Anti-TNF-alpha therapy for orofacial granulomatosis

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I read with great interest the article by Lee and colleagues (Gut 2005; 54:1541–5) regarding the accuracy of endoscopic ultrasonography (EUS) in diagnosing ascites and predicting peritoneal metastases in patients with gastric cancer. I would like to thank the authors for quoting our study. Lee and colleagues commented that the sensitivity of detection of ascites was lower in our study and that this might be due to the use of catheter probe. I would however like to point out that such a comparison was unfair as the two studies were fundamentally different in two ways.

(1) The patient populations of the two studies were different. Our study excluded all patients with evidence of ascites on physical examination or computed tomography (CT) scan. We believe that there is no need for an additional EUS to confirm the presence of ascites in such patients. Moreover, such patients should have paracentesis for cytological examination rather than a locoregional staging investigation like EUS.

During the study period of our paper (September 1995 to January 2002), 89 patients had evidence of ascites on CT scan or physical examination. There would be no difficulty in detecting ascites in these patients by EUS. If we included these patients, the detection rate by EUS would have been 25.3% (36/142 = 25.3%). The overall incidence of ascites was 29.5% (36/120 = 29.5%). The “adjusted” sensitivity would be 84.8% (34/95/56 = 123/145), not much lower than the 87.1% reported by Lee et al.

(2) CT scan was performed for all patients in our study. Of the 89 patients who were excluded from the study, 69 had evidence of ascites on CT scan. The sensitivity of CT scan for detection of ascites was 47.6% (69/145), higher than the 16.1% sensitivity (combined US and CT scan) reported by Lee et al. We suspect the lower sensitivity may be due to the predominant use of US scan (231 patients) rather than CT scan (99 patients) in their study. A direct comparison however is not possible as the study populations of the two studies may be different.

In summary, I would like to applaud Lee et al for their systematic study. The comment that the sensitivity of detection of ascites was lower in our study was unfair.

K-M Chu

Correspondence to: Professor K-M Chu, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong, China; chukm@hku.hk

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Reference

Author’s reply

We would like to thank Dr Chu for his interest in our paper and for supplementing some of the data missing in his previous publication. We agree that both studies had fundamental difference in study design and we would like to point out the major difference for discussion.

One of the major differences lies in the definition of presence of ascites. Chu et al used positive laparoscopic detection of ascites as the gold standard when comparing with their endoscopic ultrasonography (EUS) findings. However, in our study, we combined all investigation results (ultrasound (US), computed tomography (CT), EUS, and operation) to determine the status of ascites. We believe that a small amount of fluid, such as several millilitres as detected by EUS, might not be visibly appreciated during operation.

Another major difference is the type of EUS used in the two studies. We used an echoendoscope (7.5–12 MHz) with a higher penetration depth, which allowed scanning through thick tumours. In contrast, Chu et al used a miniprobe (20 MHz) in their study, which actually had a limited depth of penetration. This may explain why the overall incidence of ascites was higher in our study (37.2%) compared with Chu’s series (29.5%), the supplemented data combining CT, physical examination, and operative findings. In our study, EUS was more sensitive (87.1%) than the operative findings (40.9%) in detecting ascites. Therefore, we do not agree with Chu’s conclusion that “laparoscopy and laparotomy remain the reference standard for the detection of ascites” as “ascites was missed by EUS in nearly 40% of patients”.

We suspect if an echoendoscope was used in Chu’s study, the sensitivity of EUS would have increased and CT decreased, and the projected results would then have come close to ours.

In fact, CT scan is not our routine in the preoperative assessment of patients with gastric cancer, especially in those early gastric cancers, or if EUS showed no local invasion. There is no evidence in the literature showing that CT scan is better than US in the detection of ascites. CT scan could not be used as the gold standard as, according to Chu’s data, CT scan missed 20 patients with ascites which was indeed detectable on physical examination.

We are however agreed on the same conclusion that “EUS is useful for the detection of ascites in patients with gastric carcinoma” and “The presence of ascites was significantly associated with peritoneal seeding”.

Y T Lee, E K W Ng

Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong

Correspondence to: Dr Y T Lee, Institute of Digestive Disease, Chinese University of Hong Kong, Shatin NT, Hong Kong; leeytong@cuhk.edu.hk

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Reference

Anti-TNF-α therapy for orofacial granulomatosis: proceed with caution

A 56 year old female patient was reviewed at the gastrointestinal clinic. She had, since the age of 15 years, been affected by troublesome orofacial granulomatosis (OGF) manifest as lower lip swelling together with a midline fissure. In the past she had received numerous therapies, including intralesional and systemic corticosteroid (short term benefit only), cinnamon and a benzoate free diet (lack of compliance), azathioprine (intolerance), and topical tacrolimus (ineffective).

In 2001, due to increasing distress about her appearance compounded by her forthcoming wedding, we decided to treat her with an infliximab infusion at 5 mg/kg. Within seven days there was a noticeable improvement, followed by complete healing of her labial fissure six weeks later, just prior to her wedding. Two weeks after this she found out she was pregnant. She subsequently gave birth to a healthy baby boy but failed to attend the clinic and was lost to follow up for four years.

On re-referral to the clinic in 2005, she was in the midst of a course of oral prednisolone (prescribed by her general practitioner) as her OGF had once again become problematic. In view of her excellent previous response to anti-tumour necrosis factor α (TNF-α) therapy coupled with the significant risks of an infusion reaction if rechallenged with infliximab (long drug “holiday” with no concomitant immunosuppression), we elected to treat her with subcutaneous adalimumab, 80 mg initially and then 40 mg fortnightly. After five weeks of treatment there was both a subjective and objective improvement, with partial healing of the midline fissure (figs 1, 2). At eight weeks the patient noted some left sided facial pain and swelling just below the corner of her mouth. She attended her dentist who excluded any peridontal sepsis. Three days later she was admitted to our unit with fever sweats and worsening facial pain and swelling (fig 3). Clinically she had a perioral cellulitis with bilateral perioral swelling and erythema, together with pyrexia and raised inflammatory indices. She received a pre-adalimumab treatment with swollen lower lip with deep midline fissure.

Figure 1 Pre-adalimumab treatment; swollen lower lip with deep midline fissure.

Figure 2 At five weeks, after three adalimumab injections; marked improvement in midline fissure.
intraoral benzylpenicillin and flucloxacillin to which there was minimal response but there was a rapid resolution of the cellulitis with intraoral piperacillin. Her blood cultures were negative. Adalimumab therapy was terminated immediately.

OGF is a chronic inflammatory disorder of the orofacial tissues characterised by non-casting granulomas on biopsy. Numerous Crohn’s therapies have been used to treat this condition, although due to the rarity of OGF, none has been subjected to randomised controlled trials. Thus physicians have to base their treatment decisions on small case series. Anti-TNF-α therapy has been used to treat OGF, with success reported with both thalidomide and infliximab. Adalimumab is a recently developed fully human IgG1 monoclonal antibody to TNF-α and preliminary data have shown this drug to have similar efficacy to infliximab in those Crohn’s patients intolerant to or in whom response has become attenuated with infliximab. It has become commonplace for gastroenterologists to actively exclude sepsis when considering infliximab therapy for inflammatory bowel disease, as will be the case for adalimumab if and when it is fully licensed. This is clearly difficult in OGF, a disease characterised by facial pain, swelling, erythema, and mucosal breaks. In addition, the oropharyngeal mucosa, the presumed portal of bacterial entry in this case, is colonised by a wide variety of organisms in health, thus swabbing this region prior to anti-TNF therapy will almost certainly give positive results, but is unlikely to assist in the decision to give or withhold therapy. Furthermore, patients will almost certainly learn to self-administer this medication and without proper warnings it is conceivable that patients could continue to take this medicine in the context of worsening sepsis. This case highlights that while anti-TNF-α therapy may have a therapeutic role in OGF, patients intolerant to or withholding from the study because of adverse events. We would like to comment on the side effects of AZA, which we observed in a double blind, double dummy, randomised, prospective, multicentre study on the efficacy and safety of AZA and placebo for prevention of postoperative relapse of Crohn’s disease.

Seventy nine patients (AZA, 42; 5-ASA, 37) were randomised within two weeks after surgery. TPMT genotyping was performed at baseline in order to exclude subjects with homozygous TPMT deficiency. However, the study was stopped prematurely because an interim analysis revealed that the hypothesis in Crohn’s disease. In summary, we could not provide evidence for the superiority of AZA over 5-ASA in our prospective clinical trial. In contrast with the trials described above, we observed a higher rate of adverse drug reactions leading to withdrawal from the study in the AZA group. Placebo controlled trials are needed urgently to address the question of best postoperative immunosuppressive management. However, our results may indicate the difficulties that may arise in future trials for reaching an adequate statistical power to provide a valid answer to this question.

H Herforth
Department of Internal Medicine, University of Regensburg, Regensburg, Germany

C Tjaden
Department of Surgery, University of Heidelberg, Heidelberg, Germany

M Lukas
IV Interni Klinika, Charles University, Praha, Czech Republic

F Obermeier
Department of Internal Medicine, University of Regensburg, Regensburg, Germany

K Dilger, R Müller
Dr Falk Pharma GmbH, Freiburg, Germany

J Schömmerich
Department of Internal Medicine, University of Regensburg, Regensburg, Germany

A Z-T1 Study Group
Correspondence to: Professor H Herforth, Division of Gastroenterology and Hepatology, CB 2800 Bioinformatics Bldg, University of North Carolina, Chapel Hill, 27599 North Carolina, USA; hherf@med.unc.edu

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