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

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 µg three times a week subcutaneously, and the dose was increased at two week intervals to 44 µg and then to 88 µg 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)-1β, 6 and 8, and tumour necrosis factor (TNF), are increased in patients with ulcerative colitis. Levels of these cytokines have been shown to be related to disease activity. 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, anti-inflammatory treatment with aminosalicylates or corticosteroids remains the mainstay of ulcerative colitis management.

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, and to antagonise early events in the IFN-γ signalling pathway. In addition, IFN-β increases expression of the anti-inflammatory cytokine IL-10, and enhances T suppressor and natural killer cell activity. 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. Other important effects of interferons include a protective action against bacterial and parasitic infections, which has been demonstrated in various model systems.

An open study with another type 1 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), 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. 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), 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. Patients were also required to have an adequate bone marrow reserve (white cell count ≥3.5×10⁹/l, neutrophils ≥1.5×10⁹/l, thrombocytes ≥100×10⁹/l and ≤800×10⁹/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.
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 µg three times a week subcutaneously. Improvement was defined as a decrease of 1 point in the clinical component 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.

* Or matching placebo

Figure 1  Study flow chart. All patients received 22 µg of study drug three times a week (tw) for four weeks. If patients did not show clinical improvement the dose was doubled every two weeks up to 88 µg tw. “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.
The study population were well balanced with regard to sex, placebo and 10 to receive IFN-β1a of study drug. Seven of 17 patients were randomised to receive analysed. One patient was excluded a priori (that is, before the onset of the study). All patients were included overall treatment and end point responses (defined a clinical response as a decrease of at least 1 point in the UCSS symptoms score and PGA (without the proctosigmoidoscopic score) during treatment. This was a modification of the endpoint 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 proctosigmoidoscopic 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 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-β1a 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. 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-β1a. 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-β1a 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-β1a group, two in the placebo group) stopped treatment because of progressive disease, and two (both in the IFN-β1a 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-β1a, four were escalated to the maximum dose of 88 µg three times a week, two reached 44 µg, and four remained on 22 µg. The average dose for IFN-β1a treated patients was 38.6 µg three times a week, which represents an average daily dose of 16.7 µg IFN-β1a and a cumulative total dose of 427 µg IFN-β1a.

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-β1a group and in one (15%) in the placebo group (p=0.14). Endoscopically confirmed remission was achieved in three patients in the IFN-β1a treated group and in none in the placebo group (p=0.02).

Of the five patients in whom clinical responses were achieved during IFN-β1a treatment, one was receiving 22 µg three times a week, three were receiving 44 µg, and one was receiving 88 µg. The mean time to clinical treatment response was 28 (SD 11) days in the IFN-β1a group and 28 days in the responding placebo patient. The mean cumulative dose of IFN-β1a required to achieve clinical treatment response was 449 µg.

Of the three patients in whom remission was achieved during IFN-β1a treatment, one was receiving 44 µg and two were receiving 88 µg. The mean time to remission was 52 (7) days in the IFN-β1a group. The mean cumulative dose of IFN-β1a required for induction of remission was 1115 µg.

UCSS symptom scores and PGAs tended to decrease to a greater extent in patients treated with IFN-β1a 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-β1a 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-β1a 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-β1a group; five in the placebo group). Most were influenza-like symptoms or injection site reactions, and most were mild

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**Table 1** Patient demographics and disease characteristics in the two groups

<table>
<thead>
<tr>
<th>Sex (male [n])</th>
<th>IFN-β1a (n=10)</th>
<th>Placebo (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) [median (absolute range)]</td>
<td>42.2 [32–68]</td>
<td>35 (30–63)</td>
</tr>
<tr>
<td>Duration of disease (y) [median (absolute range)]</td>
<td>9.8 [2.6–14.2]</td>
<td>9.0 [2.6–40.3]</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left sided/pancolitis/backwash ileitis</td>
<td>5/4/1</td>
<td>5/2/0</td>
</tr>
<tr>
<td>Extraintestinal manifestations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis/arthritis, urethritis, iritis [n %]</td>
<td>1 [10%]</td>
<td>1 (14.3%)</td>
</tr>
<tr>
<td>Chronic autoimmune liver disease [n %]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Baseline UCSS (median)</td>
<td>9 [7–10]</td>
<td>9 [7–12]</td>
</tr>
<tr>
<td>Baseline C reactive protein [median [Q1-Q3]]</td>
<td>4.6 [3.0–8.9]</td>
<td>8.2 [3.0–9.4]</td>
</tr>
<tr>
<td>Oral 5-ASA use [n %]</td>
<td>5 [71%]</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>Mean 5-ASA use (g)</td>
<td>3.8 g/d</td>
<td>3.6 g/d</td>
</tr>
</tbody>
</table>

IFN, interferon; UCSS, ulcerative colitis scoring system; Q1, Q3, quartiles 1 and 3.
application of IFN-β-1a may be beneficial in the treatment of ulcerative colitis. In vitro studies have shown that IFN-β can induce IL-10 release from lymphocytes obtained from patients with multiple sclerosis, 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. 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.

ACKNOWLEDGEMENTS
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REFERENCES
LETTERS

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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) method where the time period was delayed by 2.5 minutes in comparison with 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. Madauci and colleagues, comparing measurement of HHDT without any stimulus and after caerulein administration, showed that the 89% sensitivity of the test without the cholecystokinin stimulus decreased to 0% after the cholecystokinin stimulus. In addition, it is not acceptable to derive any conclusions on test sensitivity from a comparison between a scintigraphic assessment performed after a cholecystokinin 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. 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 the HHDT method 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 cholecystokinin stimulus. Reliability of the HHDT test is supported by the following studies:

1. It is reproducible in asymptomatic controls (Cicala and colleagues) and in patients with SO dysfunction (Cicala and colleagues);
2. It discriminates asymptomatic controls from SO dysfunction patients (Corazziari and colleagues).

Finally, in common with the validation process used for SO manometry, validity of a scintigraphic diagnostic test for SO dysfunction is proved if the test is comparable and has not been submitted to proper validation studies to ascertain their reliability. 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.

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References


<table>
<thead>
<tr>
<th>Reference No</th>
<th>Stimulus</th>
<th>Frame/t</th>
<th>Analysis</th>
<th>Reproducibility (controls/pts)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Versus manometry (no stimulus)</th>
<th>Versus sphincterotomy (sensitivity)</th>
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<tr>
<td>Scintigraphic HHDT (choledochoscintigraphy)</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>1, 4, 5</td>
<td>None</td>
<td>1.5 s</td>
<td>TAC</td>
<td>Rel/reli</td>
<td>83</td>
<td>100</td>
<td>93</td>
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<td>3</td>
<td>None</td>
<td>1 min</td>
<td>TAC</td>
<td>Not assessed</td>
<td>89</td>
<td>100</td>
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<td>6</td>
<td>CRL</td>
<td>1 min</td>
<td>TAC</td>
<td>Not assessed</td>
<td>0</td>
<td>100</td>
<td>Not assessed</td>
<td></td>
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<tr>
<td>Craig et al</td>
<td>CCK-OP</td>
<td>1 min</td>
<td>Static</td>
<td>Not assessed</td>
<td>13</td>
<td>95</td>
<td>Not assessed</td>
<td></td>
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<tr>
<td>Scintigraphic score</td>
<td></td>
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<td></td>
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<tr>
<td>2</td>
<td>CCK-OP</td>
<td>1 min</td>
<td>Static</td>
<td>Not assessed</td>
<td>100</td>
<td>100</td>
<td>Not assessed</td>
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</tr>
<tr>
<td>Craig et al</td>
<td>CCK-OP</td>
<td>1 min</td>
<td>Static</td>
<td>Not assessed</td>
<td>38</td>
<td>90</td>
<td>Not assessed</td>
<td></td>
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</table>

CRL, caerulein; CCK-OP, cholecystokinin octapeptide; TAC, time activity curve; Rel, reliable; Pts, patients.
The significance of ongoing PCR remission 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. 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 (Group 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-cosin (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" (RD), and "no change" (NC) (Table 1). These groups give clinically relevant information to the clinician. In particular, the category responding/residual disease (RD) 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)). 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.

References

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>
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<tr>
<th>Table 1</th>
<th>GELA histological grading system for post-treatment evaluation of gastric MALT lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Lymphoid infiltrate</td>
</tr>
<tr>
<td>CR (complete histological remission)</td>
<td>Absent or scattered plasma cells and small lymphoid cells in the LP</td>
</tr>
<tr>
<td>pMRD (probable minimal residual disease)</td>
<td>Aggregates of lymphoid cells in the LP</td>
</tr>
<tr>
<td>rRD (responding residual disease)</td>
<td>Dense, diffuse, or nodular extending around glands in the LP</td>
</tr>
<tr>
<td>NC (no change)</td>
<td>Dense, diffuse, or nodular</td>
</tr>
</tbody>
</table>

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 indispenable 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 skillful handling, perhaps play a more significant role in the transmission of HCV than permanent or temporary central venous catheters. Sharing of dialysis equipment, disassembly, re-use, 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. Gill et al. reported an outbreak of HCV occurring when a multidose vial of blood from a HCV infected patient in a reported outbreak of HCV occurring when control of the spread of HCV in this high prevalence unit. Preliminary data suggest that among various types of vascular access used for HD, arteriovenous fistula and polytetrafluoroethylene grafts which require extra skillful handling, perhaps play a more significant role in the transmission of HCV than permanent or temporary central venous catheters. Sharing of dialysis equipment, disassembly, re-use, 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. Gill et al. reported an outbreak of HCV occurring when a multidose vial of blood from a HCV infected patient in a Florida hospital. 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.

Lifestyle, 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, 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 IVDA’s on the next day after use. Most of the IVDA’s 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 pot containing water that some IVDAs used.

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 HD unit. 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 IVDA’s used.

With strict implementation of standard infection control precautions and a busy HD unit due to sharing of multidose heparin vials. 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. 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 IVDA’s is also the primary concern attributed to the continuous increase in HCV infection. However, in a recent report from Kolkata, India, 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 IVDA’s on the next day after use. Most of the IVDA’s 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 IVDA’s used.

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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 an oversight, melena, 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 melena 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
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Reference

CORRECTION

In the paper by Nikolaus et al (Gut 2002;52:1286–90, “Interferon ß-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-ß-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.

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.

www.gutjnl.com
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.hopkinscmce.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 Kenses 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