A proof of concept study establishing *Necator americanus* in Crohn's patients and reservoir donors

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DNA test for hypolactasia premature

I write in response to the article by Rasinperä and colleagues (Gut 2004;53:1571–6) in which a DNA test was proposed for “adult-type hypolactasia.”

The ability to digest the milk sugar lactose as an adult (lactase persistence) is a variable genetic trait in human populations, lactase persistence being the most frequent phenotype in Northern Europe, while lactase non-persistence or “adult-type hypolactasia” is more frequent in most other populations.1 In sub-Saharan Africa for example, lactase persistence is found only at low frequency in the majority of populations that have been tested, but in some populations, particularly pastoralist groups, it is significantly more frequent.

A CT polymorphism located 13.9 kb upstream of exon 1 of the lactase gene (LCT) was previously shown in a Finnish population to be tightly associated with the lactase persistence phenotype2 and it is this change that is proposed as a DNA test for both Europeans and Africans. We agree that presence of a T at this polymorphic site is indeed a fairly good predictor of lactase persistence in Northern Europeans,2,3 and there is evidence that this nucleotide resides in a functional element.4 However, the presence of the alternative allele C at this site is not a good predictor of lactase non-persistence or “adult hypolactasia” in many non-Northern Europeans.5 I particularly draw readers’ attention to our recent study.6 We typed this polymorphism in 1671 individuals from seven African countries, which included 20 distinct cultural groups and in seven cases it was possible to match the groups tested with groups from the literature for whom phenotypic information was available. In five of these groups the presence of the CT polymorphism was available. In five of these groups the presence of the CT polymorphism was available.

Our ongoing results support this published information and we urge the community to refrain from using DNA tests on Africans and probably other non-Northern Europeans until an appropriate DNA change has been identified.

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Conflict of interest: None declared.

References
8 Rasinperä H. A genetic test which can be used to diagnose adult-type hypolactasia in children. Gut 2004;53:1571–6.

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Conflict of interest: None declared.
abdominal symptoms leading to dehydration, in combination with repetitive bathing behaviour (Gut 2004;53:1566–70). They have concluded that these symptoms are due to cannabis use.

Cannabis has been consumed for many centuries and is currently used by millions of people in many countries. It is hard to believe that a distinctive syndrome caused by cannabis has never been noted before by users or clinicians.

The authors assert that cannabis laws are particularly liberal in South Australia. Four Australian jurisdictions now have a cannabis explication notice system which South Australia first introduced in 1986. The other four Australian jurisdictions have variations on a bond system. Several European countries have far more lenient legislative arrangements. After over a generation of liberalisation of cannabis laws in many countries around the world, there is little evidence of a subsequent increase in cannabis use.

In a comparative study using the same methodology, the prevalence of cannabis use in more “liberal” Amsterdam was lower than in the more “punitive” San Francisco.1

The title of the paper, “Cannabinoid hyperemesis” is unduly presumptive. Some of these cases appeared to improve with abstinence and then relapsed when patients were “rechallenged” with cannabis, but neither the patients nor the authors appear to have been blinded in the rechallenge. The proposed biological explanation is weak.

We suggest that alternative explanations need to be sought for these cases. This syndrome should not be accepted as being caused by cannabis without additional reports and other evidence.

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Dr Wodak is President of the Australian Drug Law Reform Foundation which supports the taxation and regulation of cannabis.

Reference

II-1 gene cluster and TNFA–307 polymorphisms in the risk of perforated duodenal ulcer

Helicobacter pylori virulence markers have been associated with duodenal ulcer (DU) but there are few studies evaluating host factors such as cytokine polymorphisms and, to the best of our knowledge, no study has evaluated these polymorphisms as risk factors for perforated DU. We investigated associations among interleukin 1 (IL1) cluster and tumour necrosis factor a (TNFA)–307 polymorphisms, and DU and perforated DU in a non-Caucasian population. We included 223 patients with DU, 29 patients with perforated DU, and 541 blood donors. H pylori status was investigated by culture, preformed urease test, stained smear, polymerase chain reaction (PCR), and the 13C-urea breath test. cagA status was assessed by PCR. In the blood donors, H pylori status and cagA status were determined by serology. IL1B–511–31, IL1B, and TNFA–307 polymorphisms were genotyped by PCR, PCR restriction fragment length polymorphism (RFLP), or PCR followed by two pair primers.1 Data were analysed in logistic models. The loci did not deviate significantly from the expected Hardy-Weinberg distribution in the control group. IL1B–511T and IL1B–31C polymorphisms were almost completely in linkage disequilibrium in all three groups (p < 10–6). We thus restricted further analyses to IL1B–31. No polymorphism remained associated with non-complicated DU, but IL1B–31T was strongly associated with perforated DU (OR 4.29 (95% CI 2.56–6.98)) in blood donors. H pylori infection,2 little change was observed

Reference

Authors’ reply
We would like to thank Byrne et al for their interest in our paper (Gut 2004;53:1566–70). It should be noted that we undertook an observational study by necessity. Cannabis is an illegal drug and double blind control trials with illicit substances are prohibited and unethical. The assertion that cannabis has been “consumed for many centuries” needs to be tempered with the fact that cannabis has been grossly under-researched clinically and, as we have shown with this syndrome, nowhere near fully understood in its pharmacology or paradoxical actions. Since publication of our article, other authors have published similar findings to ours and drawn the same conclusions.1

Conflict of Interest: None declared.

Reference

“Cannabis hyperemesis” causation questioned

The authors describe a number of cases of a bizarre syndrome of severe vomiting,
Long term exposure to gluten in coeliacs,1 and coeliac disease (CD) after 16 years of age may induce type 1 diabetes (T1D) and other autoimmune disorders. Increased prevalence of CD among diabetics and their relatives is well documented.1 Early introduction of gluten to children at high risk for T1D produces T1D associated islet autoantibodies.2 Similarly, in the absence of overt clinical symptoms of T1D, some coeliac children produce diabetes autoantibodies in a gluten dependent manner. Differences in intestinal challenge with gluten produces mucosal recruitment of lymphocytes,3 similar to that in CD patients. In diabetics, however, there is no production of CD related anti-tissue transglutaminase antibodies (anti-tTG).4

We have used a phage display assay5 to show that in CD patients, production of anti-tTG is limited to the intestine. Here, we monitored the effects of a gluten free diet (GFD) on anti-tTG antibody synthesis in the intestinal mucosa of a diabetic adult and a boy at high risk of diabetes, both carrying HLA DQ2/DQ8, but lacking serum anti-tTG. Intestinal specimens from both subjects and samples of peripheral blood lymphocytes were used to make phage-antibody libraries6 to look for lymphocytes synthesising anti-tTG antibodies.

Patient No 1 was a 35 year old man who had T1D for 20 years. During 1998–2001, serum anti-tTG responses were negative, and clinical control of T1D was good (mean glycosylated haemoglobin 6.8% (range 8.1–7.4%)) and the patient developed a GFD. He was treated diabetic retinopathy and microalbuminuria, with an average albumin excretion rate (AER) of 230 μg/min, despite treatment with angiotensin converting enzyme inhibitors. In 2001, ‘burning’ epigastric pain appeared with abdominal distension. Duodenal biopsy and number of intraepithelial lymphocytes were normal.

Patient No 2 was a two year old boy at risk of CD and T1D (diabetic father and coeliac brother) who tested positive (CD) for two out of three HLA T1DM specific genotypes (DR1*0301, DQA1*0301, DQB1*0302). Tests for anti-tTG serum antibodies were negative while anti-iselet cell antibodies (ICA) became positive at 20 months. Informed of the potential risks, the child’s parents consented to intestinal biopsy to detect possible silent CD. Duodenal biopsy and number of intraepithelial lymphocytes were normal.

In both subjects, positive tTG antibody clones (table 1) were isolated only from the intestinal lymphocyte libraries. Two control subjects aged 10 and 45 years, suffering from Helicobacter pylori gastritis and with no family history of CD or T1D, tested negative for anti-tTG. All positive subjects were HLA T1DM positive (DR1*0301, DQA1*0301, DQB1*0302). All samples of peripheral blood lymphocytes were used to make phage-antibody libraries to look for lymphocytes synthesising anti-tTG antibodies.

Table 1 Univariate and multivariate analysis of the cytokine loci between patients with perforated duodenal ulcer (n = 29) and all blood donors (n = 539), and between patients with perforated duodenal ulcer (n = 29) and Helicobacter pylori positive blood donors (n = 369)

<table>
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<th>Genotype</th>
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<th>IL-1RN</th>
<th>TNFA</th>
<th>IL-1RN</th>
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<td>OR</td>
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<td>1.85</td>
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</table>

Conflict of interest: None declared.

References


Cryptic gluten intolerance in type 1 diabetes: identifying suitable candidates for a gluten free diet
GFD; AER is still normal in the diabetic adult and the child is still negative for ICA.

In the context of genetic predisposition to gluten intolerance, in line with Maki’s data on the gradual development of CD in diabetics, we found a gluten dependent immunological response, apparently only in the intestine. In the boy, reduced response to tTG and elimination of ICA after GFD may have been due to very early intervention, indicating temporary protection from the disease. In the diabetic adult, reduction of microalbuminuria may have indicated that while a GFD is of little benefit to the pancreas, improvements can still be obtained while a GFD is of little benefit to the diabetics, on the gradual development of CD in the at risk child, and in the controls.

In conclusion, at risk subjects with HLA DQ2/8 have a higher risk of developing CD in the adult diabetic, in the at risk child, and in the controls. Similar larger scale studies are needed to confirm the benefits of a GFD.

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References


level improved partially after drug withdrawal. In previously reported cases, the inhibitor disappeared in 88% of patients overall, after a mean of 10 weeks. In patients with no identified cause, the inhibitor only disappeared in 62% of cases after a mean of 23 weeks, although this did not affect outcome. Bleeding is difficult to treat in patients with factor V inhibitor. Various approaches have been tried, such as infusion of fresh frozen plasma or, better, platelet concentrates. Thromboplastic has been used to lower antibody titre and high dose immunoglobulin to neutralise the antibodies. Steroids and immunosuppressants (azathioprine, cyclophosphamide), alone or in combination, have been used for long term inhibition of factor V inhibitor synthesis. However, the results are difficult to interpret as the series were small and included patients with heterogeneous manifestations. There is no consensus treatment.

In conclusion, the onset of hypoacugulability linked to a decline in factor V level in a cirrhotic patient should not be systematically attributed to hepatocellular insufficiency; in the absence of marked cytolysis, the presence an acquired factor V inhibitor and a possible drug related cause should be sought.

References

Acylated ghrelin stimulates food intake in the fed and fasted states but desacylated ghrelin has no effect

We were interested to read the article of Asakawa et al (Gut 2005;54:18–24) which reported that intracerebroventricular and peripheral administration of desacylated ghrelin inhibited food intake in mice in the fasted state. Acylated ghrelin (AG) has a unique biological structure with an acyl side chain on the third amino acid residue. AG is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a) and stimulates feeding and growth hormone release. In contrast, desacylated ghrelin (DAG), which does not have the acyl side chain, has no affinity for the GHS-R1a. As the authors suggest, their results might indicate the presence of an alternative receptor through which desacylated ghrelin acts.

We were interested in investigating whether DAG would modulate feeding. We injected saline, 0.3 nmol/kg AG, and 0.3 nmol/kg DAG into C57BL mice intraperitoneally on two occasions, firstly in the fed state and secondly following a 20 hour fast, and measured food intake at 1, 2, 4, 6, and 24 hours post injection (fig 1). In the fasting experiment, we also injected 0.03 nmol/kg PYY 3–36 as a positive control. All animal procedures were approved by the British Home Office Animals (Scientific Procedures) Act 1986 (project license No 70/5281). Results were analysed using a one way repeated measures ANOVA. As previously reported, AG stimulated feeding in the fed state. However, DAG had no significant effect on food intake in the fed state. In the fasting study, PYY 3–36 significantly inhibited feeding. AG stimulated cumulative food intake in fasted mice for up to six hours post injection although the percentage increase compared with saline was less than in the fed state (per cent increase two hours following ghrelin injection: fed state 320%, fasted state 30%). In contrast with the findings of Asakawa et al, DAG had no effect on food intake at any time point examined. We used a higher dose of DAG than that injected in the fasting study (approximately 3 nmol/kg over 30 days and the death rate of patients with true alcoholic hepatitis. This difference compared with the published literature may be attributable to case definition. It is possible that there were a fewer number of patients in the derivation cohort for GAHS with true alcoholic hepatitis. Some of the previous studies of alcoholic hepatitis have required liver biopsy evidence of alcoholic hepatitis as part of the case definition. This was not the case entry into the derivation cohort for the GAHS study and the case definition was based solely on clinical and biochemical evidence of liver dysfunction in patients with heavy alcohol consumption. In the validation population there was biopsy evidence of alcoholic hepatitis in only 33%.

While this may invalidate the GAHS as a means of identifying cases of alcoholic hepatitis, it does not invalidate its use in identifying patients at risk of death when admitted to hospital with liver dysfunction on a background of heavy alcohol use. This makes it far more pragmatic than tests based on biopsies as many hospitals do not have access to specialised services to perform transjugular liver biopsies in the acute setting. Furthermore, there are published

**Figure 1** Cumulative two hour food intake under (A) fed and (B) fasting states following intraperitoneal saline, 0.3 nmol/kg acylated ghrelin (AG), 0.3 nmol/kg desacylated ghrelin (DAG), and 0.03 nmol/kg PYY 3–36 (PYY). *p<0.05 versus saline and DAG; **p<0.005 versus saline.
randomised controlled trials which have not required histological evidence of alcoholic hepatitis before allocating treatment. The corollary to this is that although alcoholic hepatitis often presents with clinical features of fever, leucocytosis, and hyperbilirubinaemia, there remains a differential diagnosis which may require a biopsy to resolve.

It is important to differentiate between true alcoholic hepatitis and severe liver dysfunction in patients with heavy alcohol consumption because it will influence the choice of intervention. Randomised controlled trials that use GAHS to identify patients with alcoholic hepatitis might be greatly underpowered if the therapy (for example, steroids) is effective in alcoholic hepatitis but ineffective or harmful in other clinical conditions where abnormal clinical parameters might be associated with heavy alcohol consumption. Selection of risk stratification models should be determined by the severity of the adverse effects of the therapy under trial. Those with more severe adverse effects will warrant models with high specificity whereas drugs with minimal side effects will benefit from a model with a high sensitivity. Compared with the DFS, the GAHS has an increased specificity, decreased sensitivity, and improved accuracy, making it suited to the selection of subjects in studies using more toxic therapies. The utility of the GAHS will depend on the effect of its use in the care of patients. We suggest that the next step in the evaluation of GAHS should be a clinical trial to see if patients randomised to risk stratification with GAHS followed by appropriate interventions have a better outcome than those managed conventionally.

We believe this is an excellent study using robust clinical end points. It is a practical model which can be used easily at the bedside to give valuable prognostic information. Success of future therapeutic trials in alcoholic hepatitis will not only depend on the efficacy of the drug but also the appropriate selection of patients by models and their respective cut off points.

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IN Guha received grant support from Pfizer.
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Conflict of interest: None declared.

References


A proof of concept study establishing Necator americanus in Crohn’s patients and reservoir donors

The emergence of autoimmunity, including Crohn’s disease (CD) where the immune relationship with commensal bacteria is corrupted, has been linked to hygiene. However, repeated inoculation required and concern has been raised that aberrant migration could occur. The haematophagous hookworm, Necator americanus (NA), is proposed as an alternative. We have tested if CD patients tolerate hookworm infection, and the practical issues associated with establishing reservoir donors (RDs).

Over 700 million people remain infected with hookworms. Infective larvae (L3i) are acquired through skin contact with contaminated soil. Auto-infection, direct person to person infection, aberrant migration, and hypobiosis do not occur. Adult worms live in the host small intestine for an average of five years. Infection can be easily terminated with an anthelmintic. Anaemia is the only disease of consequence but is an unusual outcome in properly nourished individuals. Using L3i originally obtained from Madang, Papua New Guinea, but maintained in a healthy researcher in the UK, five CD subjects with longstanding disease were inoculated with L3i cultured from faeces provided by an RD, and the original CD cohort were reinoculated from week 27 to week 30. Ethics approval was granted by the Townsville Health Service District Institutional Ethics Committee. Haematological and clinical measurements are expressed as mean (95% confidence interval).

The inoculation caused a mild itch within five minutes that disappeared after a few days in eight CD subjects and a pruritic rash that lasted two weeks in the RDs, who also developed a painful transient enteropathy. Neither respiratory symptoms nor detectable aberrant migration occurred. In the CD cohort, blood eosinophilia developed from week 2 (mean 2.60 × 10³/µl) to week 1 0.18 × 10³/µl (0.10) to week 20 0.39 (0.201). Patent infection had established by week 20 in all cases. CD activity index (CDAI) remained unchanged until week 17, possibly in part due to a hookworm related enteropathy recognisable because of blood eosinophilia and faecal Charcot-Levy stools. After 20 weeks, the IBD questionnaire was improved (mean 151 (14) v 179 (20)) and the four week cumulated CDAI scores decreased was (mean 141 (31) v 87 (15)). Haemoglobin fell marginally (week 1 mean 135.6 (7.8) g/l v week 20 129.3 (4.1) g/l). Reinoculation of the five CD subjects first inoculated caused no apparent adverse effect. Disease reaction, as defined by a CDAI >150, occurred in two (CD4, CDS; table 1) after the doses of long term immune suppressive drugs had been reduced. The subject (CD3–7) driven trend was to reduce immune suppression as health improved, a strategy often associated with worsening of symptoms. The five CD subjects first inoculated were in remission at week 45 (fig 1).

Our pilot study has established a potential for NA, already a fact of life for many millions, as a candidate parasite to inoculate those with autoimmune disease. The natural advantages are lifecycle and migration predictability, ability to control the size of and eliminate a colony, and the parasite’s longevity. Inoculation proved safe, even in immune suppressed patients. Our hope that NA would suppress auto-reactivity sufficiently to allow immune suppressive therapy to be stopped was unrealistic. Recent and compelling evidence has shown that IBD is self sustaining. It may be that after remission is achieved, endoparasites will offer an alternative or adjunct to immune suppressive therapy, a priority for some people with CD.

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can be cured by *Helicobacter pylori* eradication. It would be very useful to identify, at the time of diagnosis, the 25% of cases of gastric MALT lymphoma that will not respond to *H pylori* eradication. In general, lymphomas at stage IE or above do not respond to *H pylori* eradication. However, the prognostic value of staging in stage IE cases is very limited, although tumours that involve the muscularis propria or serosa (stage IIE) show a higher failure rate than those restricted to the mucosa and submucosa (stage IE).\(^5\) Paradoxically, the majority of gastric MALT lymphomas at diagnosis are at stage IE but 20% of these cases will not respond to *H pylori* eradication.

In a previous study, we have examined the value of t(11;18)(q21;q21) in prediction of the response of gastric MALT lymphoma to *H pylori* eradication. Among the 111 cases of gastric MALT lymphoma studied (t(11;18)(q21;q21) was present in 42/63 (67%) non-responsive cases, including 35/43 (81%) at stage IE.\(^6\) Contrary, translocation was detected in only 2/38 responsive cases and the two translocation positive cases showed a temporary response to *H pylori* eradication. Based on the same series of cases, we examined the value of t(1;14)(p22;q32)/IGH-BCL10 in prediction of the response of gastric MALT lymphomas to *H pylori* eradication. Of the 111 cases examined, 75 including 35 from the complete regression group and 40 from the non-responsive group, had adequate tissue specimens for evaluation of BCL10 translocation. Two cases showed strong BCL10 nuclear staining in virtually all tumour cells (stage IE1) while the other (case No 2) had stage IE disease and showed no response 12 months after *H pylori* eradication. As shown in our previous study, both cases were t(11;18)(q21;q21) negative.\(^5\)

To ascertain whether the two cases that showed strong BCL10 nuclear staining were positive for t(1;14)(p22;q32) or variant, interphase fluorescence in situ hybridisation (FISH) with BCL10 break-apart dual colour probes, IGH break-apart probes, IGH break-apart probes, and BCL10/IGH dual colour dual fusion translocation probes were performed.\(^5\) Both cases failed to show evidence of BCL10 gene break or amplification. Case No 2 showed an IGH break, but FISH with BCL10/IGH dual colour dual fusion translocation probes failed to show evidence of BCL10/IGH translocation. To further investigate these cases, we performed real time quantitative reverse transcription-polymerase chain reaction (QRT-PCR) of BCL10 mRNA. Unfortunately, adequate tissue materials were available only in case No 2. The level (ACI = 3.4) of BCL10 mRNA expression in this case was compatible with that in MALT lymphoma with t(1;14)(p22;q32) (mean 1.60 (SD 2.37)), well above that in those without the translocation (6.94 (1.72)).\(^6\)

To further assess the impact of t(1;14)(p22;q32) on the clinical behaviour of MALT lymphoma, we retrospectively reviewed the clinical presentation of 11 cases, including six from the stomach with known BCL10 involved translocation (table 1). Of these cases, nine including all those from the stomach, were at stage IE or above. Although clinical presentation and follow up data were not available in each case, three cases (Nos 1, 2 and 7) presented unusual wide dissemination,
including pleural effusion, and blood and bone marrow involvement (table 1).

Taken together, our results suggest that gastric MALT lymphomas with strong BCL10 nuclear expression or t(1;14)(p22;q32) are mostly likely resistant to *H pylori* eradication.

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**Figure 1** BCL10 immunohistochemistry. Both cases 1 and 2 show strong BCL10 nuclear staining in virtually all tumour cells, similar to that seen in tumour cells with t(1;14)(p22;q32).

**Table 1** Clinical feature of mucosa associated lymphoid tissue (MALT) lymphoma with t(1;14)(p22;q32) or variants

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age</th>
<th>Sex</th>
<th>Primary site</th>
<th>Genetic investigations</th>
<th>BCL10 involved chromosomal translocation</th>
<th>BCL10 IHC</th>
<th>Staging*</th>
<th>Dissemination</th>
<th>Clinical follow up</th>
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<td>71</td>
<td>M</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>Strong nuclear staining</td>
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<td>Perigastric lymph nodes, omentum, spleen, pleural effusion, blood and bone marrow involvement</td>
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<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
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<td>n/a</td>
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<td>Perigastric and splenic lymph nodes, pleural effusion, bone marrow involvement</td>
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<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
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<td>IIIE</td>
<td>Perigastric lymph nodes and spleen</td>
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<td>Stomach</td>
<td>Interphase FISH</td>
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<td>Strong nuclear staining</td>
<td>IIIE</td>
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<tr>
<td>7</td>
<td>63</td>
<td>F</td>
<td>Lung</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>Blood, bilateral pulmonary involvement, pleural and ascitic effusions, retroperitoneal lymph node</td>
<td>8 year low grade B cell lymphoma, then presented an aggressive clinical course presenting with lymphomatosis, pleural and ascitic effusions, partially responsive to chemotherapy, died of disease</td>
</tr>
<tr>
<td>8</td>
<td>49</td>
<td>F</td>
<td>Lung</td>
<td>Interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>Strong nuclear staining</td>
<td>IIE</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>F</td>
<td>Lung</td>
<td>Interphase FISH</td>
<td>IGH-BCL10 fusion</td>
<td>Strong BCL10 nuclear staining</td>
<td>IIE</td>
<td>No clinical evidence</td>
<td>Data on treatment not available, but patients alive without evidence of disease for 16 years</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>F</td>
<td>Breast</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>n/a</td>
<td>IIE</td>
<td>Axillary lymph nodes</td>
<td>6 cycles of CHOP therapy followed by surgery, complete remission in two year follow up</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>F</td>
<td>Breast</td>
<td>Interphase FISH</td>
<td>IGH-BCL10 fusion</td>
<td>Strong BCL10 nuclear staining</td>
<td>IIE</td>
<td>No clinical evidence</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Ann Arbor-Musshoff staging system for extranodal lymphoma; the clinical stage was likely to have been underestimated as appropriate staging was unlikely to be carried out in each of these archival cases.

IHC, immunohistochemistry; FISH, fluorescence in situ hybridisation; n/a, not available.
Conflict of interest: None declared.

References

Interferon-β plus ribavirin for patients with hepatitis C virus genotype 1: a randomised pilot trial

The rate of sustained eradication of hepatitis C virus (HCV) in response to a combination of interferon-α and ribavirin remains unsatisfactory in patients with genotype 1 infection.1 No effective alternative treatment is currently available for non-responders. Interferon-β is also a type I interferon commonly used to treat chronic HCV infection in Japan. A previous study showed that a 24 week course of therapy with interferon-β plus ribavirin resulted in sustained loss of HCV in three of nine patients with chronic hepatitis C.2 However, the efficacy and safety of interferon-β combined with ribavirin has yet to be fully evaluated.

We report the results of a randomised pilot trial comparing interferon-β plus ribavirin with interferon-α plus ribavirin in patients with HCV genotype 1 who poorly responded to interferon-α plus ribavirin. A total of 28 patients with HCV genotype 1 were given 6 MU of recombinant interferon-α2b (Schering-Plough, Kenilworth, New Jersey, USA) by intramuscular injection daily for four weeks. Twenty seven patients (16 men and 11 women; mean age 47 (±8) years) in whom HCV RNA was detected in serum on polymerase chain reaction at week 2 were included in this study and randomly assigned to receive one of two regimens from week 5. Fifteen patients continued to receive 6 MU interferon-α2b intra muscularly, given daily from week 5 to week 8, and three times weekly from week 9 to week 24 (interferon-α group). The other 12 patients were assigned to 6 MU natural interferon-β (Toray Industries Inc., Tokyo, Japan), given by intravenous injection daily from week 5 to week 8, and three times weekly from week 9 to week 24 (interferon-β group). Ribavirin (Schering-Plough) was concurrently administered at a daily dose of 600 mg to patients who weighed 60 kg or less and 800 mg to those who weighed more than 60 kg. At the time of this study, a 24 week course of interferon-α plus ribavirin was commonly used in Japan. The data were analysed according to intention to treat.

Baseline characteristics of the patients in the treatment groups were similar. At week 4 of therapy, when treatment was randomly assigned, the proportion of patients without detectable HCV RNA in serum did not differ between the interferon-α group and interferon-β groups (table 1). The proportion of patients with HCV RNA in serum was higher in the interferon-β group than in the interferon-α group at week 12, but did not differ between the groups at the end of treatment (week 24). However, 24 weeks later (week 48), the proportion of patients with a sustained virological response was significantly higher in the interferon-β group than in the interferon-α group. During treatment, neutralising antibodies to interferon were detected in two patients in the interferon-α group and no patients in the interferon-β group (table 1). The proportion of patients with HCV RNA in serum was higher in the interferon-β group than in the interferon-α group at week 12, but did not differ between the groups at the end of treatment (week 24). However, 24 weeks later (week 48), the proportion of patients with a sustained virological response was significantly higher in the interferon-β group than in the interferon-α group. During treatment, neutralising antibodies to interferon were detected in two patients in the interferon-α group and no patients in the interferon-β group (table 1).
patients given recombinant interferon-α, can cause resistance to therapy. Both interferon-α and -β bind to a common type I interferon receptor but utilise different regions of the receptor subunits for specific signalling pathways, potentially leading to distinct biological responses. An oligonucleotide array study has shown that some interferon stimulated genes are preferentially induced by interferon-β, but not by interferon-α. We thus believe that interferon-β might be beneficial for some patients who are resistant to interferon-α. A large randomised trial of peginterferon-α plus ribavirin versus interferon-β plus ribavirin for 48 weeks is being conducted in patients with HCV genotype 1 who do not have a virological response to 12 weeks of treatment with peginterferon-α and ribavirin.

In summary, a combination of interferon-β and ribavirin produced a significantly better sustained virological response than a combination of interferon-α and ribavirin in patients with HCV genotype 1 who were resistant to interferon-α plus ribavirin. Although the overall safety profiles of the two regimens were similar, the rates of treatment discontinuation and of reduction in the dose of ribavirin were lower in patients receiving interferon-β and ribavirin than in those receiving interferon-α and ribavirin.

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References

EDITOR’S QUIZ: GI SNAPSHOT

Answer
From explorative laparotomy, the pancreatic tumour involving the head and proximal body of the pancreas was judged to be resectable. Pylorus preserving proximal pancreaticoduodenectomy was performed. Histology of the tumour was consistent with a diagnosis of renal cell cancer (RCC) metastasis to the pancreas (Fig 2). Metastases were not detected in peripancreatic lymph nodes. The patient did not receive any further adjuvant therapy and was discharged from hospital without any serious perioperative morbidity.

The vast majority of pancreatic carcinomas are primary, and among these, more than 90% are of ductal origin. Solitary pancreatic masses can be classified as secondary tumours to the pancreas in only 2% of all cases. In the latter group, RCC seems to be the most common cancer. Within the last three years, 43 new cases of RCC metastases to the pancreas have been reported (Medline review). Median interval from nephrectomy to diagnosis of pancreatic metastases is 83 months, but time intervals as long as 10–20 years were also reported. Complete resection of pancreatic metastases from RCC are associated with long term survival, particularly in cases of single tumours and/or a long disease free interval.

References