach.⁵ Bile acids precipitate at acidic pH, and lipase is only released from coated spheres once the pH is higher than 5.0, which occurs in distal segments of the gut in some EPI patients.^{6,7}

We hypothesise that potent inhibition of gastric acid secretion, by avoiding bile acid precipitation and allowing lipase release within the proximal gut, may improve the therapeutic efficacy of enteric coated pancreatic enzymes for EPI. To test this hypothesis, a prospective, consecutive, open, comparative study was carried out.

According to previous sample size calculation, 21 consecutive patients (age range 36–76 years, 16 males) newly diagnosed with fat maldigestion secondary to severe alcohol related chronic pancreatitis, were included. Severe chronic pancreatitis was confirmed by magnetic resonance pancreatography and endoscopic ultrasound. All patients had steatorrhoea with a daily fat excretion of 19.2 (10.3) g.

Patients were treated with oral pancreatic enzyme supplements in the form of capsules containing enteric coated mini-microspheres (Creon 10 000; Solvay Pharmaceuticals, Hannover, Germany) for three months. Four capsules were administered together with each of the three main daily meals (40 000 Eur Ph U lipase per meal), according to previously described protocols.⁸ Esomeprazole 40 mg (Nexium; AstraZeneca, Sweden) was then added as a single daily dose before breakfast for a further 14 days. The study was conducted in accordance with the current guidelines of good clinical practice.

Fat digestion was evaluated on the day before starting pancreatic enzyme therapy (basal), on the last day of the three month period of pancreatic enzyme monotherapy, and on the last day of the 14 day period of combined enzyme-proton pump inhibitor (PPI) therapy by means of a previously optimised, standardised, and validated ¹³C-mixed triglyceride (¹³C-MTG) breath test.⁸⁻¹⁰ Except for the basal test, four capsules of pancreatic enzymes were taken together with the test meal. In addition, esomeprazole 40 mg was given orally 30 minutes before the test meal on the last study day. Breath samples were collected at 15 minute intervals for six hours and the global cumulative recovery rate of ¹³CO₂ (¹³CO₂-CRR) was considered the result of the test. Based on previous studies, a ¹³CO₂-CRR higher than 58% was considered normal.^{8,9}

Basal ¹³CO₂-CRR was 22.6% (95% confidence interval (CI) 0–55.5%). Therapy with oral pancreatic enzymes increased ¹³CO₂-CRR to 61.0% (95% CI 37.9–100%) ($p < 0.001$ compared with basal). Addition of esomeprazole 40 mg daily to pancreatic enzyme substitution therapy further increased ¹³CO₂-CRR to 69.4% (95% CI 47.4–100%) (NS compared with enzyme monotherapy) (fig 1).

In 57% of patients, fat digestion normalised (normal ¹³C-MTG breath test result) with pancreatic enzyme substitution therapy. In this group of patients, association of esome-

Figure 1 Results of the ¹³C mixed triglyceride breath test before (basal) and during therapy with exogenous pancreatic enzymes alone and associated with esomeprazole (PPI). The lower limit of normal of the test is shown as a broken horizontal line. Individual data for patients with an adequate response to enzyme monotherapy and those with an incomplete response to this therapy are shown. Bars represent 95% confidence interval.

prazole did not further improve fat digestion (fig 1). In the 43% of patients with persisting fat maldigestion despite pancreatic enzyme therapy, addition of esomeprazole led to an absolute improvement in fat digestion of 14.3% (95% CI 3.4–47.6%) (fig 1); 67% (29% of total) normalised fat digestion. Fat maldigestion persisted in 14% of patients despite combined therapy with esomeprazole and pancreatic enzyme supplements.

The present study demonstrates the existence of two different populations of patients with EPI regarding response to enteric coated enzyme substitution therapy. More than half of patients respond properly to this therapy and fat digestion is normalised. This may be explained by preserved pancreatic bicarbonate secretion and/or reduced gastric acid secretion. On the other hand, less than half of patients show an insufficient response to enteric coated enzyme therapy, the efficacy of which improves significantly with the addition of a potent inhibitor of gastric acid secretion. These patients most probably have normal or increased gastric acid secretion together with insufficient secretion of pancreatic bicarbonate to neutralise the acidic pH of chyme.

In conclusion, addition of a PPI leads to a significant improvement and even normalisation of fat digestion in patients with EPI and an incomplete response to enzyme substitution therapy. However, patients with an adequate response to enzyme substitution therapy do not profit from additional PPI.

Acknowledgement

This study was supported by a grant from the Health Institute Carlos III, Spanish Ministry of Health, reference No G03/156.

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doi: 10.1136/gut.2006.094912

Conflict of interest: None declared.

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