- 4 Cui KM, Li WM, Gao X, *et al.* Electro-acupuncture relieves chronic visceral hyperalgesia in rats. *Neurosci Lett* 2005;376:20-3.
- 5 Han JS. Acupuncture and endorphins. *Neurosci Lett* 2004;361:258-61.
- 6 Hui KK, Liu J, Makris N, *et al.* Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. *Hum Brain Mapp* 2000;9:13-25.
- 7 Diehl DL, Chan J, Carr I, *et al.* The role of acupuncture in the treatment of irritable bowel syndrome: a pilot study. *Hepatogastroenterology* 1997;44:1328-30.
- 8 Xing J, Larive B, Mekhail N, *et al.* Transcutaneous electrical acupoint stimulation can reduce visceral perception in patients with the irritable bowel syndrome: a pilot study. *Altern Ther Health Med* 2004;10:38-42.
- 9 Tillisch K, Mayer EA, Labus JS, *et al.* Sex specific alterations in autonomic function among patients with irritable bowel syndrome. *Gut* 2005;54:1396-401.
- 10 Xiao WB, Liu YL. Rectal hypersensitivity reduced by acupoint TENS in patients with diarrhea-predominant irritable bowel syndrome: a pilot study. *Dig Dis Sci* 2004;49:312-9.
- 11 Lee OY, Mayer EA, Schmulson M, *et al.* Gender-related differences in IBS symptoms. *Am J Gastroenterol* 2001;96:2184-93.
- 12 Simren M, Abrahamsson H, Svedlund J, *et al.* Quality of life in patients with irritable bowel syndrome seen in referral centers versus primary care: the impact of gender and predominant bowel pattern. *Scand J Gastroenterol* 2001;36:545-52.
- 13 Frissora CL, Koch KL. The role of gender and biological sex in irritable bowel syndrome. *Curr Gastroenterol Rep* 2005;7:257-63.
- 14 Payne S. Sex, gender, and irritable bowel syndrome: making the connections. *Gend Med* 2004;1:18-28.
- 15 Heitkemper M, Jarrett M, Bond EF, *et al.* Impact of sex and gender on irritable bowel syndrome. *Biol Res Nurs* 2003;5:56-65.
- 16 Chial HJ, Camilleri M. Gender differences in irritable bowel syndrome. *J Gend Specif Med* 2002;5:37-45.
- 17 Miwa J, Echizen H, Matsueda K, *et al.* Patients with constipation-predominant irritable bowel syndrome (IBS) may have elevated serotonin concentrations in colonic mucosa as compared with diarrhea-predominant patients and subjects with normal bowel habits. *Digestion* 2001;63:188-94.

Authors' reply

We thank Bian for his interesting study results. Bian's findings highlight the particular problems in acupuncture research. Many experimental trials have indicated the efficacy of acupuncture in the treatment of gastrointestinal tract disorders.¹⁻⁴ However, many of these trials were not always controlled by an appropriate placebo arm. Thus it is difficult to explain the positive result with specific effects.

Acupuncture and placebo-acupuncture seem to have the same positive effect in many randomised controlled trials.⁵⁻⁸ That does not mean that an acupuncture effect is always a placebo effect. In musculoskeletal diseases in particular, acupuncture seems to be stronger than placebo.⁹⁻¹² Indeed, in functional diseases, the efficacy of acupuncture seems to rely on placebo effects. In our study, we placed the "Streitberger needle"¹³ 2 cm away from the real points to avoid acupressure effects. Nevertheless, we found definite effects of placebo acupuncture.¹⁴ Thus it seems that the physiological effects play an ancillary role.

Our results are supported by another recently published trial.¹⁵ They used sham

acupuncture on non-acupuncture points and consequently it is not clear if the effects were due to unspecific effects. Sham acupuncture trials have the disadvantage that the unspecific effect could always be due to some hypothesised unspecific needling effects and hence will always lead to the questions: "Was that really a non-acupuncture point? How do you know that sham acupuncture does not have any effect?". This was excluded with our study design.

The question arises, why are placebo-acupuncture and placebo in general¹⁶ so effective in irritable bowel syndrome? The second question is whether the results of experimental trials are really due to specific effects. If they are, why is this not reflected in clinical trials? What role does cognitive processing play in this context? Further research is required to shed light on this phenomenon. It was not possible to do a subgroup analysis from a statistical point of view as we had only nine males in our study. This was the same for the clinical subgroups. However, the placebo effect was so strong that almost 526 patients would be necessary to prove an effect. Such an effect could be interesting but may not be clinically relevant.

Acknowledgements

The trial was supported financially by the German Medical Acupuncture Association (DÄGfA). The funding source had no involvement in design, performance, or analysis of the study.

A Schneider

Department of General Practice and Health Services Research, University Medical Hospital Heidelberg, Heidelberg, Germany

P Enck

Department of Psychosomatic Medicine, University Medical Hospital Tübingen, Tübingen, Germany

K Streitberger

Department of Anaesthesiology, University Hospital Heidelberg, Heidelberg, Germany

Correspondence to: Dr A Schneider, Department of General Practice and Health Services Research, University Medical Hospital Heidelberg, University of Heidelberg, Voßstrasse 2, 69120 Heidelberg, Germany; antonius.schneider@med.uni-heidelberg.de

Conflict of interest: declared (the declaration can be viewed on the Gut website at <http://www.gutjnl.com/supplemental>).

References

- 1 Cui KM, Li WM, Gao X, *et al.* Electro-acupuncture relieves chronic visceral hyperalgesia in rats. *Neurosci Lett* 2005;376:20-3.
- 2 Jin HO, Zhou L, Lee KY, *et al.* Inhibition of acid secretion by electrical acupuncture is mediated via beta-endorphin and somatostatin. *Am J Physiol* 1996;271:G524-30.
- 3 Li P, Rowshan K, Crisostomo M, *et al.* Effect of electroacupuncture on pressor reflex during gastric distension. *Am J Physiol Regul Integr Comp Physiol* 2002;283:R1335-45.
- 4 Li Y, Tougas G, Chiverton SG, *et al.* The effect of acupuncture on gastrointestinal function and disorders. *Am J Gastroenterol* 1992;87:1372-81.
- 5 Linde K, Jobst K, Panton J. Acupuncture for chronic asthma. *Cochrane Database Syst Rev*. Oxford: Update Software, 2000; issue 2, CD000008.
- 6 Linde K, Streng A, Jürgens S, *et al.* Acupuncture for patients with migraine. *JAMA* 2005;293:2118-25.
- 7 Melchart D, Streng A, Hoppe A, *et al.* Acupuncture in patients with tension-type headache: randomised controlled trial. *BMJ* 2005;331:376-82.
- 8 White AR, Rampes H, Ernst E. Acupuncture for smoking cessation. *Cochrane Database Syst Rev*. Oxford: Update Software, 2000; issue 2, CD000009.
- 9 Kleinhenz J, Streitberger K, Windeler J, *et al.* Randomised clinical trial comparing the effects of acupuncture and a newly designed placebo needle in rotator cuff tendinitis. *Pain* 1999;83:235-41.
- 10 Manheimer E, White A, Berman B, *et al.* Meta-analysis: acupuncture for low back pain. *Ann Intern Med* 2005;142:651-63.
- 11 White P, Lewith G, Prescott P, *et al.* Acupuncture versus placebo for the treatment of chronic mechanical neck pain: a randomized, controlled trial. *Ann Intern Med* 2004;141:911-19.
- 12 Witt C, Brinkhaus B, Jena S, *et al.* Acupuncture in patients with osteoarthritis of the knee: a randomised trial. *Lancet* 2005;366:136-43.
- 13 Streitberger K, Kleinhenz J. Introducing a placebo needle into acupuncture research. *Lancet* 1998;352:364-5.
- 14 Schneider A, Enck P, Streitberger K, *et al.* Acupuncture treatment in irritable bowel syndrome. *Gut*. published online first 22 September 2005; doi: 10.1136/gut.2005.074518.
- 15 Forbes A, Jackson S, Walter C, *et al.* Acupuncture for irritable bowel syndrome: a blinded placebo-controlled trial. *World J Gastroenterol* 2005;11:4040-4.
- 16 Enck P, Klosterhalfen S. The placebo response in functional bowel disorders: perspectives and putative mechanisms. *Neurogastroenterol Motil* 2005;17:325-31.

Infliximab as a treatment for systemic amyloidosis associated with Crohn's disease

Systemic AA amyloidosis is a serious and potentially fatal complication of Crohn's disease.¹ This serious complication is associated with approximately 0.9-2.5% of patients with Crohn's disease but renal failure due to renal amyloidosis is one of the most common causes of death for patients with Crohn's disease.² Although drugs such as azathioprine, colchicine, and dimethylsulphoxide are suggested to delay the progression of renal amyloidosis, the efficacy of these drugs on renal amyloidosis has not been fully elucidated.³ Infliximab is a chimeric anti-tumour necrosis factor α (TNF- α) monoclonal antibody. This drug has been proven to induce clinical response and remission in Crohn's disease patients with rapid onset of mucosal healing, and improve perianal disease, thus increasing quality of life.³ Recent studies provided evidence that infliximab also improved the extraintestinal complications of Crohn's disease, such as spondyloarthritis⁴ and psoriasis.⁵ With regard to amyloidosis, recent studies demonstrated the efficacy of infliximab on secondary amyloidosis associated with rheumatic inflammatory diseases.^{6,7} However, no clinical reports showing the therapeutic effects of infliximab on amyloidosis associated with Crohn's disease have been found. Thus, here we present, for the first time, a patient with systemic AA amyloidosis associated with Crohn's disease that significantly responded to infliximab.

A 34 year old male Crohn's disease patient was admitted to our hospital with acute

Figure 1 Serum C reactive protein (CRP) and creatinine levels of the patient after treatment with infliximab.

progression of renal dysfunction on 4 April 2004. This patient was diagnosed as having Crohn's disease with ileocolitis in 1990 based on clinical, endoscopic, and histological criteria. A small amount of proteinuria was observed in 1992, and AA type amyloid deposition was systemically detected in biopsy specimens from his colon, terminal ileum, stomach, duodenum, and kidney.² Before admission, he had been treated with elemental diet,² prednisolone, and dimethylsulphoxide. After admission, he underwent parental nutrition therapy. However, inflammatory parameters and renal function did not improve in two weeks, and we decided to use infliximab. He received an infusion of infliximab 5 mg/kg on 16 April 2004, and his renal function as well as C reactive protein dramatically improved (fig 1). Furthermore, serum amyloid protein level also decreased significantly (from 762 to 30.2 µg/ml) in 10 days. The Crohn's disease activity index (CDAI) of the patient decreased from 235.5 to 148.2 points in eight weeks.

Although the detailed mechanism is unknown, it is noteworthy that infliximab not only decreased serum amyloid protein level but also ameliorated the renal function of our patient with systemic AA amyloidosis associated with Crohn's disease. Therefore, we hope that clinical trials assessing the efficacy of infliximab in systemic amyloidosis associated with Crohn's disease will soon be conducted. There have been many patients with Crohn's disease who have suffered from severe and fatal extraintestinal complications. Infliximab may shed light on therapeutic strategies for such patients.

M Iizuka, S Konno, Y Horie, H Itou, K Shindo, S Watanabe

Department of Internal Medicine, Akita University School of Medicine, Akita, Japan

Correspondence to: Dr M Iizuka, Department of Internal Medicine, Akita University School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan; maiizuka@doc.med.akita-u.ac.jp

doi: 10.1136/gut.2005.087577

Conflict of interest: None declared.

References

- 1 Lovat LB, Madhoo S, Pepys MB, *et al*. Long-term survival in systemic amyloid A amyloidosis complicating Crohn's disease. *Gastroenterology* 1997;112:1362-5.
- 2 Horie Y, Chiba M, Miura K, *et al*. Crohn's disease associated with renal amyloidosis successfully

treated with an elemental diet. *J Gastroenterol* 1997;32:663-7.

- 3 Assche GV, Vermeire S, Rutgeerts P. Medical treatment of inflammatory bowel diseases. *Curr Opin Gastroenterol* 2005;21:443-7.
- 4 Bosch FVD, Kruithof E, Vos MD, *et al*. Crohn's disease associated with spondyloarthritis: effect of TNF-α blockade with infliximab on articular symptoms. *Lancet* 2000;356:1821-2.
- 5 Reich K, Nestle FO, Popp K, *et al*. Infliximab induction and maintenance therapy for moderate to severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367-74.
- 6 Fernández-Nebro A, Tomero E, Ortiz-Santamaría V, *et al*. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. *Am J Med* 2005;118:552-6.
- 7 Anelli MG, Torres DD, Manno C, *et al*. Improvement of renal function and disappearance of hepatitis B virus in a patient with rheumatoid arthritis and renal amyloidosis following treatment with infliximab. *Arthritis Rheum* 2005;52:2519-20.

Do baseline ALT levels predict complications of chronic hepatitis B?

We read with interest the paper by Yuen *et al* (*Gut* 2005;54:1610-4). This study included a large patient cohort with chronic hepatitis B and analysed the determinants predicting outcome. The authors concluded that low level viraemia and mildly elevated serum alanine aminotransferase (ALT) levels more commonly led to the development of complications. This conclusion however was not supported by their findings as the independent predictive factors were male sex, age, stigmata of chronic liver disease, and others, whereas serum ALT and hepatitis B virus (HBV) DNA levels were not.

It is questionable if patients with mildly elevated baseline ALT levels are truly associated with a higher risk of complications. As shown in fig 2 of their paper, the incidence of complications in the group with ALT >2-6 × upper limit of normal (ULN) and the group with ALT >6 × ULN was still significantly higher compared with the group with ALT <0.5 × ULN that had the lowest risk of complications. More importantly, serum ALT level was not an independent risk factor predicting poor outcome in the Cox multivariate analysis, suggesting lower serum ALT and/or HBV DNA levels were only associated but not independent factors. Although HBV DNA levels were tested to correlate with clinical course, it should be noted that DNA levels were measured at different time points (21 patients before, nine at, and 80 after the complication developed) and this inhomogeneous information makes the analysis of the impact of HBV DNA level on disease course less useful. Interestingly, entirely different conclusions were reported from a recent study that prospectively investigated 4841 Taiwanese men who were HBV carriers.¹ A higher baseline HBV DNA level was associated with an increased risk of the development of hepatocellular carcinoma (HCC), with a risk ratio of up to 7.3-fold.¹ In addition, a positive baseline hepatitis B e antigen consistently predicted a higher risk of HCC.^{1,2} The contrast between these studies can be best explained by the fact that patient data were collected at different time points in the natural history of chronic hepatitis B. In this regard, the necessity of serial multiple

measurements of clinical parameters in patients with chronic hepatitis B has been emphasised to reveal important information associated with long term outcome.³

Another potential flaw in this study is that the authors defined ascites, spontaneous bacterial peritonitis, and encephalopathy as complications of chronic hepatitis B. It should be noted that these are rather late complications of cirrhosis and may not be directly related to HBV infection. As the time interval from silent cirrhosis to the development of complications may vary widely and many cirrhotic patients never develop significant cirrhosis related complications in their natural history, the complication should be defined as formation of cirrhosis or HCC which is directly linked with chronic HBV infection.

In summary, end points evaluated should be cirrhosis or HCC rather than cirrhosis related complications which are not directly related to HBV infection. Lower serum ALT and HBV DNA levels more likely reflect a later stage of chronic hepatitis B and are possibly associated with increasing age of these patients who may already have severe fibrosis or subclinical cirrhosis.

T-I Huo, J-C Wu, S-D Lee

Taipei Veterans General Hospital and National Yang-Ming University, School of Medicine, Taipei, Taiwan

Correspondence to: Dr T-I Huo, Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; tihuo@vghtpe.gov.tw

Conflict of interest: None declared.

References

- 1 Yu MW, Yeh SH, Chen PJ, *et al*. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005;97:265-72.
- 2 Yang HI, Lu SN, Liaw YF, the Taiwan Community-Based Cancer Screening Project Group, *et al*. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med* 2002;347:168-74.
- 3 Chen CJ. Time-dependent events in natural history of occult hepatitis B virus infection: the importance of population-based long-term follow-up study with repeated measurements. *J Hepatol* 2005;42:438-40.

Authors' reply

We would like to thank Dr Huo *et al* for their comments. The following are point by point responses to their comments.

(1) Serum alanine aminotransferase (ALT) levels were not considered in our analysis of prognostic factors because stratification into five groups rendered it too complicated for statistical calculation by multivariate analysis. In addition, we aimed to examine independently the differences in outcome in patients with different ALT levels, as elevated ALT level is the most commonly used criterion for initiation of treatment. As for HBV DNA levels, our conclusion was that development of cirrhosis was related to prolonged low level viraemia up to the time of development of complications. Baseline HBV DNA levels would be of little help in determining whether HBV DNA levels are important. A good example is high HBV DNA levels in children; this does not mean that they are at risk of cirrhotic complications when they are young.