Anti-TNF-alpha therapy for orofacial granulomatosis

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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 (29.9%), the supplemented data combination of CT, physical examination, and operative finding. 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”.

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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
intraarticular bupivacaine and penicillamine to which there was minimal response but there was a rapid resolution of the cellulitis with intraarticular piperacillin. Her blood cultures were negative. Adalimumab therapy was terminated immediately.

OFG is a chronic inflammatory disorder of the orofacial tissues characterised by non-casating granulomas on biopsy. Numerous Crohn’s therapies have been used to treat this condition, although due to the relative rarity of OFG, 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 OFG, 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 OFG, 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 OFG, extreme caution and close monitoring must be undertaken in those patients who receive it.

**Adverse events in clinical trials with azathioprine and mesalazine for prevention of postoperative recurrence of Crohn’s disease**

We read with great interest the study by Ardizzzone and colleagues (Gut 2006;55:47–53) and the excellent review of Sands (Gut 2006;55:437–41) commenting on the efficacy and side effects of azathioprine (AZA) in the therapy of ulcerative colitis. Ardizzzone et al observed in their investigator blinded study, which included patients with steroid dependent ulcerative colitis, more mild to moderate adverse events in azathioprine than in mesalazine (5-ASA) treated patients (26% vs 6%; p = 0.046). However, only 36 patients on AZA were withdrawn 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, prospectively multicentre study on the efficacy and safety of AZA (2.0–2.5 mg/kg/day) and 5-ASA (4 g/day) for prevention of postoperative endoscopic recurrence in 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 of superiority of AZA versus 5-ASA could not be tested with the planned sample size. In 37 patients (AZA, 18; 5-ASA, 19) who completed the study according to the protocol (treatment for one year), the primary study end point (treatment failure: severe endoscopic relapse, withdrawal due to clinical relapse or to adverse drug reaction) was evaluated. Treatment failure was found to be equally high in each group (AZA, 9 of 18; 5-ASA, 9 of 19; p = 1.00, two sided Fisher’s exact test). Six of 18 patients on AZA and two of 19 patients on 5-ASA therapy were withdrawn because of adverse drug reactions (33% vs 11%; p = 0.12, two sided Fisher’s exact test); reasons were leucopenia/anaemia (AZA, 1; 5-ASA, 1), elevated liver enzymes, arthralgia/myalgia, vomiting, abdominal pain, macroscopic fecal excretion of study medication (AZA, 1 each), and pancreatitis (5-ASA, 1). Clinical or severe endoscopic relapse was observed in three of 18 patients on AZA therapy and in seven of 19 patients on 5-ASA therapy (17% vs 37%; p = 0.27, two sided Fisher’s exact test). Considering all 79 patients, adverse events were reported in approximately 70% of patients in each group (AZA, 29 of 42; 5-ASA, 26 of 37). Furthermore, in three of 42 “non-completers” an intolerable adverse event led to withdrawal (AZA, ileus; 5-ASA, cholecystitis, ankylosing spondylitis). Two further trials investigating the efficacy and side effects of AZA to prevent postoperative relapse of Crohn’s disease have been published recently.1,3

In an open label study by Ardizzzone and colleagues, adverse events were observed more frequently (39% vs 25%) in patients receiving AZA (2 mg/kg/day) than in those receiving 5-ASA (3 g/day). Fifteen of 69 patients in the AZA group and six of 69 patients in the 5-ASA group were withdrawn because of adverse events (22% vs 9%; p = 0.04); reasons for withdrawal were leukopenia/thrombocytopenia (AZA, 7; 5-ASA, 0), elevated liver enzymes (AZA, 4; 5-ASA, 1), pancreatitis (AZA, 3; 5-ASA, 0), epigastric intolerance (AZT, 1; 5-ASA, 2), and increased serum creatinine (AZT, 0; 5-ASA, 3). In a double blind trial performed by Hanauer and colleagues,4 nine of 47 (19%) patients receiving a relatively low dose of 6-mercaptopurine (6-MP 30 mg/day), six of 44 (14%) patients receiving 5-ASA (3 g/day), and four of 40 (10%) patients receiving AZA were withdrawn from the study because of adverse events, respectively; reasons for withdrawal were diarrhoea (6-MP, 2, 5-ASA, 2), leucopenia (6-MP, 2, 5-ASA, 0), alopecia (6-MP, 2, 5-ASA, 0), elevated liver enzymes (6-MP, 0; 5-ASA, 1), flatus, gastrointestinal bleeding, phlebitis (6-MP, 1 each), and allergic reaction, bowel obstruction, and arthralgia (5-ASA, 1 each).

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 observations indicate the difficulties that may arise in future trials for reaching an adequate statistical power to provide a valid answer to this question.

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