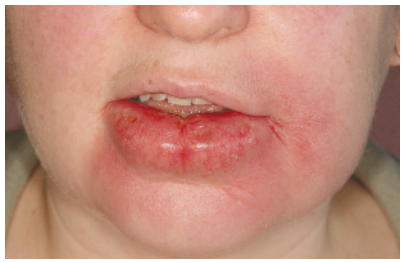

Figure 3 At eight weeks, after four adalimumab injections; although the midline fissure continued to heal, there was now a florid bilateral perioral cellulitis and the patient was systemically unwell.

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

OFG is a chronic inflammatory disorder of the orofacial tissues characterised by non-caseating granulomas on biopsy. [1] 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.[2 3] 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[4] or in whom response has become attenuated[5] 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 oropharygeal 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.

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Adverse events in clinical trials with azathioprine and mesalamine for prevention of postoperative recurrence of Crohn's disease

We read with great interest the study by Ardizzone 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. Ardizzone *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 mesalamine (5-ASA) treated patients (26% *v* 6%; p = 0.046). However, only two of 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, prospective, 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% *v* 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% *v* 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 2]

In an open label study by Ardizzone and colleagues,[1] adverse events were observed more frequently (39% *v* 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% *v* 9%; p = 0.04); reasons for withdrawal were leucopenia/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 placebo controlled trial by Hanauer and colleagues,[2] nine of 47 (19%) patients receiving a relatively low dose of 6-mercaptopurine (6-MP 50 mg/day), six of 44 (14%) patients receiving 5-ASA (3 g/day), and four of 40 (10%) patients on placebo 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.[3] 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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Impaired portal circulation resulting from L-arginine deficiency in patients with lysinuric protein intolerance

Lysinuric protein intolerance (LPI) is a rare autosomal recessive defect of the dibasic amino acid transporter, which is caused by mutations in the *SLC7A7* gene and results in L-arginine deficiency.[1] L-arginine is the only known substrate for nitric oxide (NO) production,[2] and thus the availability of L-arginine is crucial for regulation of NO production.[3] NO is an endothelium derived vascular relaxation factor that plays an important role in vascular endothelial function.[4–6] However, the effects of L-arginine deficiency on portal circulation in humans have not been studied.

Portal circulation was evaluated in seven Japanese LPI patients (six males). Seven healthy subjects (six males) without liver disease served as controls. The study was approved by the ethics committee of our university. Mean age of the LPI patients was 18.9 (10.7) years (range 5–32) and that of the controls 15.6 (7.3) years (range 7–26). Mean body weight of the patients was 38.0 (11.4) kg (range 14.6–50.3) and that of the controls 42.1 (13.6) kg (range 19.0–58.0). There was no significant difference in age or body weight between the two groups. Also, there was no significant difference in body mass index between the two groups (LPI patients 18.7 (1.9) kg/m^2 (range 16.4–21.2); controls 17.4 (2.0) kg/m^2 (range 13.2–18.9)).

Six patients were homozygotes of a common mutation in the *SLC7A7* gene (R410X) and one was a compound heterozygote with two mutations (S238F and R410X).[7 8] In all LPI patients, plasma levels of L-arginine (38.5 (8.1) nmol/ml (range 22.9–47.6)) were lower than the lower limit of the normal range (54–130 nmol/ml), and plasma levels of L-lysine and L-ornithine were also less than the normal range, except for one patient.

Portal blood flow volume (PBFV) and portal vein diameter (PVD) were determined by ultrasonography.[9 10] Serum levels of NO derivatives and PBFV before and after administration of L-arginine or an NO donor, isosorbide dinitrate (ISDN), were evaluated. Fasting serum levels of NO derivatives in patients (67.3 (8.9) μmol/l) were significantly lower than those in controls (120.3 (19.2) μmol/l) ($p<0.01$) (fig 1A). PBFV in patients (411.3 (173.1) ml/min) was significantly lower than in controls (837.5 (214.2) ml/min) ($p<0.01$) (fig 1B). PVD in patients (6.1 (1.4) mm) was also significantly lower than in controls (8.5 (1.3) mm) ($p<0.01$) (fig 1C). Serum NO levels increased from baseline in the three patients given ISDN and in the three patients given L-arginine: from 71.8 (8.9) to 103.5 (6.2) μmol/l in patients receiving ISDN, and from 64.5 (10.3) to 95. 6 (9.1) μmol/l in patients receiving L-arginine. Serum NO levels after administration of ISDN or L-arginine to patients were almost restored to those in controls. PBFV increased from baseline in the three patients given ISDN and in the three patients given L-arginine: from 301.3 (96.8) to 687.6 (111.8) ml/min in patients receiving ISDN and from 521.3 (170.9) to 1119.3 (192.6) ml/min in patients receiving L-arginine. PBFV after administration of ISDN or L-arginine was restored to close to that in controls (fig 1D, E).

It is still not known whether L-arginine administration can improve portal circulation

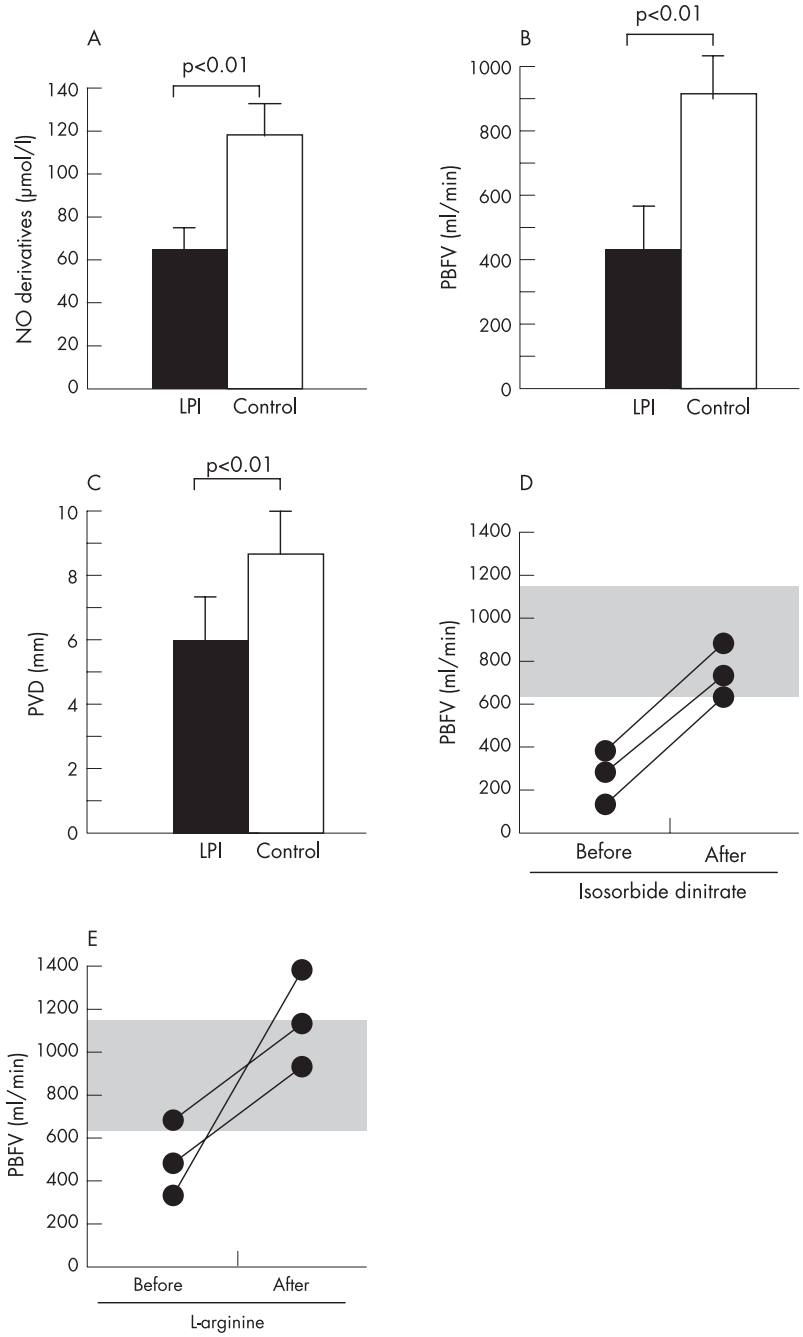

Figure 1 Serum levels of nitric oxide (NO) derivatives (nitrite and nitrate) were measured with an NO2/NO3 Assay Kit-FII (Wako Pure Chemical Industries, Osaka, Japan). Isosorbide dinitrate (5 mg/5 kg up to a maximum of 40 mg) was administered to three patients transdermally for three hours, and L-arginine hydrochloride (0.5 g/kg) was infused to three other patients intravenously for one hour. Statistical analysis was performed using the Mann-Whitney U test or Wilcoxon signed rank test. (A) Fasting concentrations of serum NO derivatives in patients with lysinuric protein intolerance (LPI) and controls. Baseline data for portal vein flow in LPI patients and controls. Baseline portal blood flow volume (PBFV) (B) and baseline portal vein diameter (PVD) (C). Changes in PBFV in LPI patients before and after isosorbide dinitrate (D) or L-arginine (E) administration. The shaded area represents the mean (SD) of the PBFV in controls. Three LPI patients were given isosorbide dinitrate (D) and three were given L-arginine (E).