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,3 and there is evidence that this nucleotide resides in a functional element.4–6 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.7

I particularly draw readers’ attention to our recent study.8 We typed this polymorphism in 1671 individuals from seven African countries, which included 20 distinct cultural groups. 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 published frequencies of lactase persistence were <25%. We found the T allele in Cameroon but it was so rare elsewhere that it cannot explain the frequency of the lactase persistence phenotype throughout Africa and we devised a statistical test to show that these results were unlikely to have been obtained by chance.

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

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Conflict of interest: None declared.

References

Authors’ reply

Dr Swallow raises a question about another DNA variant underlying adult-type hypolactasia in sub-Saharan populations and does not recommend analysis of the C/T–13910 variant as a genetic test in African and non-Northern European populations. Although the studies performed by us2–4 and others3 do not support the existence of another variant, we agree with Dr Swallow that well conducted studies are needed to confirm this. The significance of the C/T–13910 variant underlying adult-type hypolactasia was questioned in the article by Mulcare.9 Their doubt is based on several assumptions that make it difficult to evaluate the significance of the findings. These assumptions can be listed as following:

(1) It is not known whether or not the study subjects presented with adult-type hypolactasia. Thus there is a risk of wrong conclusions being drawn. It is well documented that the clinical diagnosis of adult-type hypolactasia is difficult to assess due to inaccurate diagnostic tests and variable, usually mild, symptoms.9–11 The diagnosis is usually based on indirect tests (lactose tolerance test or breath hydrogen test) whose specificity has been ideal due to the high rate (up to 30%) of false positive results.11 The specificity of the breath hydrogen test varies between 89% and 100% and sensitivity from 69% to 100%.12 There is evidence that the breath hydrogen test may be an indicator of bacterial overgrowth rather than lactose malabsorption.13–14

(2) Definition of ethnic origin was based on self definition and spoken language. As the authors themselves clarified, African populations have complex demographic histories. Many of the analysed groups were very small, hence chance may have played a role. In contrast with the findings of Mulcare,9 our genotyping data in nomadic pastoralists, Fulani–Sudanese were in agreement with the previously published figures of lactase persistence in this population.

(3) There was no statistics shown against the C/T–13910 variant, only speculation presented in Mulcare’s paper.9

When conducting phenotype-genotype correlation studies in lactase persistence/non-persistence, detailed clinical studies are essential. The studies are difficult as it is impossible to take an intestinal biopsy from a healthy subject that would give the most reliable diagnosis. Measurement of lactase activity from hospitalised patients with a clinical indication for intestinal biopsy may reflect a disease in the gut and the result obtained may not correlate with the genotype. These uncertainties should be taken into account when interpreting the genotyping results in adult-type hypolactasia.

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Conflict of interest: None declared.

References
3 Rasinpera I. A genetic test which can be used to diagnose adult-type hypolactasia in children. Gut 2004;53:1571–6.
5 Troelsen JT. An upstream polymorphism associated with lactase persistence has increased enhancer activity. Gastroenterology 2003;125:1686–94.
Conflict of interest: None declared.

was described by Mulcare and colleagues.

diagnoses (for example, based on breath comparisons of "true" diagnoses (for exam-
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without error. In fact, not only did we assume 
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within our statistical method that the n values we obtained were not as low as
we would have had we applied a naive test such as a y^2 test. Our

Author's reply

I write as the statistician on the paper by Mulcare and colleagues,1 which was criticised by Kolho and Jarvela above. I wish to correct two assertions made by Kolho and Jarvela. The first is their claim that with our statistical procedure “there is a risk of wrong conclu-
sions being drawn” because “adult-type hypolactasia is difficult to assess due to inaccurate diagnostic tests”. This would indeed be true had we applied a “naive” test (for example, a y^2 test) in which we had assumed the diagnoses of hypolactasia to be without error. In fact, not only did we assume
diagnoses occurred with error, but we did not even presume to know exactly what that level of error was. Instead, our uncer-
tainty about the true level of error was modelled in a Bayesian framework and the fact that we incorporated these additional sources of error into our method means that the p values we obtained were not as low as
would have been had we applied a naive test such as a y^2 test. Our

Reference

regarding perforated DU, as measured by surgical interventions in emergency services.1 Knowing who, among all *H pylori* infected subjects, will develop a perforated DU is therefore an important issue in treatment.

Garcia-Gonzales and colleagues2 and Zambron and colleagues,3 evaluating Spanish and Italian populations, respectively, did not find associations between single IL-1 polymorphisms and DU. Conversely, Furuta and colleagues4 found that IL-1RN allele 2 and IL-1B−511T/T were protective factors for DU in a Japanese population.

In this investigation, in accordance with previous studies,5–7 no role could be established for IL-1B−31T/T or IL-1B−31C alleles in non-complicated DU. However, IL-1B−31C and TNFA−307A carriage was negatively associated with perforated DU. Thus the same IL-1B and TNFA polymorphisms which were associated with atopy and increased gastric carcinoma risk in Caucasian populations5 were found to be inversely associated with perforated DU.

The mechanism by which overproduction of IL-1β and TNF-α due to IL-1B−31C and TNFA−307 polymorphisms protects from DU perforation may not differ from that associated with gastric carcinoma. The prevailing mechanism is probably inhibition of gastric acid production. Consequently, bacteria spread to the corpus where they accentuate the inflammation, lowering acid production, with the net effect of diminishing the risk of DU perforation.

Even though our results are biologically plausible, several factors may contribute to geographical specificities, as already seen in studies on other gastrointestinal diseases.2,8 Also, we have previously demonstrated5 in our population that the distribution of the inflammatory alleles at IL-1 loci is intermediate between Asians and Caucasians.

In conclusion, one of the questions that motivated the studies associating host cytokine polymorphisms with *H pylori* associated diseases was the possibility of explaining why some infected individuals develop gastric carcinoma, others peptic ulcer, and the majority remain otherwise without complications. These polymorphisms may play a role in the genesis of *H pylori* associated diseases but are probably insufficient to completely answer this question. Our study demonstrated independent inverse associations between IL-1B−31C and TNFA−307A polymorphic alleles and perforated DU, but no association with non-complicated DU.

### Table 1

<table>
<thead>
<tr>
<th>Genotype</th>
<th>p</th>
<th>OR 95% CI</th>
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<td>Multivariate</td>
<td>H pylori positive subjects</td>
<td>Univariate</td>
<td>Multivariate</td>
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<td>0.05−0.96</td>
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### References


### Cryptic gluten intolerance in type 1 diabetes: identifying suitable candidates for a gluten free diet

Long term exposure to gluten in coeliac,1 and coeliac disease (CD) for at least 16 years of age may induce type 1 diabetes (TID) and other autoimmune disorders. Increased prevalence of CD among diabetes and their relatives is well documented.1 Early introduction of gluten to children at high risk for TID produces TID associated islet autoantibodies.2 Similarly, in the absence of overt clinical symptoms of TID, some coeliac children produce diabetes autoantibodies in a gluten dependent manner with the net effect of diminishing the risk of DU perforation.

In this investigation, in accordance with previous studies,5–7 no role could be established for IL-1B−31T/T or IL-1B−31C alleles in non-complicated DU. However, IL-1B−31C and TNFA−307A carriage was negatively associated with perforated DU. Thus the same IL-1B and TNFA polymorphisms which were associated with atopy and increased gastric carcinoma risk in Caucasian populations5 were found to be inversely associated with perforated DU.

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</table>

Conflict of interest: None declared.

### References


www.gutjnl.com
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 Mak’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 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 intestine.

In conclusion, at risk subjects with HLA DQ2/8 may develop intestinal anti-tTG antibodies on extended exposure to gluten. Similar large scale studies are needed to prove that gluten is harmful in these subjects and confirm the benefits of a GFD.

References

Acquired factor V inhibitor associated with valproic acid use in a cirrhotic patient

Acquisition of factor V inhibitor is a rare event. The inhibitor most frequently encountered in clinical practice is directed against human factor V in vivo. Other noteworthy causes are blood transfusion, cancer, treatment with betalactam antibiotics or streptomycin, major surgery (usually in patients having received transfusions or betalactam agents), and autoimmune disorders (coeliac disease, bullous pemphigoid, Sjögren’s syndrome, Hashimoto thyroiditis) associated with congenital factor V deficiency. No case was found in nearly 20% of cases. To date, no cases have been linked to dental extraction or other minor surgeries. Anti-factor V antibodies can appear at all ages but most reported cases occurred after age 65 years. The inhibitor was discovered fortuitously in nearly 40% of cases following an isolated increase in prothrombin time. Bleeding was the main presenting sign in 60% of cases, and was life threatening in 22%.

To our knowledge, this is the first reported case of factor V inhibitor associated with valproate acid therapy. It is noteworthy that valproic acid inhibits fatty acid beta oxidation, potentially leading to life threatening microvesicular steatosis. However, our patient had no clinical or biological signs of hepatitis. Rare cases of cutaneous vasculitis or lupus-like syndrome have been linked to valproic acid or its produrg valproamide. Factor V inhibitors have occasionally been detected in patients with such syndromes, but our patient had no clinical or biological signs of an autoimmune process. Factor V inhibitor appeared after three years of treatment with valproic acid, and prothrombin

Table 1 Clones isolated from intestinal biopsies and number of anti-transglutaminase positive clones before and after 12 months of a gluten free diet in the adult diabetic, in the at risk child, and in the controls

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (y)</th>
<th>HLA</th>
<th>ICA</th>
<th>% of tTG positive clones</th>
<th>Different antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>35</td>
<td>DQ2/8</td>
<td>–</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Adult during GFD</td>
<td>2</td>
<td>DQ2/8</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Child</td>
<td>2</td>
<td>DQ2/8</td>
<td>–</td>
<td>50.3</td>
<td>5</td>
</tr>
<tr>
<td>Child During GFD</td>
<td>10</td>
<td>DQ2/8</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control subject</td>
<td>10</td>
<td>DQ2/8</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control subject</td>
<td>45</td>
<td>DQ2</td>
<td>–</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

GFD, gluten free diet; ICA, islet-cell antibodies; anti-tTG, anti-transglutaminase antibodies; Different, number of different clones determined by sequencing.

Acknowledgements

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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. Plasminogen 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 studies were small and included patients with heterogeneous manifestations. There is no consensus treatment.

In conclusion, the onset of hypocoagulability 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 cytology, the presence of an acquired factor V inhibitor and a possible drug related cause should be sought.

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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 AG, and 0.3 nmol DAG into C57Bl6 male 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 PYY3-36 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, PYY3-36 significantly inhibited feeding. AG stimulated cumulative food intake in fasted mice for up to 6 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 administered by Asakawa et al (approximately 7.5 nmol v 3 nmol per mouse) and therefore the absence of a feeding effect associated with DAG is unlikely to be explained by differences in dosing.

In conclusion, we have observed that acylated ghrelin stimulated food intake in the fasting as well as in the fed state. In contrast with the findings of Asakawa et al, there was no alteration in feeding in either the fed or fasting state following desacylated ghrelin. Our results suggest that circulating acylated ghrelin stimulates feeding independently of desacylated ghrelin.

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Conflict of interest: None declared.

References

Future use of the Glasgow alcoholic hepatitis score

We read with interest the findings of Forrest and colleagues (Gut 2005;54:1174-9) regarding their prognostic algorithm for alcoholic hepatitis, the Glasgow alcoholic hepatitis score (GAHS). The study uses robust clinical end points to develop an algorithm that has diagnostic advantages over the modified discriminant function score (DFS). We would like to discuss some of the future implications of this important study.

The overall death rate in the study was 23% at 28 days and the death rate of patients with a DFS >32 was 29% at 28 days in the derivation population. The latter figure is lower than the placebo arms of many of the randomized controlled trials of alcoholic hepatitis that range between 35% and 50%. 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 for 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/g acylated ghrelin (AG), 0.3 nmol/g desacylated ghrelin (DAG), and 0.03 nmol/g PYY3-36 (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.

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. A gradual decline in endoparasites but one argument that might explain this phenomenon. Weinstock and colleagues have successfully tested the pig whipworm, Trichuris suis, in patients with inflammatory bowel disease (IBD). However, repeated inoculation was required and concern has been raised that aberrant migration could occur. The haematophasous hookworm, Necator americanus (NA), is proposed as an alternative. We have tested if CD patients tolerate钩worm 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-reinfection, 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 but mostly inactive disease and three RDs each received a carefully measured inoculum (table 1). Subsequently, four additional CD subjects with chronic and mostly active 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 5 (mean 2.60 x 10^9/L (1.89) v week 1 0.18 x 10^9/L (0.10) v week 20 0.39 (0.20)). 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 faceal Charcot-Leydon crystals. After 20 weeks, the IBD questionnaire was improved (mean 151 (14) v 179 (20)) and the four week cumulated CDAI scores decreased (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 exposed caused no apparent adverse effect. Disease reactivation, as defined by a CDAI >150, occurred in two (CD4, CD5; table 1) after the doses of long term immune suppressive drugs had been reduced. The 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. Infection proved safe, even in immune suppressed patients. Our hope that NA would suppress autoreactivity 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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Conflict of interest: None declared.

Figure 1: Initial Crohn’s disease activity index (CDAI) score for each CD patient versus score at week 20 and at week 45 for the first five inoculated cases (mean 165 (95% confidence interval 145) v 64 (25), p = 0.132; mean 165 v 75 (29), p = 0.246).

Conflict of interest: None declared.
Strong BCL10 nuclear expression identifies gastric MALT lymphomas that do not respond to *H pylori* eradication

Approximately 75% of gastric mucosa associated lymphoid tissue (MALT) lymphomas 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 IIE or above do not respond to *H pylori* eradication. In a recent study of 111 cases of gastric MALT lymphoma, t(11;18)(q21;q21) was present in 42/63 (67%) non-responsive cases, including 26/43 (60%) at stage IIE. However, the prognostic value of staging in stage IIE 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 IIE). Paradoxically, the majority of gastric MALT lymphomas at diagnosis are at stage IIE 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 26/43 (60%) at stage IIE. In contrast, translocation was detected in only 2/48 responsive cases and the two translocation positive cases showed a temporary response to *H pylori* eradication.

To further assess the impact of BCL10 nuclear expression on the response of gastric MALT lymphoma to *H pylori* eradication, we retrospectively reviewed the clinical presentation of 11 cases, including six from the stomach with known *H pylori* infection. Unfortunately, adequate tissue materials were available only in case No 2. The level of BCL10 mRNA expression in this case was compatible with that in MALT lymphoma (Ct = 3.4) of *H pylori* eradication.

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### Table 1

<table>
<thead>
<tr>
<th>ID, age (y), sex</th>
<th>Initial inoculation trial</th>
<th>Re inoculation trial</th>
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<td></td>
<td>Time (weeks)</td>
<td>Time (weeks)</td>
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<tr>
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<td>0-4</td>
<td>5-8</td>
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<tr>
<td></td>
<td>9-12</td>
<td>13-16</td>
</tr>
<tr>
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<td>17-20</td>
<td>27</td>
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<tr>
<td></td>
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<td>35</td>
</tr>
<tr>
<td></td>
<td>39-41</td>
<td>45</td>
</tr>
</tbody>
</table>

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<th>ID, age (y), sex</th>
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<td>0-4</td>
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<td>35</td>
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<tr>
<td></td>
<td>39-41</td>
<td>45</td>
</tr>
</tbody>
</table>

L3i, n 3rd stage *N americanus* larvae inoculated percutaneously; P, prednisone n mg/day; A, azathioprine n mg/day; M, methotrexate n mg/week.
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.

**Acknowledgements**

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---

### 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>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>67</td>
<td>M</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH, molecular cloning</td>
<td>t(1;14)(p22;q32)</td>
<td>Strong nuclear staining</td>
<td>IV E</td>
<td>Perigastric lymph nodes, omentum, spleen, pleural effusion, blood</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q32)</td>
<td>n/a</td>
<td>IV E</td>
<td>Perigastric and splenic hilar lymph nodes, pleural involvement, bone marrow involvement? Perigastric lymph nodes and spleen</td>
<td>4 cycles of MCP chemotherapy, partial remission, alive at two year follow up</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>M</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;2)(p22;q12)</td>
<td>Strong nuclear staining</td>
<td>III E</td>
<td>Perigastric and mesenteric lymph nodes</td>
<td>Chemotherapy with chlorambucil, complete remission in three year follow up</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>F</td>
<td>Stomach</td>
<td>Interphase FISH</td>
<td>Yes</td>
<td>Strong nuclear staining</td>
<td>IV E</td>
<td>Perigastric mesenteric and splenic lymph nodes</td>
<td>Low dose chlorambucil chemotherapy, complete remission at 1.5 year follow up</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>M</td>
<td>Stomach</td>
<td>Interphase FISH</td>
<td>Yes</td>
<td>Strong nuclear staining</td>
<td>IV E</td>
<td>Lung</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>n/a</td>
<td>n/a</td>
<td>Stomach</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q22)</td>
<td>Strong nuclear staining</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<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>III E</td>
<td>Perigastric lymph nodes, omentum, spleen, pleural effusion, retroperitoneal lymph node</td>
<td>8 year low grade B cell lymphoma, then presented an aggressive clinical course presenting with lymphocytosis, pleural and ascitic effusions, partially responsive to chemotherapy, died of disease</td>
</tr>
<tr>
<td>8†</td>
<td>57</td>
<td>F</td>
<td>Lung</td>
<td>Karotyping, interphase FISH</td>
<td>t(1;14)(p22;q12)</td>
<td>Strong nuclear staining</td>
<td>I IV</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>F</td>
<td>Lung</td>
<td>Karotyping, interphase FISH</td>
<td>IGH-BCL10 fusion</td>
<td>Strong nuclear staining</td>
<td>I IV</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;q12)</td>
<td>n/a</td>
<td>IV E</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 nuclear staining</td>
<td>I IV</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-2b (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 at 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-2b intramuscularly, 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 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 in 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 in 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 in 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 in 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.
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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Conflict of interest: None declared.

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.1 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.2 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.3

References
Future use of the Glasgow alcoholic hepatitis score

I N Guha and W M Rosenberg


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