

INFLAMMATORY BOWEL DISEASE

Interferon β -1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study

S Nikolaus, P Rutgeerts, R Fedorak, A H Steinhart, G E Wild, D Theuer, J Möhrle, S Schreiber

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See end of article for authors' affiliations

Correspondence to:
Dr S Schreiber, 1st
Department of Medicine,
Christian-Albrechts-University,
Schiffenhelmstrasse 12,
24105 Kiel, Germany;
s.schreiber@mucosa.de

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Background and aims: Administration of interferon (IFN)- β may represent a rational approach to the treatment of ulcerative colitis through its immunomodulatory and anti-inflammatory effects. The present study was performed to evaluate the efficacy and tolerability of IFN- β -1a.

Methods: Patients (n=18) with moderately active ulcerative colitis were randomised to receive IFN- β -1a or placebo. IFN- β -1a was started at a dose of 22 μ g three times a week subcutaneously, and the dose was increased at two week intervals to 44 μ g and then to 88 μ g if no response was observed. The maximum duration of treatment was eight weeks. End points were clinical treatment response, defined as a decrease of at least 3 points from baseline in the ulcerative colitis scoring system (UCSS) symptoms score and induction of endoscopically confirmed remission.

Results: Baseline characteristics and disease severity were similar in both groups. Data from 17 patients are included in this report (10 patients in the IFN- β -1a group and seven patients in the placebo group). Clinical response was achieved in five patients (50%) in the IFN- β -1a group and in one (14%) in the placebo group ($P=0.14$). Remission was achieved in three patients in the IFN- β -1a group and in none in the placebo group ($p=0.02$). Most adverse reactions associated with IFN- β -1a were influenza-like symptoms or injection site reactions, and were mild or moderate in severity.

Conclusions: IFN- β -1a may represent a promising novel treatment approach in ulcerative colitis.

Although the aetiology of ulcerative colitis has not been fully elucidated, immunological factors are believed to play an important role. Plasma and tissue concentrations of proinflammatory cytokines, including interferon (IFN)- γ , interleukins (IL)-1 β , 6 and 8, and tumour necrosis factor (TNF), are increased in patients with ulcerative colitis.¹⁻⁵ Levels of these cytokines have been shown to be related to disease activity.⁶ Such findings suggest that immunomodulatory therapy might be beneficial in the treatment of ulcerative colitis. However, although there is evidence that immunosuppressive therapy with agents such as azathioprine or 6-mercaptopurine may prolong remission,⁷⁻¹⁰ anti-inflammatory treatment with aminosalicylates or corticosteroids remains the mainstay of ulcerative colitis management.¹¹

Immunomodulatory therapy with IFN- β represents a potentially useful new treatment strategy in ulcerative colitis due to the diverse effects of this cytokine on immunological and inflammatory processes. IFN- β has been shown to inhibit the production of IFN- γ and TNF,^{12,13} and to antagonise early events in the IFN- γ signalling pathway.¹⁴ In addition, IFN- β increases expression of the anti-inflammatory cytokine IL-10,¹⁵ and enhances T suppressor and natural killer cell activity.^{16,17} Antiviral effects of interferons result from induction of the enzyme 2'-5'oligoadenylate synthetase as well as protein kinase C. These two enzymes also convey antiproliferative and cell growth inhibitory activities.¹⁸ Other important effects of interferons include a protective action against bacterial and parasitic infections, which has been demonstrated in various model systems.¹⁹⁻²²

An open study with another type I interferon, IFN alpha, obtained a remission rate of 82% in patients with refractory ulcerative colitis after six months of treatment (3-9 million units/thrice weekly subcutaneously),²³ but few studies to date have examined the effect of IFN- β . One exception is a recent open pilot study in which remission was achieved in 22 of 25 patients treated three times a week with IFN- β 0.5 or 1 million

U, for a mean of one year.²⁴ The present study was performed to investigate the efficacy and tolerability of subcutaneous administration of recombinant IFN- β -1a in the treatment of moderately active ulcerative colitis.

MATERIALS AND METHODS

The trial was a randomised, double blind, intraindividual, dose escalating study performed at six centres in Belgium, Canada, and Germany. It was conducted from October 1998 to March 2000 according to the principles of Good Clinical Practice and the Declaration of Helsinki, and was approved by institutional review boards or local ethics committees at each centre. Written informed consent was obtained from all patients prior to entry into the study.

Patients

Patients were eligible for inclusion in the study if they were at least 18 years of age and had moderately active ulcerative colitis, as defined by a score of 6-10 on the ulcerative colitis scoring system (UCSS),²⁵ with a proctosigmoidoscopy score of 2. The UCSS is a combination of rating scales for stool frequency, rectal bleeding, endoscopic activity, and physician's global assessment (PGA) (each 0-3 for no activity-severe disease). The maximum total UCSS score is 12 for severe disease.²⁵ Patients were also required to have an adequate bone marrow reserve (white cell count $\geq 3.5 \times 10^9/l$, neutrophils $> 1.5 \times 10^9/l$, thrombocytes $\geq 100 \times 10^9/l$ and $\leq 800 \times 10^9/l$, and haemoglobin ≥ 9 g/dl). Female patients were required to be either postmenopausal or surgically sterile, or to be using adequate contraception.

Abbreviations: IFN, interferon; IL, interleukin; TNF, tumour necrosis factor; UCSS, ulcerative colitis scoring system; PGA, physician's global assessment.

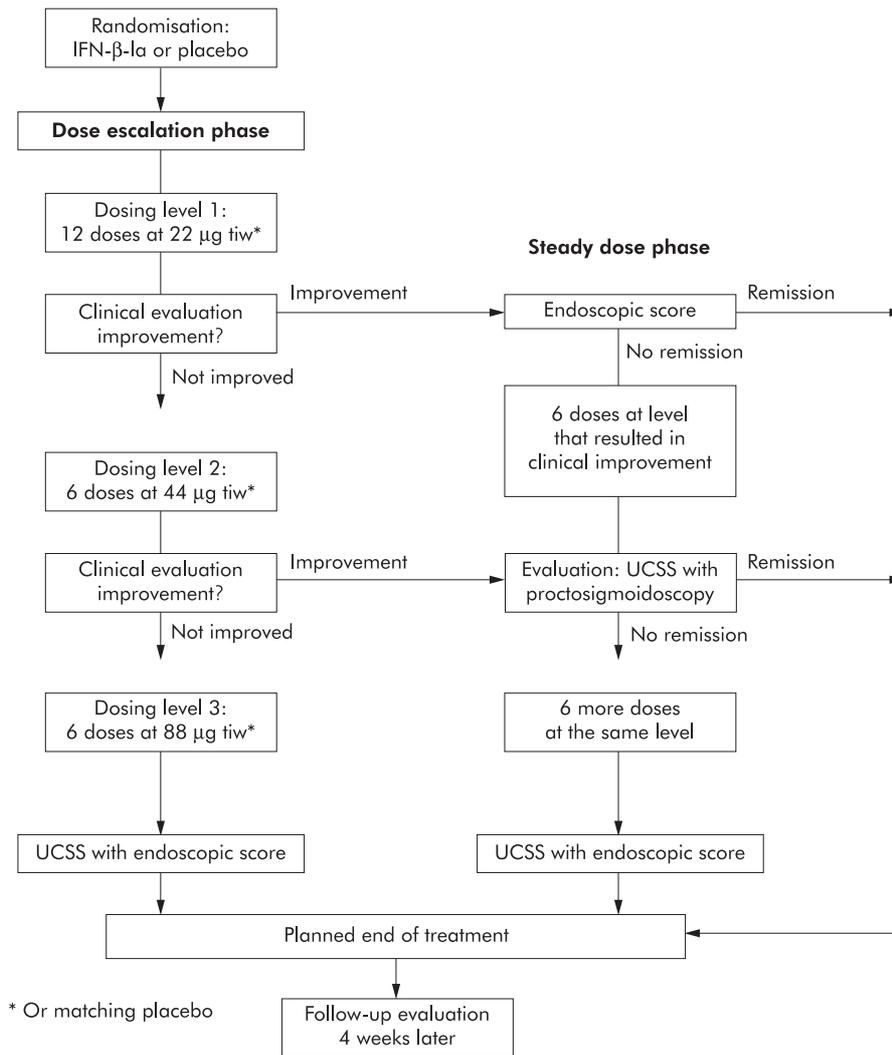


Figure 1 Study flow chart. All patients received 22 μ g of study drug three times a week (tiw) for four weeks. If patients did not show clinical improvement the dose was doubled every two weeks to up to 88 μ g tiw. "Improvement" was defined as a decrease in the clinical component of the ulcerative colitis scoring system (UCSS) score (that is, stool frequency, rectal bleeding, and physician's global assessment) by at least 1 point. If clinical symptoms improved, a sigmoidoscopy was performed. If patients were in remission by the combined UCSS score, a study end point was reached. Otherwise, the treatment dose was kept stable for two or four more weeks, respectively. The maximum duration of treatment was eight weeks and the minimum duration was four weeks. End points: remission was defined as a UCSS score of 0 for the clinical component as well as a score of 0 or 1 in the endoscopic part of the UCSS score. Clinical response was defined as a decrease of 3 or more points from baseline in the clinical components of the UCSS score. Patients discontinued due to adverse events were advanced to study end examination, including complete assessment of the UCSS.

Exclusion criteria included severe ulcerative colitis, defined as a UCSS PGA score of 3, planned or emergency surgery, previous interferon therapy, or cytokine/anticytokine therapy within the previous six months. Patients were also ineligible if they had inadequate liver or renal function, a history of cancer (other than basal cell carcinoma), active infectious disease, other serious medical conditions, or a history of alcohol or drug abuse.

Concomitant therapies

Only stable oral doses of 5-ASA were allowed (up to 3 g/day, stable for eight weeks prior to inclusion, no topical rectal treatment) as concomitant and prior therapy. The following treatments were not allowed during the study treatment and had to be discontinued before inclusion: immunosuppressives (azathioprine/6-mercaptopurine, methotrexate, cyclosporin A, all to be discontinued at least 12 weeks prior to randomisation), antibiotics (discontinued two weeks prior), antiperistaltic medication (that is, loperamide or opiates, discontinued two weeks prior), and non-steroidal anti-inflammatory drugs except paracetamol (discontinued two

weeks prior). Prestudy use of glucocorticoids was permitted only with a maximum of two single doses within the four weeks prior to randomisation. Any investigational drug or colitis relevant experimental procedure within four weeks prior to the study was forbidden.

Protocol and end points

Eligible patients were randomised by means of a computer generated list produced at the Corporate Biometrics Department of Serono International SA (Geneva, Switzerland) to receive either IFN- β -1a (Rebif; Serono) or placebo. Randomisation was stratified by centre with a block size of three (2:1 IFN- β -1a:placebo). Treatment with IFN- β -1a was started at a dose of 22 μ g three times a week subcutaneously. Improvement was defined as a decrease of 1 point in the combined score of UCSS symptoms and PGA. If no improvement was observed after six injections, the dose was increased to 44 μ g (three times a week subcutaneously), and increased further to 88 μ g (three times a week subcutaneously) if no improvement was observed after six injections with the 44 μ g dose. If improvement was observed after six injections at any dose, the

Table 1 Patient demographics and disease characteristics in the two groups

	IFN- β -1a (n=10)	Placebo (n=7)
Sex (male (n))	4	2
Age (y) (median (absolute range))	42.2 (32–68)	35 (30–63)
Duration of disease (y) (median (absolute range))	9.8 (2.6–14.2)	9.0 (2.6–40.3)
Extent of disease		
Left sided/pancolitis/backwash ileitis	5/4/1	5/2/0
Extraintestinal manifestations:		
Arthritis/arthralgia, uveitis/iritis, skin (n (%))	1 (10%)	1 (14.3%)
Chronic autoimmune liver disease (n (%))	0	0
Baseline UCSS (median)	9 (7–10)	9 (7–12)
Baseline C reactive protein (median (Q1–Q3))	4.6 (3.0–8.9)	8.2 (3.0–9.4)
Oral 5-ASA use (n (%))	5 (71%)	7 (70%)
Mean S-ASA use (g)	3.8 g/d	3.6 g/d

IFN, interferon; UCSS, ulcerative colitis scoring system; Q1, Q3, quartiles 1 and 3.

patient entered a maintenance treatment phase of 6–12 injections at that dose. If no improvement was observed after six injections at 88 μ g, or if remission occurred at any point, treatment was stopped. Details of the dose rising scheme are detailed in fig 1. The treatment period was concluded by a four week follow up phase after the last study drug administration.

Efficacy was assessed by means of the UCSS every two weeks during treatment, at the end of the treatment period, and at the end of the four week follow up period. Efficacy end points were treatment response and remission. Treatment response was defined as a decrease of at least 3 points from baseline in the UCSS symptoms score and PGA (without the proctosigmoidoscopic score) during treatment. This was a modification of the end point in the original protocol, which defined a clinical response as a decrease of at least 1 point in the UCSS symptoms score and PGA. Remission was defined as complete resolution of clinical symptoms (all clinical UCSS subscores equal to 0), with a proctosigmoidoscopy score of 0 or 1 at any time during treatment. Secondary end points included overall treatment and end point responses (defined as a decrease in UCSS symptoms score, PGA, and proctosigmoidoscopic scores of at least 1 point during or at the end of treatment), and clinical end point responses (a decrease of at least 1 point from baseline in UCSS symptoms scores and PGA, without the proctosigmoidoscopic score).

Information on adverse events was collected throughout the study. All events were graded according to the modified World Health Organization (WHO) Recommendations for Grading of Acute and Subacute Toxicities (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life threatening). Blood samples for standard haematology and clinical chemistry investigations were obtained at the start of treatment, at the end of each dose escalation period, and at the end of the follow up period. In addition, serum samples for measurement of neutralising antibodies to IFN- β -1a were obtained at the end of the follow up period. Neutralising antibodies in these samples were measured by enzyme linked immunosorbent assay.

The trial design was exploratory. Therefore, no formal sample size calculation was performed. Response/remission rates were compared between the two treatment groups by one sided Fisher's exact test.²⁶ All analyses were performed on an intention to treat basis, with missing data being replaced according to the last observation carried forward principle.

RESULTS

Study population and patient disposal

Of the 18 patients enrolled, data from 17 patients were analysed. One patient was excluded a priori (that is, before the code was broken) from the analysis because of misallocation of study drug. Seven of 17 patients were randomised to receive placebo and 10 to receive IFN- β -1a. Baseline demographics of the study population were well balanced with regard to sex,

age, and disease characteristics (table 1). The median UCSS score was 9 for patients receiving IFN- β -1a and 8.5 for patients receiving placebo. There were no significant differences between treatment groups in the use of concomitant therapies prior to initiation of the study drugs. During the course of the study, six patients (four in the IFN- β -1a group, two in the placebo group) stopped treatment because of progressive disease, and two (both in the IFN- β -1a group) for other reasons. All patients were included in the intention to treat and safety analyses.

The median duration of treatment was 35.5 days. Of the 10 patients on subcutaneous interferon- β -1a, four were escalated to the maximum dose of 88 μ g three times a week, two reached 44 μ g, and four remained on 22 μ g. The average dose for IFN- β -1a treated patients was 38.6 μ g three times a week, which represents an average daily dose of 16.7 μ g IFN- β -1a and a cumulative total dose of 627 μ g IFN- β -1a.

Efficacy

Clinical response, as defined by a decrease of at least 3 point in the UCSS, was achieved in five patients (50%) in the IFN- β -1a group and in one (15%) in the placebo group ($p=0.14$). Endoscopically confirmed remission was achieved in three patients in the IFN- β -1a treated group and in none in the placebo group ($p=0.02$).

Of the five patients in whom clinical responses were achieved during IFN- β -1a treatment, one was receiving 22 μ g three times a week, three were receiving 44 μ g, and one was receiving 88 μ g. The mean time to clinical treatment response was 28 (SD 11) days in the IFN- β -1a group and 28 days in the responding placebo patient. The mean cumulative dose of IFN- β -1a required to achieve clinical treatment response was 449 μ g.

Of the three patients in whom remission was achieved during IFN- β -1a treatment, one was receiving 44 μ g and two were receiving 88 μ g. The mean time to remission was 52 (7) days in the IFN- β -1a group. The mean cumulative dose of IFN- β -1a required for induction of remission was 1115 μ g.

UCSS symptom scores and PGAs tended to decrease to a greater extent in patients treated with IFN- β -1a than in those receiving placebo, but the differences were not statistically significant (table 2).

Safety

A total of 92 adverse events were reported, of which 57 occurred in the IFN- β -1a group and 35 in the placebo group; all patients experienced at least one adverse event. The majority of adverse events (97%) were graded as mild or moderate in severity; only one adverse event in the IFN- β -1a group (pain related to disease progression) was rated as severe.

Adverse events that were considered to be possibly or probably treatment related occurred in 15 patients (10 in the IFN- β -1a group; five in the placebo group). Most were influenza-like symptoms or injection site reactions, and most were mild

Table 2 Change in UCSS symptom scores from baseline, and response and remission rates during treatment in the two groups

	IFN- β -1a (n=10)	Placebo (n=7)	p Value
Stool frequency	-1.0 (1.2)	-0.14 (0.89)	NS
Rectal bleeding	-0.4 (1.1)	-0.42 (0.79)	NS
PGA	-0.56 (1.2)	-0.38 (0.92)	NS
Proctosigmoidoscopy score	-0.8 (1.1)	0.14 (0.69)	NS
Clinical response	5 (50%)	1 (15%)	0.14
Remission	3 (30%)	0 (0%)	0.02

IFN, interferon; UCSS, ulcerative colitis scoring system; PGA, physician's global assessment.

Table 3 Adverse events considered possibly related to treatment

	IFN- β -1a (n=10) (total)	Placebo (n=8)* (total)
At least one adverse event	10 (100%)	5 (63%)
Anaemia	2 (20%)	
Headache	2 (20%)	2 (25%)
Influenza-like symptoms	3 (30%)	2 (25%)
Injection site inflammation	5 (50%)	
Injection site pain	3 (30%)	2 (25%)
Injection site reaction	2 (20%)	
Nausea	2 (20%)	1 (13%)
Pain	2 (20%)	
Rash	2 (20%)	1 (13%)
Other (in one patient per group)	14	5
Total	37	13

*One patient who was originally assigned to the placebo group was removed prior to the analysis (for details see "study population and patient disposal"). This patient was removed from the efficacy analysis but not from analysis of side effects.
IFN, interferon.

or moderate in severity (table 3). One patient in the IFN- β -1a group withdrew from the study because of treatment related side effects (influenza-like symptoms).

Five patients in the IFN- β -1a group showed an increase in lymphocyte counts to at least WHO grade 3 before starting treatment; in three of these, lymphocyte counts had returned to values similar to before the start of study treatment by the end of the study. Three patients (two in the IFN- β -1a group, one in the placebo group) showed a 2 point increase in WHO grade for some blood chemistry variable during the study. These were graded by the investigators as without major clinical impact. No other significant laboratory abnormalities (based on WHO classifications) were observed. All patients were tested for neutralising antibodies before the study and after the end of follow up. No neutralising antibodies to IFN- β -1a were detected.

DISCUSSION

The results of this pilot study suggest that subcutaneous application of IFN- β -1a may be beneficial in the treatment of moderately severe ulcerative colitis. Patients treated with escalating doses of IFN- β -1a tended to show higher clinical response and remission rates than those receiving placebo, although the differences between the groups did not reach statistical significance. It should be noted however that this was an exploratory study that was not powered to detect significant differences in response rates. Allocation of patients showed some imbalances between the two groups (in sex distribution and disease localisation), which are to be expected in a small trial but which may also have influenced the outcome.

The mean dose of IFN- β -1a required to induce a new clinical treatment response was 449 μ g subcutaneously, given for approximately 28 days. This is equivalent to a mean dose of 35 μ g given three times a week. The mean dose required to induce remission was 1115 μ g over a mean of 52 days, which corresponds to a dose of 50 μ g given three times a week. These

may be considered the minimal effective doses for use in ulcerative colitis, and are comparable with those previously shown to be effective in patients with multiple sclerosis.²³⁻²⁹

Subcutaneous application of IFN- β -1a was well tolerated in this study. The majority of adverse events were mild or moderate, and consisted of influenza-like symptoms and injection site reactions. Thus the adverse event profile of IFN- β -1a in these patients with ulcerative colitis was comparable with that seen previously in large studies in multiple sclerosis patients.^{27, 28}

The finding that subcutaneous application of IFN- β -1a can induce clinical responses in patients with ulcerative colitis is consistent with those of open studies with IFN alpha in this condition,^{23, 30} and of a long term pilot study with IFN- β .²⁵ This raises important questions about the potential mechanisms of action of IFN- β in ulcerative colitis. In vitro studies have shown that IFN- β can induce IL-10 release from lymphocytes obtained from patients with multiple sclerosis,^{15, 25} which suggests that IFN- β could induce an anti-inflammatory response in the colonic mucosa. Furthermore, a study in patients with Crohn's disease and concomitant herpes virus infection has shown that IFN alpha can induce an antiviral reaction that was associated with reduced intestinal inflammation.³¹ At present however the clinical significance of such findings remains to be established.

In conclusion, mild to moderate uncomplicated ulcerative colitis is a condition that favours exploration of the efficacy of IFN- β -1a in this disease. However, the side effect profile of IFN- β -1a suggests that it might find its place in the therapy of more serious disease as an alternative to glucocorticoids, if effective. Further studies are warranted to confirm and extend these findings, and to define the potential benefits offered by IFN- β as an alternative to glucocorticoids.

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Authors' affiliations

S Nikolaus, S Schreiber, Christian-Albrechts University, Kiel, Germany
P Rutgeerts, KUL Gasthuisberg, Leuven, Belgium
R Fedorak, University of Alberta, Edmonton, Canada
A H Steinhart, Mount Sinai Hospital, Toronto, Canada
G E Wild, McGill University, Montreal, Canada
D Theuer, Heidelberg University, Heidelberg, Germany
J Möhrle, Serono International SA, Geneva, Switzerland

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Scintigraphic assessment of SO dysfunction

As diagnosis of sphincter of Oddi (SO) dysfunction may require perendoscopic manometric assessment of the sphincter, which is an invasive technique carrying a significant risk of pancreatitis, non-invasive scintigraphy has been proposed as an alternative diagnostic method. Craig *et al* (*Gut* 2003;52:352-7) reported their experience in assessing SO dysfunction in post-cholecystectomy patients with scintigraphy using the hepatic hilum-duodenum transit time (HHDT) of Cicala and colleagues¹ and the scoring system of Sostre and colleagues.² In the study of Craig *et al*, scintigraphic data after cholecystokinin octapeptide (CCK-OP) infusion were compared with SO basal pressure, the latter recorded at manometry in the absence of any stimulus.

Craig *et al* concluded that none of the above scintigraphic variables was sufficiently sensitive to diagnose SO dysfunction identified at SO manometry. Although it is evident that the scintigraphic method of Craig *et al* used in their study was indeed poorly sensitive, the conclusion of their study cannot be extended to interpret the validity of scintigraphy, as performed in other centres.

It is necessary to identify regions of interest (ROIs) that are repeatable. In the original description of the method it was pointed out that only HHDT performed with the correct ROIs and subtractions was repeatable, com-

pared with other scintigraphic variables related to hepatic uptake and clearance of radiolabelled bile.¹ Noticeably in the original HHDT method, ROIs were the heart, right external liver parenchyma, hepatic hilum, and duodenum, whereas in Craig's study ROIs were the right lobe of the liver and the common bile duct (CBD), which are not sufficient reference sites to construct a transit measurement from the hepatic hilum to the duodenum. In addition, an ROI placed on the CBD cannot correctly discriminate CBD activity from that of the major bile ducts at the hepatic hilum.

Furthermore, analysis of time threshold performed on visual assessment of three minute composite images implies a measurement error of several minutes. In addition, assessment of radiolabelled bile at different sites cannot be performed correctly with a visual method that is significantly delayed in comparison with assessment based on time activity curves (TAC), provided that frame timing is adequate. For example, this methodological error is clearly described and illustrated in figure 3 of the article by Cicala and colleagues,¹ with the original description of the HHDT method where the time period assessed with static images at 2.5 minutes apart was delayed by 2.5 minutes in comparison with the assessment based on the TAC constructed on 15 second frame timing. Use of a cholecystokinetic stimulus to assess HHDT is also questionable as CCK is known to affect hepatic bile secretion and SO motor activity, either accelerating the transit of bile under normal conditions or slowing it in the case of SO paradoxical response. Madacsy and colleagues,³ comparing measurement of HHDT without any stimulus and after caerulein administration, showed that the 89% sensitivity of the test without the cholecystokinetic stimulus decreased to 0% after the cholecystokinetic stimulus. In addition, it is not acceptable to derive any conclusions on test sensitivity from a comparison between a scintigraphic assessment performed after a cholecystokinetic stimulus and manometric recordings performed in the absence of a stimulus. Craig *et al*'s study refers to >9 minutes as an abnormal threshold of HHDT, as indicated in the study of Cicala and colleagues.¹ Use of a reference threshold from another centre does not apply when a different technique is used. The technique of Craig *et al* should be validated with correct

reference standards defined in a control group, which was lacking in their study.

Several studies have used similar but not comparable scintigraphic techniques to assess SO dysfunction by means of the hepatic duodenum transit time or a score (see table 1).

All but one of the studies in table 1 have compared scintigraphy with manometry and have shown a high specificity of the test and, with the exception of Craig *et al*, have also shown a satisfactory sensitivity in the absence of a cholecystokinetic stimulus. Reliability of the HHDT test is supported by the following studies:

(1) it is reproducible in asymptomatic controls (Cicala and colleagues¹) and in patients with SO dysfunction (Cicala and colleagues⁴); and

(2) it discriminates asymptomatic controls from SO dysfunction patients (Corazziari and colleagues⁵).

Finally, in common with the validation process used for SO manometry, validity of a scintigraphic diagnostic test for SO dysfunction is proved if the tested variable (that is, HHDT or a score) normalises after, and predicts the outcome of, treatment of the abnormality that the test is designed to detect. Both of the above demonstrations for HHDT have been presented in the study by Cicala and colleagues.⁴

We are aware that information concerning reliability and outcome prediction of HHDT derive from a single group of investigators and confirmation studies with comparable techniques performed in other centres would be welcome. However, we would caution against making comparisons and drawing conclusions with techniques that are not comparable and have not been submitted to proper validation studies to ascertain their reliability.

E Corazziari, M Cicala, F Scopinaro, O Schillaci, I F Habib, N Pallotta
Università La Sapienza, Rome, Italy

Correspondence to: Dr E Corazziari, Dipartimento di Scienze Cliniche Policlinico, Umberto I V. le del Policlinico, Italy; enrico.corazziari@uniroma1.it

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Table 1 Scintigraphic tests for sphincter of Oddi (SO) dysfunction

Reference No	Stimulus	Frame/t	Analysis	Reproducibility (controls/pts)	Versus manometry (no stimulus)		Versus sphincterotomy (sensitivity)
					Sensitivity (%)	Specificity (%)	
Scintigraphic HHDT (choledochoscintigraphy)							
1, 4, 5	None	15 s	TAC	Rel/rel	83	100	93
3	None	1 min	TAC	Not assessed	89	100	Not assessed
3	CRL	1 min	TAC	Not assessed	0	100	Not assessed
6	None	1 min	Static	Not assessed	Not assessed		Not assessed
Craig <i>et al</i>	CCK-OP	1 min	Static	Not assessed	13	95	Not assessed
Scintigraphic score							
2	CCK-OP	1 min	Static +TAC	Not assessed	100	100	Not assessed
Craig <i>et al</i>	CCK-OP	1 min	Static +TAC	Not assessed	38	90	Not assessed

CRL, caerulein; CCK-OP, cholecystokinin octapeptide; TAC, time activity curve; Rel, reliable; Pts, patients.

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Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma

Gastric MALT lymphoma (GML) development is closely associated with *Helicobacter pylori* infection cases.¹ The majority of stage IE GML regress following *H pylori* eradication but assessing cure of the disease requires prolonged follow up. Residual lymphoid infiltrate in post-treatment gastric biopsies can be very difficult to interpret and histological criteria for the diagnosis of minimal residual disease or complete remission are not clearly defined. Molecular follow up by polymerase chain reaction (PCR) for the rearranged immunoglobulin heavy chain variable region shows that persistent monoclonal bands is observed in 44% of cases showing apparent complete histological remission.² The significance of ongoing PCR monoclonality in the absence of histological disease is still under investigation.

Thus histological evaluation of gastric biopsies remains the cornerstone to assess lymphoma response to therapy. In 1993, Wotherspoon *et al* proposed a histological scoring system that was initially designated to express the degree of confidence of a diagnosis of GML on gastric biopsies.³ This

histological scoring has been used to evaluate the response to therapy in a number of subsequent trials but many investigators have found the system difficult to apply and of low interobserver reproducibility. Other studies have used the criteria of partial and complete remission defined by Neubauer and colleagues.⁴ Criteria of lymphoma response to therapy need to be standardised using a system that can be easily applied so that results of future clinical trials can be compared.

As part of multicentre clinical trials on GML, GELA (Groupe d'Etude des Lymphomes de l'Adulte) pathologists and one of the authors (ACW) established a post-treatment histological grading system based on evaluation on haematoxylin-eosin (H&E) stained sections of three essential diagnostic features: the lymphoid infiltrate, presence of lymphoepithelial lesions (LEL), and stromal changes. We classified the morphological features observed in post-treatment gastric biopsies as follows: "complete histological response" (CR), "probable minimal residual disease" (pMRD), "responding/residual disease" (rRD), and "no change" (NC) (table 1). These groups give clinically relevant information to the clinician. In particular, the category responding/residual disease (rRD) implies that overt lymphoma is present in association with features that suggest a degree of regression. This would imply to the clinician an ongoing response that does not require immediate use of alternative therapies.

To assess the reproducibility of this histological grading system, we selected at random 10 patients with GML enrolled in the GELA clinical trial (seven men and three women; median age 60 years (range 35–74)).⁵ A total of 45 sets of gastric biopsies stained with H&E were evaluated separately by each histopathologist blind to the clinical follow up data using the new follow up system. Three to six sequential gastric biopsies were analysed for all patients with a mean follow up of 19 months after *H pylori* eradication therapy. Interobserver agreement evaluated by the weighted kappa value gave excellent results, with values over 0.84, indicating very good agreement among the seven observers.

Assessing the lymphoma remission status is of great importance for clinical practice. Developing tools to evaluate residual disease are needed, not only for clinical practice but also to conduct clinical trials that aim to define therapeutic guidelines. We propose in this study a histological grading system for

the evaluation of post-treatment gastric biopsies. Testing of this scheme in a small number of cases within the group developing this scheme has shown it to be highly reproducible. These results encourage further evaluation of this scheme on larger series, as well as investigation of its clinical significance and impact on clinical guidelines. In combination with molecular studies, this scheme could provide an interesting tool for the evaluation of residual disease in prospective studies on GML.

C Copie-Bergman, P Gaulard

Département de Pathologie, EA 2348, Hôpital Henri Mondor, AP-HP, 94010 Créteil, France

A Lavergne-Slove

Service d'Anatomie Pathologique, Hôpital Lariboisière, AP-HP, Paris, France

N Brousse

Service d'Anatomie Pathologique, Hôpital Necker Enfants-Malades, AP-HP, Paris, France

J F Fléjou

Service d'Anatomie Pathologique, Hôpital Saint-Antoine, AP-HP, Paris, France

K Dordonne

Service de Biostatistiques et d'Informatique, Hôpital Henri Mondor, AP-HP, Créteil, France

A de Mascarel

Service d'Anatomie Pathologique, CHU de Bordeaux, France

A C Wotherspoon

Department of Histopathology, Royal Marsden Hospital, London, UK

for the Groupe d'Etude des Lymphomes de l'Adulte (GELA)

Correspondence to: Dr C Copie-Bergman, Département de Pathologie, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France; christiane.copie@hmn.ap-hop-paris.fr

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Remarkable resemblance in the mode of transmission of HCV infection among haemodialysis patients and IVDAs

Hepatitis C virus (HCV) infection is widespread among patients on long term haemodialysis (HD) and among intravenous drug abusers (IVDAs). However, there appear to be striking similarities in the mode of

Table 1 GELA histological grading system for post-treatment evaluation of gastric MALT lymphoma

Score	Lymphoid infiltrate	LEL	Stromal changes
CR (complete histological remission)	Absent or scattered plasma cells and small lymphoid cells in the LP	Absent	Normal or empty LP and/or fibrosis
pMRD (probable minimal residual disease)	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD (responding residual disease)	Dense, diffuse, or nodular extending around glands in the LP	Focal LEL or absent	Focal empty LP and/or fibrosis
NC (no change)	Dense, diffuse, or nodular	Present, "may be absent"	No changes

MM, muscularis mucosa; LP, lamina propria; SM, submucosa; LEL, lymphoepithelial lesions.

transmission between the two groups as both are at high risk for parenterally transmitted HCV infection.

The indispensable requirement of having a vascular access site possibly adds to the risk of acquiring HCV infection among patients on long term HD through nosocomial transmission, especially in high HCV prevalence units. Preliminary data suggest that among various types of vascular access used for HD, arteriovenous fistula and polytetrafluoroethylene grafts which require extra skilful handling, perhaps play a more significant role in the transmission of HCV than permanent or temporary central venous catheters.¹ Sharing of contaminated dialysis equipment, dialyser reuse, and the physical proximity of an infected patient during HD are additional important factors incriminated in the transmission of HCV in the busy HD unit.² Gilli *et al* reported an outbreak of HCV in an Italian HD unit due to sharing of multidose heparin vials.³ Another recent study from the USA reported an outbreak of HCV occurring when a multidose saline vial was contaminated with blood from a HCV infected patient in a Florida hospital.⁴ Breakdown in the implementation of standard infection control safety measures recommended by the CDC is essentially responsible for the rapid rise in HCV infection among HD patients worldwide.

Likewise, sharing of contaminated equipment (needles and syringes) among IVDAs is also the primary concern attributed to the continuous increase in HCV infection. However, in a recent report from Kolkata, India,⁵ dissemination of HCV accelerated, paradoxically from a baseline prevalence rate of 17% in 1996 to 66% in 2002 and to 80% during the next year, regardless of the supply of fresh needles and syringes on a daily basis, under the supervision of trained field workers, with the equipment being taken away from IVDAs on the next day after use. Most of the IVDAs did not share their syringes or needles; none the less, they shared the multidose vials of the drugs. Indirectly sharing of the drug ampoules suggested contaminated body fluids/blood being the means of transmission of HCV through direct access to the blood circulation. Transmission of virus was also suspected to occur from sharing of a small pot containing water that some IVDAs used to clean the syringes and needles before using them again.

With strict implementation of standard infection control precautions and probably isolation of anti-HCV positive patients, it may be possible to effectively control the spread of HCV infection among patients on long term HD.⁶ However, promiscuous sexual behaviour, lack of personal and community hygiene, and absolute disregard for life, prevalent among IVDAs, are the major practical problems preventing implementation of interventional measures for the control of the spread of HCV in this high risk group.

**A K Saxena, B R Panhotra,
A M Al-Arabi Al-Ghamdi**

King Fahad Hospital, Al-Hasa, Saudi Arabia

Correspondence to: A K Saxena, Division of Nephrology, Post-graduate Department of Medicine, King Fahad Hospital and Tertiary Care Centre Hofuf, Al-Hasa, Ea 31982, Saudi Arabia; dranil_31982@yahoo.com

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Physician-technician

I have every sympathy with Dr Neale's opinion and feel he is entirely correct in worrying about the apparently overwhelming tendency for technological investigation and expertise instead of a more considered diagnostic and management approach (*Gut* 2003;**52**:770–1). I would also agree with his view of the aspirations of many gastroenterological specialist registrars, apparent from talking to many of them. He has highlighted the potential problems of such a technical dictum and not even mentioned what might happen when further advances in imaging obviate the need particularly for diagnostic colonoscopy.

What will all the technicians do?

However, Dr Neale has perhaps been a little over cautious in condemning colonoscopy in case No 1. I would agree that colonoscopy in case No 2 with a macrocytic anaemia and possible haematemesis must be regarded as a very doubtful indication. However, in case No 1, with a marked microcytic anaemia and recurrent melaena without a definite cause in the upper gastrointestinal tract, many would regard visualisation of the colon by whatever means prudent, although given the likely comorbidity a non-invasive test might have been better, depending on resources. It is clear that in both of these typical cases appropriate thought had not gone into the diagnostic approach but also interestingly that in these days of great service pressures it was possible to perform oesophagogastroduodenoscopy and colonoscopy before haematinic estimations. In both cases the colonoscopist must share the blame for taking an overly technical view; bowel preparation may be rather unpleasant but that is no reason to continue and perform an unnecessary investigation if the patient turns up on a list. I would echo Dr Neale's thoughtful suggestion that we need to concentrate more on efficacy and safety of care.

I Beales

School of Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ, UK; i.beales@uea.ac.uk

Author's reply

I thank Dr Beales for his comments. Clearly, it is always easy to be wise in retrospect. However, we teach students to make a

diagnosis by listing the positive findings and linking these to build a coherent diagnosis.

In case No 1, the house officer noted aspirin ingestion, melaena, a hard liver edge, and thrombocytopenia. He suggested cancer of the gut with hepatic metastases. This was reasonable enough even though it did not include thrombocytopenia.

The next logical step might have been scanning of the upper abdomen in which case splenomegaly would have been added to the list and from there it was only a short step to hepatic cirrhosis and possible reinterpretation of the erythematous/exudative gastritis.

We also teach that patients be told the risk-benefit ratio of any procedure.¹ Frank melaena is a rare presentation of cancer of the colon and the risk of colonoscopy is perhaps 0.2%.

I leave the reader to decide if the present day gastroenterologist should concentrate on honing specialist technical skills to gather information or should develop as a consultant who weighs the evidence as it unfolds.

G Neale

Clinical Safety Research Unit, Academic Department of Surgery, 10th Floor QEQM, St Mary's Hospital, Praed St, London W2 2NY, UK; g.neale@ic.ac.uk

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CORRECTION

In the paper by Nikolaus *et al* (*Gut* 2002;**52**:1286–90, "Interferon β -1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study") an exploratory study in 17 patients is reported. In the paper a p value for the comparison between remission in the IFN group (3/10) and the placebo group (0/7) is quoted with 0.023. This is an error and should be 0.23. The conclusions ("Patients treated with escalating doses of IFN- β -1a tended to show higher clinical response and remission rates than those receiving placebo, although the differences between the groups did not reach statistical significance") remain correct, as they were not based on any statistical significance.

NOTICES

Sir Francis Avery Jones British Society of Gastroenterology Research Award 2004

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years old or less on 31 December 2004 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

British Society of Gastroenterology Hopkins Endoscopy Prize 2004

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to the Council the recipient of the 2004 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TEN COPIES) should be made to the Endoscopy Section Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

British Society of Gastroenterology Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United

Kingdom for specialist experience and training in endoscopy.

Specialist registrars who have not achieved their CCST are expected to have the approval of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applicants are expected to provide confirmation that they have been accepted for training in the unit that they wish to visit.

Successful applicants will be expected to provide a brief written report to the Endoscopy Committee of the outcome of their visit.

Application forms are available from the British Society of Gastroenterology Office, 3 St Andrew's Place, London NW1 4LB. Email: bsg@mailbox.ulcc.ac.uk

3rd Congress of the European Chapter of the American College of Nutrition

This meeting will be held on 14–15 November 2003 in Göttingen, Germany. **Abstract deadline: 01 October 2003.** Main topics: Metabolic Syndrome, Plant-genomics, Treatment of Obesity, Hormonal Regulation of the Body Weight, Pediatric Nutrition, Malnutrition, Food-induced Diseases, Food and Allergy. Further details: G Schickedanz, Congress Secretary, Department of Gastroenterology and Endocrinology, University of Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany. Tel +49 551 396326; fax: +49 551 3919125; email: nutrition2003@med.uni-goettingen.de; website: www.nutrition-europe.org

European Course on Laparoscopic Endoscopy

This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Haute 322, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straeb.asmb@

proximedia.be; website: www.straeb-asmb.com

Hong Kong-Shanghai International Liver Congress 2004

This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is "Liver Diseases in the Post-Genomic Era". Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org

PET/CT and SPECT/CT Imaging in Medical, Radiation, Surgical and Nuclear Oncology

This continuing medical education programme will take place on 19–20 March 2004 at Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. Further details: Office of Continuing Medical Education, Johns Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205-2195. Tel: +1 410 955 2959; fax: +1 410 955 0807; email: cmenet@jhmi.edu; website: www.hopkinscme.org

39th Annual Meeting of the European Association for the Study of the Liver

This meeting will be held on 15–19 April 2004 in Berlin, Germany. Further details: Secretariat, c/o Kenes International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0488; fax: +41 22 732 2850; email: info@easl.ch; website: www.easl.ch/easl2004

- Deadline for receipt of abstracts: 16 November 2003
- Deadline for early registration 10 February 2004