Non-invasive evaluation of hepatic fibrosis using magnetic resonance and ultrasound techniques

In his recent commentary, Pinzani discussed approaches to non-invasive evaluation of liver fibrosis and addressed some of the methods currently under investigation (*Gut* 2006;**55**:310–12). We agree that liver histology is a surrogate end point and Pinzani emphasised the need for longitudinal studies based on hard clinical endpoints. However, he states ''At present, CT and MR can indicate the presence of cirrhosis with high specificity but with very low sensitivity''. In reply, we wish to counter this statement and would like to present data from emerging technologies, including magnetic resonance spectroscopy (MRS), ultrashort echo time (UTE) MR imaging (MRI), and microbubble ultrasound.

We used 31P MRS in vivo to characterise hepatic fibrosis in chronic hepatitis C (CHC) infection.[1] The phosphomonoester to phosphodiester (PME/PDE) ratio provided an index of cell membrane turnover and was found to correlate closely with disease severity, assessed by liver histology (Ishak system). A PME/PDE ratio $\geqslant$0.3 provided a sensitivity and specificity of 82% and 81%, respectively, for the diagnosis of cirrhosis, comparable with many indirect serological markers. There was a monotonic increase in PME/PDE ratio with increasing disease activity and statistically significant differences between mild hepatitis, moderate/severe hepatitis, and cirrhosis.[1] We also demonstrated the potential utility of UTE MRI[2] and showed the relaxation time, T2*, was significantly different between controls and patients with cirrhosis. Functionally decompensated liver disease (Child's grade C) differed significantly from functionally compensated liver disease (Child's A/B). Significant differences in diffusion weighting MRI indices between patients with cirrhosis and normal volunteers have also been reported.[3]

Pinzani highlighted the controversy surrounding usage of Doppler ultrasonography (US) parameters. The study he cited of Doppler-US indexes, in conjunction with clinical signs and biochemical measures, should be interpreted with caution as the diagnostic accuracy of Doppler-US variables on an intention to diagnose basis was 87%, based on a protocol in which three variables were assessed in a stepwise manner.[4] However, in contrast, our analysis of Doppler-US in the assessment of CHC fibrosis demonstrated no significant difference between Doppler indexes with increasing severity of liver disease.[5]

It should be noted that US microbubble contrast agents have also been employed to evaluate liver fibrosis, through hepatic vein transit time (HVTT) measurements.[6 7] HVTT decreases with increasing severity of liver disease, due to associated circulatory changes, which include arterialisation of the hepatic sinusoidal bed, the presence of intrahepatic and intrapulmonary shunting, and the hyperdynamic circulation present in patients with cirrhosis.[6] An HVTT of less than 24 seconds was 100% sensitive and 96% specific for diagnosis of cirrhosis.[6 8] In a cohort of 85 CHC patients, HVTT demonstrated 100% sensitivity and 80% specificity for cirrhosis, and 95% sensitivity and 86% specificity for differentiation of mild hepatitis from more severe liver disease.[7] There was also a significant difference between moderate/severe hepatitis and these groups. Such a clear difference between Ishak grades of disease severity may, perhaps, inform treatment decisions.

For a non-invasive biomarker of liver disease to be employed in a clinical setting, its place in clinical practice must be appraised. In the context of CHC, a role in the decision to start antiviral therapy and in monitoring of treatment response would be important. Biomarkers may also have a role in the stratification of patients with cirrhosis according to the risk of clinical outcomes, such as variceal bleeding and the development of hepatocellular carcinoma, as has been suggested for transient elastography by Foucher and colleagues.[9] While it is ideal to find a single biomarker, a profile of tests embracing different modalities, including imaging and serological markers, is more realistic and will probably add value to clinical management algorithms.

J F L Cobbold, M Wylezinska, C Cunningham, M E Crossey, H C Thomas, I J Cox, N Patel, S D Taylor-Robinson

Division of Medicine, Faculty of Medicine, Imperial College London, London, UK

Correspondence to: J F L Cobbold, Division of Medicine, Faculty of Medicine, Imperial College London, Robert Steiner MR Unit, Hammersmith Hospital Campus, Du Cane Rd, London W12 0HS, UK; j.cobbold@imperial.ac.uk

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Author's reply

I thank Cobbold *et al* for their thoughtful and expert comments. However, these authors may have missed a key point concerning the aim of the commentary—that is, to shed some light on the current confusion and speculation in the area of so-called ''non invasive evaluation of hepatic fibrogenesis'', and particularly the use of serum ''surrogate'' markers. Accordingly, the commentary was not aimed at detailing recent progress obtained with imaging techniques or future perspectives in this area of investigation. I appreciate very much the work performed by this group of investigators, of which I was aware, and I am confident that imaging techniques will likely be the best diagnostic option for the evaluation of chronic liver disease progression in the near future. However, at present, all imaging techniques do not perform better than other non-invasive methods, at least when presented in cross sectional studies involving a very limited number of cases (for example, seven normal subjects versus 12 cirrhotic patients, as in Chappell and colleagues[1]). This is due to the complexity of the biological and anatomical changes occurring in chronic hepatic wound healing, limitations in the available technology, and an overall limited interest of radiologists in the investigation of diffuse (rather than focal) parenchymal liver pathological phenomena.

I would like to take this opportunity to encourage further efforts in this area and to provide evidence of the diagnostic efficacy of imaging methods in longitudinal studies. Finally, I agree fully with the final remarks of Cobbold *et al*—that is, evaluation of the fibrogenic progression of chronic liver disease should employ different modalities, including serum markers, imaging, and transient elastography, etc.

M Pinzani

Correspondence to: Professor M Pinzani, Department of Internal Medicine, Centre for Research, High Education and Transfer, Denothe, Università di Firenze, Firenze I-50134, Italy; m.panzani@dmi.unifi.it

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Safe and effective application of anti-TNF-α in a patient infected with HIV and concomitant Crohn's disease

Mortality as a result of human immunodeficiency virus (HIV) infection has declined significantly due to application of highly active antiretroviral therapy (HAART).[1] However, an effect of this therapy is its promotion of immune reconstitution, which leaves patients more vulnerable to developing immune related illnesses, such as Crohn's disease (CD).[2 3]

CD causes an increase in tumour necrosis factor α (TNF-α) that seems to play a fundamental role in the condition. Thus anti-TNF-α therapies represent a step forward in the management of CD.[4] Elevated TNF-α levels are also observed during all stages of HIV, and consequently the use of anti-TNF-α agents has been also suggested for HIV patients.[5] To date, three controlled trials of anti-TNF-α based therapies[6–8] in HIV patients

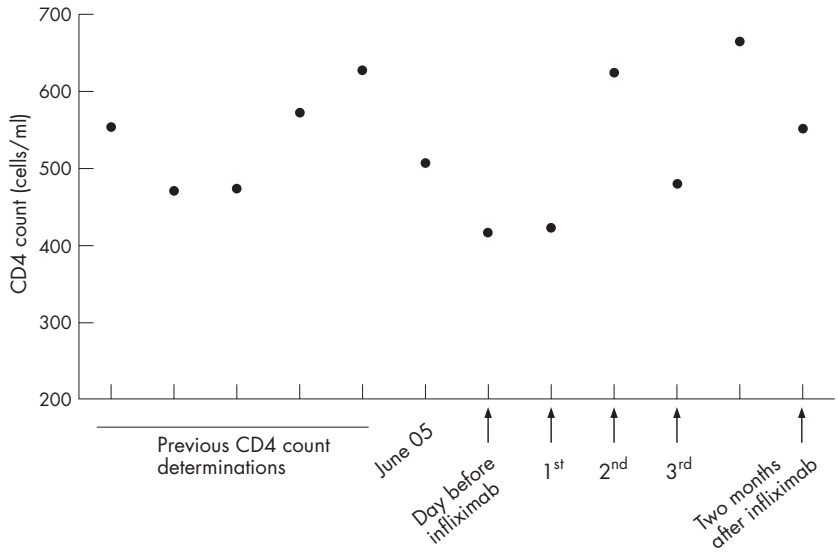

Figure 1 CD4 counts. Previous CD4 counts refer to years before and after diagnosis of Crohn's disease (CD). June 05 shows the CD4 count before the acute flare where it was decided to administer infliximab infusion. 1st, 2nd, and 3rd refer to infliximab infusions.

have been reported. Each study registered a decrease in serum TNF-α levels, and no change in the CD4 cell count or plasma HIV RNA, or any adverse side effects. However, the safety and efficacy of anti-TNF-α agents in CD in the context of chronic viral infections is unclear. This is the first report of a patient affected concomitantly by CD and HIV and treated with an anti-TNF-α agent (infliximab).

A 42 year old Caucasian woman was infected with HIV through heterosexual contact in 1997. HAART therapy had controlled the infection (CD4 counts usually >250; fig 1) and no opportunistic infections had appeared. In October 2003 she was diagnosed with inflammatory bowel disease (IBD) based on a flare up of rectal bleeding, diarrhoea, and fever. Left colonoscopy revealed multiple erosions and several deep geographic ulcerations. Histology was compatible with indeterminate colitis. Cytomegalovirus (CMV) and other viral, bacterial, and parasite infections were ruled out. At the time of IBD diagnosis, the patient's CD4 count was 555 cells/ml and her viral HIV load was <200 copies. The patient initially responded to corticosteroids.

In August 2005, the subject suffered an acute IBD flare up with severe rectal bleeding, which was medically controlled with intravenous corticosteroids and antibiotics. Colonoscopy revealed IBD activity in the sigma and throughout the colon. Additionally, two fistulae orifices were observed in the anal canal. Nuclear magnetic resonance imaging showed a 5 cm intersphincter (internal and external) fistula. This time the histology was compatible with CD. Again, CMV, other viruses, and infestation of bacteria or parasites were excluded. The last CD4 count before this episode had been 505 cells/ml (June 2005).

We decided to employ an anti-TNF-α agent (infliximab) for both inducing remission and treating the perianal disease. A mantoux test and a booster were performed, which were both negative. Infliximab was then administered according to the usual scheduled programme (at weeks 0, 2, and 6). We measured the CD4 count and viral HIV load before the first infusion of infliximab, 48 hours after each consecutive administration, and two months after the third infusion. No significant modification of the CD4 count was detected (see fig 1). Viral load never exceeded 200 copies. The patient experienced complete clinical and endoscopic remission, with closure of the fistulae.

The use of infliximab in subjects with HIV infection and CD seems to be safe and effective. The patient is now receiving maintenance therapy with infliximab. Regular CD4 counts will confirm the reliability of this therapeutic approach. However, if the CD4 count drops below 250 cell/ml, the programme would need to be re-evaluated because of the risk of opportunistic infections.

Future experience will help to clarify the long term immunological effects of anti-TNF-α therapy in such circumstances. However, the benefits obtained with infliximab in a case of severe CD in the context of a well controlled HIV infection are highly relevant, particularly as they were not accompanied by deterioration in HIV infection

B Beltrán, P Nos, G Bastida, M Iborra, M Hoyos, J Ponce
Department of Gastroenterology, Hospital Universitari de Valencia, Spain

Correspondence to: Dr B Beltrán, Servicio de Medicina Digestiva (Department of Gastroenterology), Hospital Universitari La Fe, Avda Campanar 21, 46009 Valencia, Spain; beltran_belen@yahoo.es

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Predictive value of microsatellite instability for benefit from adjuvant fluorouracil chemotherapy in colorectal cancer

We read with interest the study by Jover and colleagues (*Gut* 2006;**55**:848–55) on the predictive value of the DNA mismatch repair (MMR) or microsatellite instability (MSI) phenotype for response of colorectal cancer patients to 5-fluorouracil (5-FU) chemotherapy. We are concerned however about the conclusion reached by the authors and the accompanying commentary (*Gut* 2006;**55**:759–61) that MSI status should be considered in decisions on the use of 5-FU. While the clinical utility of MSI status for screening of hereditary non-polyposis colorectal cancer (HNPCC) is unquestioned, we are of the opinion that currently available data cannot justify exclusion of patients with MSI tumours from receiving 5-FU treatment.

The authors state that ''5-FU based chemotherapy may not be useful in stage II and III MMR deficient colorectal cancer and a revision in the management of this subgroup should be considered''. However, examination of the results shown in fig 3B and table 4 of their paper indicates a benefit from 5-FU treatment for patients with MMR deficient (MSI-H or MSI+) tumours, with survival rates of 89.5% and 82.4% for treated and non-treated patients, respectively. A similar observation was recently made by Benatti and colleagues[1] who reported a five year survival rate of 100% for stage II MSI+ patients treated with 5-FU compared with approximately 90% for those treated by surgery alone. In both studies, the authors appear to have reached the opposite conclusion to what is suggested by their own data. In the absence of appropriately powered studies, it seems quite astonishing to conclude that MSI+ patients should not be treated with adjuvant 5-FU chemotherapy, particularly for stage III cases.

The view that MSI+ tumours do not respond to 5-FU chemotherapy has also been promulgated by other workers.[2–5] In direct contrast with this view, other authors, including ourselves, have published evidence that patients with MSI+ tumours either gain