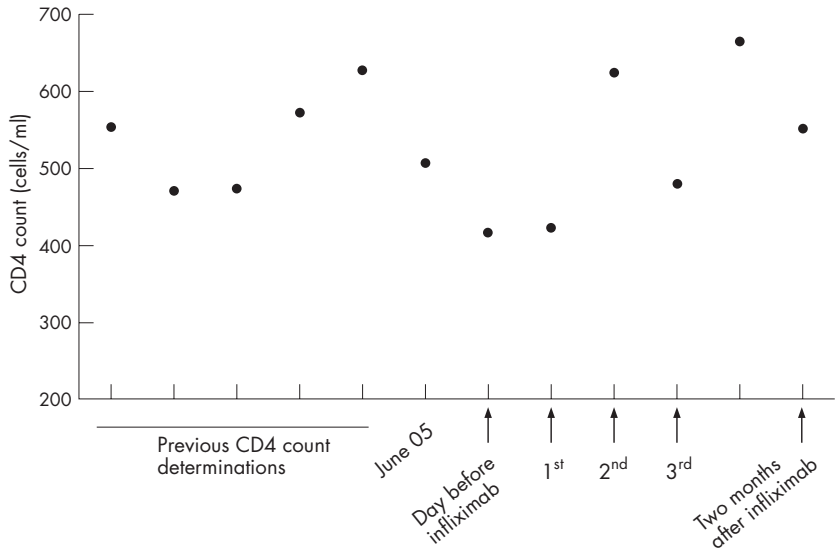

Figure 1 CD4 counts. Previous CD4 counts refer to years before and after diagnosis of Crohn's disease (CD). June 05 shows the CD4 count before the acute flare where it was decided to administer infliximab infusion. 1st, 2nd, and 3rd refer to infliximab infusions.

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

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References

1 **Palella FJ Jr**, Delaney KM, Folks TM, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV outpatient study investigators. *N Engl J Med* 1998;**338**:853–60.
2 **Bernstein BB**, Gelb A, Tabanda-Lichauco R. Crohn's ileitis in a patient with longstanding HIV infection. *Am J Gastroenterol* 1994;**89**:937–9.
3 **Moreno SD**, Solis HJA, Medina AJ, *et al.* Subclinical Crohn's disease in acquired immunodeficiency syndrome. *Rev Esp Enferm Dig* 1993;**84**:395–8.
4 **van Dullemen HM**, van Deventer SH, Hommes DW, *et al.* Treatment of Crohn's disease with anti-tumour necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 1995;**109**:129–35.
5 **Whalen C**, Horsburgh CR, Hom D, *et al.* Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med* 1995;**151**:125–35.
6 **Walker RE**, Spooner KM, Kelly G, *et al.* Inhibition of immunoreactive tumor necrosis factor-alpha by a chimeric antibody in patients infected with human immunodeficiency virus type 1. *J Infect Dis* 1996;**174**:63–8.
7 **Sha BE**, Valdez H, Gelman RS, *et al.* Effect of Etanecept (Enbrel) on interleukine-6, tumor necrosis factor-alpha and marker of immune activation in HIV-infected subjects receiving interleukin 2. *AIDS Res Hum Retroviruses*, 2002;**18**:661–5.
8 **Wallis RS**, Kyambadde P, Johnson JL, *et al.* A study of the safety, immunology, virology and microbiology of adjunctive etanercept in HIV-1-associated tuberculosis. *AIDS* 2004;**18**:257–64.

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

a survival advantage from 5-FU chemotherapy[6–8] or have extremely good survival when treated with 5-FU.[9–11] There are several possible reasons for these discordances, including the methods used to evaluate MSI status and the small sample size and short follow up time of most studies. The Jover *et al* study examined only 19 MSI+ patients with a median follow up time of just two years.

Another potentially important issue that has been widely overlooked is the fact that MSI+ tumours show different molecular profiles according to patient age and genetic background. For example, both *BRAF* mutation and tumour suppressor gene methylation are rare in MSI+ tumours from young patients and HNPCC patients, but frequent in sporadic MSI+ tumours from older patients.[12 13] This observation may not be relevant if the MSI+ phenotype itself is directly involved in the response to 5-FU. However, it becomes a critical issue if *BRAF* mutations, DNA methylation, or other related phenotypic features are more important for 5-FU response than MSI. Evidence that DNA methylation is a predictive marker for good survival benefit in 5-FU treated colorectal cancer patients has already been published.[14 15]

It is therefore reasonable to hypothesise that non-methylated MSI+ tumours from younger or HNPCC patients do not respond to 5-FU whereas the heavily methylated MSI+ tumours typically seen in older sporadic patients do respond. In support of this, the only study on the predictive value of MSI+ carried out exclusively on HNPCC patients found no survival benefit from the use of 5-FU.[16] None of the other published studies on the predictive significance of MSI has taken into account the molecular heterogeneity of this phenotype in relation to patient age and genetic background (HNPCC or sporadic), particularly with respect to DNA methylation. Until this issue is addressed, we believe it is premature and potentially irresponsible to herald the arrival of MSI+ as a predictive marker to guide the use of 5-FU in colorectal cancer.

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References

1 **Benatti P**, Gafa R, Barana D, *et al.* Microsatellite instability and colorectal cancer prognosis. *Clin Cancer Res* 2005;**11**:8332–40.
2 **Ribic CM**, Sargent DJ, Moore MJ, *et al.* Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003;**349**:247–57.
3 **Carethers JM**, Smith EJ, Behling CA, *et al.* Use of 5-fluorouracil and survival in patients with microsatellite-unstable colorectal cancer. *Gastroenterology* 2004;**126**:394–401.
4 **Lynch HT**, Boland CR, Gong G, *et al.* Phenotypic and genotypic heterogeneity in the Lynch syndrome: diagnostic, surveillance and management implications. *Eur J Hum Genet* 2006;**14**:390–402.
5 **Ward RL**, Turner J, Williams R, *et al.* Routine testing for mismatch repair deficiency in sporadic colorectal cancer is justified. *J Pathol* 2005;**207**:377–84.
6 **Elsaleh H**, Powell B, McCaul K, *et al.* P53 alteration and microsatellite instability have predictive value for survival benefit from chemotherapy in stage III colorectal carcinoma. *Clin Cancer Res* 2001;**7**:1343–9.
7 **Liang JT**, Huang KC, Lai HS, *et al.* High-frequency microsatellite instability predicts better chemosensitivity to high-dose 5-fluorouracil plus leucovorin chemotherapy for stage IV sporadic colorectal cancer after palliative bowel resection. *Int J Cancer* 2002;**101**:519–25.
8 **Brueckl WM**, Moesch C, Brabletz T, *et al.* Relationship between microsatellite instability, response and survival in palliative patients with colorectal cancer undergoing first-line chemotherapy. *Anticancer Res* 2003;**23**:1773–7.
9 **Hemminki A**, Mecklin JP, Jarvinen H, *et al.* Microsatellite instability is a favorable prognostic indicator in patients with colorectal cancer receiving chemotherapy. *Gastroenterology* 2000;**119**:921–8.
10 **Watanabe T**, Wu TT, Catalano PJ, *et al.* Molecular predictors of survival after adjuvant chemotherapy for colon cancer. *N Engl J Med* 2001;**344**:1196–206.
11 **Taal BG**, van Tinteren H, van t Veer L. Adjuvant treatment in colorectal cancer. *Br J Cancer* 2002;**86**:1525–6.
12 **Lubomierski N**, Plotz G, Wormek M, *et al.* BRAF mutations in colorectal carcinoma suggest two entities of microsatellite-unstable tumors. *Cancer* 2005;**104**:952–61.
13 **Iacopetta B**, Li W, Grieu F, *et al.* BRAF mutation and gene methylation frequencies of colorectal tumours with microsatellite instability increase markedly with patient age. *Gut* 2006;**55**:1213–14.
14 **Van Rijnsoever M**, Elsaleh H, Joseph D, *et al.* CpG island methylator phenotype is an independent predictor of survival benefit from 5-fluorouracil in stage III colorectal cancer. *Clin Cancer Res* 2003;**9**:2898–903.
15 **Nagasaka T**, Sharp GB, Notohara K, *et al.* Hypermethylation of O6-methylguanine-DNA methyltransferase promoter may predict nonrecurrence after chemotherapy in colorectal cancer cases. *Clin Cancer Res* 2003;**9**:5306–12.
16 **de Vos tot Nederveen Cappel WH**, Meulenbeld HJ, Kleibeuker JH, *et al.* Survival after adjuvant 5-FU treatment for stage III colon cancer in hereditary nonpolyposis colorectal cancer. *Int J Cancer* 2004;**109**:468–71.

Coeliac disease: between ''pizza'' and ethics

Van Heel and West (*Gut* 2006;**55**:1037–46) published a very complete and up to date review on coeliac disease (CD), dealing very clearly with all aspects of CD, from clinical problems to basic science. In the last paragraph they introduce a very ''hot topic'', future therapeutic perspectives of CD, involving immunosuppressive drugs, introduction of non-toxic cereals, development of inhibitors of the enzyme tissue transglutaminase, etc. However, the possibility of introducing drug based therapy for CD brings forth some ethical considerations.

A gluten free diet (GFD) is currently the only available therapy, and resolves the intestinal damage, normalises serological markers, and leads to disappearance of symptoms in the vast majority of cases. Compliance with GFD is not perfect because of the widespread use of gluten in Western diets, but clearly improves if patients are clinically followed up.[1] Moreover, so called ''hidden gluten'' is a problem that frightens CD patients, although not a proven danger to their prognosis, and the outcome of sporadic gluten ingestion in asymptomatic patients is unknown.

For these reasons, there is considerable interest in the development of alternative therapies.[2] However, GFD remains the only treatment that does not involve drugs, side effects, or long term risks, and has an almost 100% success rate, and so any ''better than GFD'' therapy should therefore not only allow gluten ingestion without stimulating an immunological response but also have no side effects, no long term risks, and be highly effective and cheap. This is a very difficult goal and poses ethical problems for future trials.

Three strategies can be considered for alternative therapy: (1) a vaccine-like therapy; (2) an on-demand therapy available during sporadic gluten intake; and (3) life long immune therapy allowing complete or partial gluten reintroduction. However, all of these pose problems: a ''vaccine'' must be safe and have no long term consequences on immunity, and an on-demand approach requires knowing the exact amount of gluten that can be blocked by the drug and, given that gluten induced damage is dose independent, estimating possible intake frequencies. It is also important to note that compliance with drug based therapies is not perfect and that determining drug effectiveness requires a very long follow up because it is well known that CD can relapse after many years of a gluten containing diet.[3]

Another problem concerns the selection of trial patients because heavily symptomatic patients may have difficulty in giving consent and asymptomatic patients could have different degrees of intestinal involvement.[1]

In general, presenting possible new therapies to patients should include a clear explanation of the pros and cons in order to allow their free and informed adherence to experimental trials.

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References

1 **Bardella MT**, Molteni N, Prampolini L, *et al.* Need for follow up in coeliac disease. *Arch Dis Child* 1994;**70**:211–13.
2 **Sollid LM**, Khosla C. Future therapeutic options for celiac disease. *Nat Clin Pract Gastroenterol Hepatol* 2005;**2**:140–7.
3 **Hogberg L**, Stenhammar L, Falth-Magnusson K, *et al.* Anti-endomysium and anti-gliadin antibodies as serological markers for a very late mucosal relapse in a coeliac girl. *Acta Paediatr* 1997;**86**:335–6.

The statistics of targets

Targets play an increasing role in medicine. Using the recent target of caecal intubation in over 90% of colonoscopies,[1] I herewith outline some statistical issues implicated. Typical trainees need three years to achieve competence. CUSUMs[2] are useful in assessing progress during the learning curve, but ''test endoscopies'' are needed to calculate and prove performance statistically more robust. But how many?

A trainee at the end of his learning curve with a true and unchanging success rate of 93%, which sample size is necessary to confidently prove competence? A small sample