Background and aims: Hepatic concentrations of the powerful vasoconstrictor and fibrogen endothelin 1 (ET-1) and its receptors increase in human and experimental cirrhosis, suggesting a major role for ET-1 in the pathology of chronic liver disease. We investigated whether ET-1 receptor antagonism, after the development of fibrosis and cirrhosis, arrests/reverses the progression of chronic liver disease.

Methods: Chronic liver injury was induced in rats by carbon tetrachloride (CCl4) treatment (0.15 ml/kg intraperitoneally twice a week) in conjunction with phenobarbital in drinking water (0.4 g/l) for four (group 1: fibrosis) and eight (group 2: cirrhosis) weeks. Rat were then treated concurrently with the ET-1 receptor antagonist TAK-044 (10 mg/kg/day) and CCl4/phenobarbital for a further four weeks.

Results: Histopathological examination revealed significant arrest of progression to cirrhosis in group 1 and reversal of cirrhosis in group 2 rats. TAK-044 treatment caused significant amelioration of portal hypertension, systemic hypotension, and liver injury (reduced activities of serum aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase), and improved hepatic synthetic capacity (increased serum albumin concentration) in both groups of rats relative to vehicle treated rats. TAK-044 treatment reduced collagen synthesis, as evidenced by decreased hepatic hydroxyproline content, mRNA expression of collagen-α type I, and tissue inhibitors of matrix metalloproteinases 1 and 2, and mRNA and protein expression of a potent fibrogenic cytokine, transforming growth factor β1.

Conclusions: The results emphasise the role of ET-1 in the development of cirrhosis and strongly suggest that blockade of its actions can be a rational therapy for chronic liver disease and its complications.
Reversal of cirrhosis by TAK-044

**Figure 1** Effect of carbon tetrachloride (CCl₄) and TAK-044 treatment on hepatic endothelin 1 (ET-1) and preproET-1 mRNA. Rats were treated with CCl₄ for 4, 8, and 12 weeks. During CCl₄ treatment between four and eight weeks and eight and 12 weeks, 50% of the rats each received TAK-044 or saline. Hepatic ET-1 content and mRNA expression of preproET-1 were determined in tissue samples from three rats in each group, each assay performed in triplicate. Details are described in the methods section. (A) Hepatic ET-1 concentration. (B) Hepatic preproET-1 mRNA expression normalised with respect to that of β-actin with equal amounts of cDNA used in the polymerase chain reaction. *p<0.05. **p<0.01 versus control; ††p<0.01 versus CCl₄.

**Materials and Methods**

**Induction of liver cirrhosis**

The experimental protocols were approved by the University of Pittsburgh Institutional Animal Care and Use Committee according to the guidelines of the National Institutes of Health. Chronic liver injury was induced in male Sprague-Dawley rats (230–250 g), as described previously, by CCl₄ administration (0.15 ml/kg intraperitoneally twice a week) in conjunction with phenobarbital (0.4 g/l) in drinking water. Control rats received injection of the carrier (peanut oil) and phenobarbital anaesthesia, a PE-50 catheter was inserted into the femoral artery to monitor arterial blood pressure. The hepatic trigone was exposed via laparotomy and the portal vein was skeletonised. The intestines and abdominal cavity were covered with warm saline soaked sponges during the entire experimental period. A 23 gauge needle in a PE-50 catheter was inserted into the portal vein to measure portal pressure. After stable recordings of arterial and portal venous pressure, blood was drawn from the femoral artery. The liver was excised, washed in ice cold phosphate buffered saline, and snap frozen in liquid nitrogen, after storing a slice of left lateral lobe in 10% buffered formalin.

**Determination of ET-1 and its receptors**

ET-1 was extracted and its concentration measured by ELISA (Peninsula Laboratories, Sunnyvale, California, USA). Hepatic ET-1 receptors were determined by saturation and competition binding assays, essentially as described previously.

**Biochemical parameters**

Serum total protein, albumin, bilirubin, γ-glutamyl transferase (γ-GT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were estimated using a kit from Stanbio Laboratory (Boerne, Texas, USA).

**Morphology and scoring of liver cirrhosis**

Sections of 4 μm thickness were prepared from formalin fixed liver slices embedded in paraffin and stained with haematoxylin-eosin and Masson’s trichrome stain. Liver pathology was graded by VMS in a blinded manner using an established scoring system, as described previously; a score of “5” was considered as complete cirrhosis and “0” as normal. Sections were also treated with anti-α-smooth muscle actin (SMA) antibody (Dako, Carpinteria, California, USA;
smooth muscle actin-1A4) to determine activated stellate cells/myofibroblasts, as described previously.26-29

Determination of RNA expression
Relative mRNA expressions of preproET-1, ET-1 receptors, collagen α type I, and TGF-β1 were determined by semiquantitative reverse transcriptase-polymerase chain reaction (RT-PCR), essentially as described previously.26 The same amount of cDNA was used to determine expression of β-actin mRNA for normalisation. The number of PCR cycles employed was in the linear range of the reaction for each product.

Quantitative real time PCR (QRT-PCR) was performed for mRNA expression of tissue inhibitors of metalloproteinases (TIMPs) using a Prism 7700 Sequence Detector from Applied Biosystems Inc. (ABI, Foster City, California, USA) with data acquisition and analysis by Sequence Detector software v. 1.7a. Assay of cDNA levels was performed using Taqman Universal Master Mix (ABI) and the primer probe sets from Invitrogen (Rockville, Maryland, USA). Primers were designed using Primer Express software (ABI). Threshold cycle numbers were determined for TIMP-1 and TIMP-2 and corrected using the equivalent data for β-actin.

Determination of hydroxyproline and collagenase
Hepatic hydroxyproline content was measured as described previously using the chloramine T/p-dimethylaminobenzaldehyde procedure.26-30

For determination of collagenase, the liver was homogenised in 0.3 M Tris HCl buffer (pH 7.4) and centrifuged at 200 rpm for five minutes. Enzyme activity was determined in the supernatant with an assay kit from Chemicon International Inc (Temecula, California, USA) which measures matrix degrading metalloproteinases (MMP)-1, MMP-8, and MMP-13, but not gelatinases (MMP-2).

Determination of collagenase
Hepatic hydroyproline content was measured as described previously using the chloramine T/p-dimethylaminobenzaldehyde procedure.26-30

Results are expressed as mean (SEM). Physiological, histopathological, and biochemical findings represent averages of seven rats (CCl4 or CCl4+TAK-044 treatment) and three rats (control) for each time point. Results of molecular assays represent averages of samples from at least three rats in each group, each analysed in duplicate or triplicate. Statistical significance was derived by the non-parametric Mann-Whitney two tailed variance test using the SPSS program to determine significance between multiple groups. A p value of <0.05 was considered statistically significant.

RESULTS
Endothelin and its receptors
Hepatic concentrations of ET-1 increased by threefold, fourfold, and sevenfold, respectively, after 4, 8, and 12 weeks of CCl4 treatment (fig 1A); similar increases were also observed in the preproET-1 mRNA transcript (figs 1B, 2A). ET-1 concentration was 40% and 20% less in TAK-044 treated rats than in saline treated rats at eight and 12 weeks, respectively.

ETA receptor density increased by 40%, 60%, and 80% after 4, 8, and 12 weeks of CCl4 treatment, respectively (fig 3A). ETB receptor density increased by 1.5-fold at four weeks, and 2.0-fold at eight and 12 weeks. During CCl4 treatment, 50% of rats each received TAK-044 or saline. Hepatic ETA receptor (A) and ETB receptor (C) densities were determined by competition binding analysis and relative mRNA expression by semiquantitative reverse transcriptase-polymerase chain reaction in tissue samples from three rats in each group, each assay performed in triplicate. mRNA expression of respective receptors normalised with respect to that of β-actin are shown in (B) and (D). *p<0.05, **p<0.01, ***p<0.001 versus control; tp<0.05 versus CCl4.
and 12 weeks did not alter \( \text{ET}_A \) or \( \text{ET}_B \) receptor density. \( \text{ET}_A \) receptor mRNA increased by 50% at four weeks, and by 70–90% at eight and 12 weeks of CCl\(_4\) treatment (figs 2B, 3B); \( \text{ET}_B \) mRNA expression increased by 25%, 85%, and 110% at 4, 8, and 12 weeks of CCl\(_4\) treatment, respectively (figs 2B, 3D). \( \text{ET}_A \) as well as \( \text{ET}_B \) mRNA expression was approximately 20% less in TAK-044 treated rats than in saline treated rats both at eight and 12 weeks (figs 2B, 3B, 3D).

### Table 1 General characteristics of the study animals

<table>
<thead>
<tr>
<th></th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CCl(_4)</td>
<td>Control</td>
<td>CCl(_4)</td>
<td>TAK + CCl(_4)</td>
</tr>
<tr>
<td>Body wt (g)</td>
<td>360 (4)</td>
<td>270 (22)*</td>
<td>390 (12)</td>
<td>313 (16)*</td>
<td>332 (9)*</td>
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<tr>
<td>Spleen wt (g)</td>
<td>0.83 (0.03)</td>
<td>0.77 (0.1)</td>
<td>0.86 (0.05)</td>
<td>1.5 (0.21)*</td>
<td>1.17 (0.03)*</td>
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<tr>
<td>Ascites (g)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11 (3)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Serum</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5 (3)</td>
<td>86 (15)</td>
</tr>
<tr>
<td>Protein (g/dl)</td>
<td>7.13 (0.1)</td>
<td>6.43 (0.1)**</td>
<td>7.1 (0.1)</td>
<td>6.5 (0.12)*</td>
<td>6.7 (0.3)</td>
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<tr>
<td>Albumin (g/dl)</td>
<td>4.73 (0.03)</td>
<td>4.34 (0.06)*</td>
<td>4.7 (0.1)</td>
<td>3.99 (0.17)*</td>
<td>4.38 (0.11)</td>
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<tr>
<td>Bilirubin (mg/dl)</td>
<td>2.85 (0.1)</td>
<td>3.5 (0.16)*</td>
<td>2.83 (0.08)</td>
<td>3.62 (0.1)*</td>
<td>3.02 (0.14)</td>
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<tr>
<td>LDH (U/dl)</td>
<td>284 (17)</td>
<td>424 (24)*</td>
<td>268 (19)</td>
<td>397 (17)*</td>
<td>296 (13)†</td>
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<tr>
<td>ALT (U/dl)</td>
<td>19 (1)</td>
<td>54 (3)***</td>
<td>18 (1)</td>
<td>306 (22)***</td>
<td>172 (12)***†</td>
</tr>
<tr>
<td>AST (U/dl)</td>
<td>47 (1)</td>
<td>113 (10)***</td>
<td>71 (6)</td>
<td>251 (15)***</td>
<td>184 (10)***†</td>
</tr>
<tr>
<td>ALP (U/dl)</td>
<td>54 (2)</td>
<td>60 (3)***</td>
<td>53 (2)</td>
<td>181 (8)***</td>
<td>146 (10)***†</td>
</tr>
<tr>
<td>c-GT (U/dl)</td>
<td>1.7 (0.3)</td>
<td>14.0 (1.3)**</td>
<td>1.3 (0.1)</td>
<td>17.2 (1.2)***</td>
<td>7.1 (0.6)***†</td>
</tr>
</tbody>
</table>

Rats were treated with vehicle or carbon tetrachloride (CCl\(_4\)) for 4, 8, and 12 weeks. In the last two groups, 50% of rats each were treated with TAK-044 or saline between four and eight weeks or eight and 12 weeks. Various determinations were made, as described in the methods section. Results are means (SEM) of three control, seven CCl\(_4\) treated, and seven TAK-044 + CCl\(_4\) treated rats.

For biochemical parameters, each assay was performed in duplicate for each rat. LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; c-GT, \( \gamma \)-glutamyl transferase.

\* \( p < 0.05 \), ** \( p < 0.01 \), *** \( p < 0.001 \) versus control; † 0.05, †† 0.01 versus CCl\(_4\).
General characteristics (table 1)

The body weight of CCl4 treated rats was 25%, 20%, and 30% lower than that of paired controls at 4, 8, and 12 weeks, respectively. TAK-044 treatment of rats receiving CCl4 improved body weight by 5% and 23%, respectively, at eight and 12 weeks. The weight of the spleen increased significantly after eight and 12 weeks of CCl4 treatment; TAK-044 prevented the increase in spleen weight at eight weeks to a small extent but not at 12 weeks. All of the CCl4 treated rats developed ascites at eight and 12 weeks; the volume of ascites was nearly eight times greater at 12 weeks than at eight weeks of CCl4 treatment. TAK-044 treatment caused 50% and 75% reduction in ascites at eight and 12 weeks, respectively. The synthetic capacity of the liver was reduced in CCl4 treated rats, as indicated by decreased serum albumin, which was normalised by TAK-044 treatment. Liver injury, as estimated by serum LDH, AST, ALT, and γ-GT, also improved significantly in TAK-044 treated rats. No mortality occurred in TAK-044+CCl4 treated rats, and mortality was less than 5% in saline+CCl4 treated rats at eight and 12 weeks of treatment.

Histological assessment

Figure 5 shows normal hepatic architecture in control rats. Liver fibrosis was evident, with the beginning of septum formation after four weeks of CCl4 treatment (fig 4B). In control livers, α-SMA positive cells were present in portal veins and hepatic arteries (fig 5A) but staining of cells in the fibrous areas indicate the presence of activated hepatic stellate cells/myofibroblasts. (C) Eight weeks of CCl4 treatment with saline treatment between four and eight weeks. Abundant α-SMA staining in the fibrous areas indicate the presence of activated hepatic stellate cells/myofibroblasts. (D) Eight weeks of CCl4 treatment with concurrent TAK-044 treatment between four and eight weeks. The number of α-SMA positive cells in the fibrous areas is reduced significantly. (E) Twelve weeks of CCl4 treatment with saline treatment between eight and 12 weeks. Cells in wide fibrous septa facing liver parenchyma as well as intralobular cells express α-SMA. (F) Twelve weeks of CCl4 treatment with concurrent TAK-044 treatment between eight and 12 weeks. Number of α-SMA positive cells is significantly decreased. Original magnification ×200.

Figure 6 shows histopathological assessment of cirrhotic livers after four weeks of carbon tetrachloride (CCl4) treatment, eight weeks of CCl4 treatment with four weeks of concurrent saline or TAK-044 treatment, and 12 weeks of CCl4 treatment with four weeks of concurrent saline or TAK-044 treatment. Scores were rated between “5” (cirrhotic) and “0” (normal morphology). Results are means (SEM) of three CCl4 treated rats at four weeks, and seven rats each for CCl4+saline or CCl4+TAK-044 treatment at eight and 12 weeks. *p<0.02 versus control. The body weight of CCl4 treated rats was 25%, 20%, and 30% lower than that of paired controls at 4, 8, and 12 weeks, respectively. TAK-044 treatment of rats receiving CCl4 improved body weight by 5% and 23%, respectively, at eight and 12 weeks. The weight of the spleen increased significantly after eight and 12 weeks of CCl4 treatment; TAK-044 prevented the increase in spleen weight at eight weeks to a small extent but not at 12 weeks. All of the CCl4 treated rats developed ascites at eight and 12 weeks; the volume of ascites was nearly eight times greater at 12 weeks than at eight weeks of CCl4 treatment. TAK-044 treatment caused 50% and 75% reduction in ascites at eight and 12 weeks, respectively. The synthetic capacity of the liver was reduced in CCl4 treated rats, as indicated by decreased serum albumin, which was normalised by TAK-044 treatment. Liver injury, as estimated by serum LDH, AST, ALT, and γ-GT, also improved significantly in TAK-044 treated rats. No mortality occurred in TAK-044+CCl4 treated rats, and mortality was less than 5% in saline+CCl4 treated rats at eight and 12 weeks of treatment.

Histological assessment

Figure 4A shows normal hepatic architecture in control rats. Liver fibrosis was evident, with the beginning of septum formation after four weeks of CCl4 treatment (fig 4B). In control livers, α-SMA positive cells were present in portal veins and hepatic arteries (fig 5A) but staining of cells in the fibrous areas indicate the presence of activated hepatic stellate cells/myofibroblasts. (C) Eight weeks of CCl4 treatment with saline treatment between four and eight weeks. Abundant α-SMA staining in the fibrous areas indicate the presence of activated hepatic stellate cells/myofibroblasts. (D) Eight weeks of CCl4 treatment with concurrent TAK-044 treatment between four and eight weeks. The number of α-SMA positive cells in the fibrous areas is reduced significantly. (E) Twelve weeks of CCl4 treatment with saline treatment between eight and 12 weeks. Cells in wide fibrous septa facing liver parenchyma as well as intralobular cells express α-SMA. (F) Twelve weeks of CCl4 treatment with concurrent TAK-044 treatment between eight and 12 weeks. Number of α-SMA positive cells is significantly decreased. Original magnification ×200.
Reversal of cirrhosis by TAK-044

During CCl4 treatment between four and eight weeks or eight and 12 weeks, 50% of rats each received TAK-044 or saline. A significant amelioration of the pathology by TAK-044 after histopathology scores depicted in a bar graph (fig 6) shows concurrent TAK-044 treatment between four and eight weeks reduced the development of fibrosis (fig 4D) which was caused marked reduction of fibrosis (fig 4F) which was associated with marked reduction in the number α-SMA positive cells (fig 5F and fig 5E). A summary of the histopathology scores depicted in a bar graph (fig 6) shows significant amelioration of the pathology by TAK-044 after both eight weeks and 12 weeks of CCl4 treatment.

**Collagen mRNA, hydroxyproline, collagenase, and TIMP mRNA**

mRNA expression of collagen α type I increased respectively by 4, 9, and 13-fold at 4, 8, and 12 weeks of CCl4 treatment (fig 7). mRNA expression of collagen I in rats treated concurrently with TAK-044 and CCl4 was 50% less than in saline+CCl4 treated rats at both eight and 12 weeks (fig 7).

Figure 7: Effect of carbon tetrachloride (CCl4) and TAK-044 treatment on collagen α type I mRNA. Rats were treated with CCl4 for 4, 8, and 12 weeks. During CCl4 treatment between four and eight weeks or eight and 12 weeks, 50% of rats each received TAK-044 or saline. (A) Representative gel showing mRNA expression of collagen α type I and β-actin using the same amount of cDNA in reverse transcriptase-polymerase chain reaction. (B) Bar graph showing mRNA expression of collagen α type I normalised with respect to that of β-actin, representing averages from duplicate determinations from three rats in each group. *p<0.01, **p<0.001 versus control; †p<0.05, ††p<0.01 versus CCl4.

CCl4 treatment increased hepatic hydroxyproline by twofold at four weeks and by 10-fold at eight and 12 weeks (fig 8). A significant (35%) reduction in hydroxyproline occurred in rats receiving TAK-044 relative to those receiving saline between four and eight weeks as well as eight and 12 weeks of CCl4 treatment. Hepatic collagenase activity increased by 64% at four weeks and by twofold at eight and 12 weeks of CCl4 treatment (fig 9). Concurrent TAK-044 and CCl4 treatment caused 30% and 20% decreases in collagenase activity at eight and 12 weeks, respectively (fig 9).

Matrix metalloproteinases (MMPs) are important in liver fibrogenesis and its resolution but we were unable to obtain any conclusive evidence for changes in expression of MMP-1 and MMP-13 in CCl4 and TAK-044+CCl4 treated rat livers (not shown). TIMP-1 and TIMP-2 modulate fibrosis by inhibiting MMPs.51-53 QRT-PCR demonstrated 33%, 300%, and 150% increases in TIMP-1 mRNA, and 65%, 260%, and 260%

Figure 8: Effect of carbon tetrachloride (CCl4) and TAK-044 treatment on hepatic hydroxyproline content. Rats were treated with CCl4 for 4, 8, and 12 weeks. During CCl4 treatment between four and eight weeks or eight and 12 weeks, 50% of rats each received TAK-044 or saline. Values are means (SEM) of three control and three CCl4 treated rat livers (four weeks) and three control, seven CCl4+saline treated, and seven CCl4+TAK-044 treated rat livers at eight and 12 weeks, each sample assayed in triplicate. *p<0.01, **p<0.001 versus control; †p<0.05 versus CCl4.

Figure 9: Effect of carbon tetrachloride (CCl4) and TAK-044 treatment on collagenase activity. Rats were treated with CCl4 for 4, 8, and 12 weeks. During CCl4 treatment between four and eight weeks or eight and 12 weeks, 50% of rats each received TAK-044 or saline. Collagenase activity was determined as described in the methods section. Values are means (SEM) of three control and three CCl4 treated rat livers (four weeks) and three control, seven CCl4+saline treated, and seven CCl4+TAK-044 treated rat livers at eight and 12 weeks, each sample assayed in triplicate. *p<0.05, **p<0.01 versus control; †p<0.05 versus CCl4.
Mean arterial and portal venous pressure

Mean arterial pressure (MAP) was not significantly different between control and CCl₄ treated rats at four weeks (fig 12A). At both eight and 12 weeks of CCl₄ treatment, MAP decreased by nearly 30% compared with paired controls. Between four and eight weeks of concurrent TAK-044 treatment, MAP tended to rise but the change did not reach statistical significance. On the other hand, significant improvement (almost to normal levels) in MAP occurred on TAK-044 treatment between eight and 12 weeks (fig 12A).

Portal venous pressure increased significantly in rats treated with CCl₄ for eight and 12 weeks (100–150% increase), indicative of portal hypertension (fig 12B). In both groups, TAK-044 reduced portal hypertension remarkably, with portal pressure being only 30–50% higher than in control rats.

DISCUSSION

The profound haemodynamic and metabolic effects of ET-1 in the normal liver,1 15 progressive increase in the ET-1 system from initiation of CCl₄ induced liver injury to development of cirrhosis,36 and upregulation of the ET-1 system in experimental biliary cirrhosis37 and human cirrhosis of various aetiologies38 39 indicate that ET-1 is a major factor in the pathogenesis and complications of the chronic...
Rats were treated with CCl₄ for 4, 8, and 12 weeks. During CCl₄ treatment, mean arterial pressure (MAP) and portal pressure of cirrhotic rats. CCl₄ detoxification of TAK-044 concurrent with CCl₄ arrests progression of fibrosis to cirrhosis and reverses cirrhosis. Activated hepatic stellate cells and portal myofibroblasts accumulating in fibrous areas are primarily responsible for excessive deposition of extracellular matrix (ECM) components and architectural distortion; both cell types express α-SMA. We observed α-SMA positive cells both within the fibrous septa and at the interface between the parenchyma and fibrous tissue at four and eight weeks of CCl₄ treatment. In the wide fibrous septa, observed at 12 weeks of CCl₄ treatment, α-SMA positive cells were found predominantly at the interphase, and a substantial number within the parenchyma. With increased deposition of the ECM, cells likely migrate to the outer region of the fibrous tissue. Rats treated with TAK-044 had substantially decreased numbers of α-SMA positive cells and fibrous tissue deposition, morphological findings concordant with the beneficial effects of the inhibitor.

ET-1 likely mediates hepatic fibrogenesis by stimulating the synthesis of and/or by influencing the activities of mediators such as TGF-β, platelet derived growth factor, and tumour necrosis factor α, all of which can cause activation, proliferation, and fibrogenesis in stellate cells. mRNA and protein expression of the powerful fibrogenic cytokine TGF-β1 was reduced in TAK-044 treated rats. Type I collagen is a major component of the ECM deposited in liver fibrosis, and TAK-044 both prevented the increase in collagen type I mRNA expression during CCl₄ treatment between four and eight weeks, and reduced its expression remarkably at 12 weeks. TAK-044 also caused marked reduction in hepatic hydroxyproline content. Together, these results suggest that ET-1 plays an important role in fibrogenesis by modulating TGF-β1 and collagen synthesis. However, such effects of ET-1 may be indirect as ET-1 stimulates synthesis of collagen and TGF-β1 in normal but not in activated stellate cells.

Increased deposition of collagen in the fibrotic liver is a result of its enhanced synthesis and reduced degradation. Paradoxically, hepatic collagenase activity measured in vitro is significantly increased in CCl₄ treated rats (present study, and also Okazaki and Maruyama and Montfort and Perez-Tamayo) and decreased by TAK-044 treatment. Either collagen synthesis far exceeds its degradation or collagenase activity measured in vitro is strongly suppressed in vivo by TIMPs which are increased in the fibrotic liver. The rapid decrease in TIMP expression seen during spontaneous recovery from CCl₄ induced advanced fibrosis likely increases collagenase activity in vivo, reversing ECM deposition. This is consistent with our finding of decreased TIMP-1 and TIMP-2 expression in rats receiving TAK-044.

The present 58% and 60% decreases in portal hypertension in TAK-044 treated rats at eight and 12 weeks, respectively, are combinations of the resolution of fibrosis and inhibition of the contractile component. Acute infusion of TAK-044 in cirrhotic rats affects only the contractile component, giving a more modest (20%) decrease in portal hypertension. Both ET₁ receptor subtypes appear to be critical in the haemodynamic component of portal hypertension, with sinusoidal and presinusoidal constriction caused by ETₐ and ETₐ receptors, respectively. Mixed ETA+ETB antagonists reduce portal hypertension in cirrhotic rats but do not affect portal pressure in normal rats. Thus the haemodynamic component of portal hypertension in cirrhosis includes major participation of the upregulated ET₁ and ET₂ receptors, and increased endogenous ET₁.

Decreased MAP in cirrhosis is attributed to increased production of several vasodilatory mediators, including NO and PAF. In the present study, MAP was found to increase in rats treated with TAK-044. Therefore, inability of the acute treatment with ET₁ receptor antagonist to improve systemic hypertension suggests requirement of long term antagonism of ET₁ receptors in the liver, and possibly in the systemic vasculature. As ET₁ antagonist is unable to alter arterial pressure in cirrhotic rats, our results also suggest that ET₁ plays a primary role in systemic hypotension in cirrhosis. Indeed, ET₂a has been shown to stimulate the synthesis of NO and PAF, respectively, in endothelial and Kupffer cells; the latter effect is augmented in cirrhosis. ET₂a on the other hand, seems to limit systemic hypotension as intraarterial infusion of the ET₂a antagonist BQ-123 caused a greater increase in forearm blood flow in cirrhotic patients compared with normal volunteers.

Cirrhosis causes upregulation of the hepatic ET-1 system in both rats and humans. Both ETA and ETB receptors appear to play important roles in the development and complications of cirrhosis, and review of the literature suggests that simultaneous antagonism of both receptor subtypes is necessary to achieve beneficial effects. Rockey and Chung found that essentially concurrent administration of the mixed antagonist bosentan and CCl₄ (bosentan from day 0, CCl₄ from day 2) significantly decreased hepatic
collagen mRNA (stellate cells) and protein (liver section) at day 22. This short term (~3 week) study also showed that bosentan inhibited activation (measured as α-SMA expression) of stellate cells. In contrast, a long term experiment used CCl4/phenobarbital from week 0 and RO48-5695, a mixed ETA/ETB inhibitor optimised from bosentan, from week 8. At week 17, cirrhotic rats had significantly elevated ALT, γ-GT, bilirubin, portal pressure, and significantly decreased MAP and serum proteins. Hepatic histology also showed cirrhotic changes. However, there was no significant normalisation of any parameter with RO 48-5695 treatment. The effectiveness of RO 48-5695 in vivo has been demonstrated in experimental models of hypercholesterolaemia,11,25 and inflammatory bowel disease and gastric ulcerogenesis,64 but RO 48-5695 is also ineffective in the reduced renal mass model of glomerular sclerosis.65 Obviously, a comparative study of TAK-044 and RO 48-5695 in cirrhosis would be of interest.

In summary, simultaneous antagonism of both ET-1 receptor subtypes slows the progression of fibrosis to cirrhosis, and reverses cirrhosis. In addition, TAK-044 can reduce portal hypertension and systemic hypotension, major complications that are almost always present in cirrhosis. These observations, and the similarity between the changes in the hepatic ET-1 system in human and experimental cirrhosis, suggest that mixed ET A/ET B antagonists such as TAK-044 have strong therapeutic potential in chronic liver disease.

ACKNOWLEDGEMENTS

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REFERENCES


Editor’s Quiz: GI Snapshot

Answer

From question on page 1000

During menses, colonoscopy showed a large multilobulate polyp (3.5 cm in diameter) of the sigmoid colon with a hyperaemic and friable mucosa (fig 1). Histological examination showed a normal mucosa with the presence of some branched crypts and marked inflammation in the lamina propria.

During the intermenstrual period (on the eighth day of the cycle), polyp size had decreased; its surface appeared only slightly lobulate without friability and with hyperaemia, which was reduced at two red spots (fig 2). Histopathological evaluation showed the presence of endometriotic foci in the context of a mucosa containing branched crypts.

The patient was submitted to a gynaecological examination which was found to be normal. Pelvic and vaginal ultrasounds did not show evidence of endometriotic lesions. Magnetic resonance imaging detected a 1.8 cm area with a T1 hyperintense and T2 hypointense signal in the sigmoid wall.

Medical treatment with leuprolide acetate depot, a gonadotropin releasing hormone agonist (GnRH-a) (3.75 mg intramuscularly every four weeks for three months) was started. Abdominal pain and bloody diarrhoea promptly disappeared. At the four month follow up she was still free of symptoms and anaemia had reversed (haemoglobin 12.3 g/dl). At the one year follow up, colonoscopy showed a flat lesion without hyperaemia or friability at the site of the endometriotic polyp. Histological examination of multiple biopsies was normal and a magnetic resonance imaging showed complete disappearance of the previously detected lesion. After 18 months of follow up, the patient remains completely asymptomatic.

Endometriosis is defined as the presence of endometrial tissue in sites other than the uterus. The rectosigmoid is the most frequently involved site. Heterotopic endometrium generally adheres to serosal surfaces and may invade the bowel wall. However, appearance as a polyp is rarely reported. Infiltration of the mucosa is uncommon and therefore the endoscopic biopsy may not be diagnostic. The variable appearance on endoscopy is related to the cyclic endometrial tissue changes.

Surgical resection is indicated for massive rectal bleeding or obstruction but the role of surgery is less clear when the clinical course is not life threatening. Medical treatment with a GnRH-a is commonly used in pelvic endometriosis but studies on its efficacy in intestinal endometriosis are still lacking.

To our knowledge this is the first case reported in the literature showing that an endometriotic colonic polyp may be successfully treated by medical therapy with a GnRH-a. This case further illustrates that endometriosis may appear as a colonic polyp and that polypectomy is not curative.

REFERENCES

LETTERS

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An alternative to prophylactic colectomy for colon cancer prevention in HNPCC syndrome
The French Ad-Hoc Committee on Hereditary Non-polyposis Colon Cancer (HNPCC) management meeting on behalf of the French Health Minister has recently released its statement. The report on prophylactic colorectal resections for HNPCC related adenocarcinomas (Gut 2003;52:1752–5) is in contrast with ours and we would like to discuss this point.

Use of decision analysis models is a smart approach in dealing with such complex situations. However, life expectancy related to the occurrence of metachronous colorectal carcinoma should be balanced against the negative impact on quality of life in the case of prophylactic extensive colorectal resections. Thus quality adjusted life expectancy, integrating the individual patient’s choice, might be a more accurate approach. Comprehensive, fair, and loyal information of what the patient can hope for is mandatory (that is, what the patient can hope for is mandatory). de Vos tot Nederveen Cappel and colleagues’ statement. de Vos tot Nederveen Cappel and colleagues’ statement. de Vos tot Nederveen Cappel and colleagues’ statement.

We read with great interest the paper “Pro-hepcidin: expression and cell specific localisation in the liver and its regulation in hereditary haemochromatosis, chronic renal insufficiency, and renal anaemia” (Gut 2004;53:735–43).

We have two observations. Firstly it was shown that pro-hepcidin and hepcidin were colocalised within the liver and in Hep-G2 cells. However, it was not possible, using serum ELISA, to identify the C terminus of hepcidin (the mature form of hepcidin 29). Is it possible that the functional N terminal antibody used for serum analyses represents non-functional precursor amino acids and not the active molecule? This might explain the lack of correlation between iron parameters and hepcidin seen from the patient data.

Furthermore, the authors comment on the paradoxically elevated levels of pro-hepcidin in patients with chronic renal insufficiency on erythropoietin (EPO). All of these patients were reported to have normal haemoglobin levels. Previous studies have shown that EPO inhibits hepatic hepcidin expression. The authors speculate that the elevated circulating hepcidin levels may reflect reduced renal clearance of the molecule in these patients. However, other studies have suggested chronic inflammatory diseases are associated with elevated serum hepcidin (in animal models) and urine hepcidin in humans. Another possibility, therefore, is that patients have elevated iron stores, in relation to chronic disease, and this may have a direct effect on hepcidin release. It would be interesting to know the iron metabolic parameters in these patients, as obviously haemoglobin in isolation is not an accurate measure of iron stores. It is unclear from the paper whether fig 8 represents data from patients with haemochromatosis (HFE). All of these patients were reported to have normal haemoglobin levels. Previous studies have shown that EPO inhibits hepatic hepcidin expression. The authors speculate that the elevated circulating hepcidin levels may reflect reduced renal clearance of the molecule in these patients. However, other studies have suggested chronic inflammatory diseases are associated with elevated serum hepcidin (in animal models) and urine hepcidin in humans. Another possibility, therefore, is that patients have elevated iron stores, in relation to chronic disease, and this may have a direct effect on hepcidin release. It would be interesting to know the iron metabolic parameters in these patients, as obviously haemoglobin in isolation is not an accurate measure of iron stores. It is unclear from the paper whether fig 8 represents data from patients with haemochromatosis (HFE). All of these patients were reported to have normal haemoglobin levels. Previous studies have shown that EPO inhibits hepatic hepcidin expression. The authors speculate that the elevated circulating hepcidin levels may reflect reduced renal clearance of the molecule in these patients. However, other studies have suggested chronic inflammatory diseases are associated with elevated serum hepcidin (in animal models) and urine hepcidin in humans. Another possibility, therefore, is that patients have elevated iron stores, in relation to chronic disease, and this may have a direct effect on hepcidin release. It would be interesting to know the iron metabolic parameters in these patients, as
Clearly future clinical studies in this field hold much promise.

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References

Use of oesophageal dilatation in clinical practice

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Variant Creutzfeldt-Jakob disease: update

Two years ago we reported current thinking on the potential for gastrointestinal endoscopy to act as a vector for patient to patient transmission of variant Creutzfeldt-Jakob disease. In that article we stressed that the advice would be updated if new evidence became available. Gastroenterologists may be aware of a recently published article in the Lancet7 that describes the tissue distribution of abnormal prion protein (PrPSc) in monkeys that have been inoculated with brain homogenate from first passage animals with bovine spongiform encephalopathy (BSE) via oral route, which is the route by which the vast majority of patients developing vCJD will have become infected. As the prion protein responsible for vCJD is found in all lymphoid tissue, our advice was to reduce “random” biopsies to an absolute minimum and ensure that re-usable biopsy forceps were meticulously cleaned and decontaminated according to

the strict British Society of Gastroenterology (BSG) guidelines. We also advised on the use of disposable biopsy forceps, particularly in the ileum, as it was felt that biopsies from this area posed the greatest risk to both endoscope and forces becoming contaminated. Other inexpensive accessories such as cleaning brushes and the rubber cap covering the biopsy port were also to be disposed of if a biopsy had been taken.

The paper from Herzog and colleagues6 is the first to look specifically at the tissue distribution of PrPSc after oral and intravenous inoculation in a primate model utilising Cynomolgus macaques. The findings confirm that the highest concentration of PrPSc is in the tonsil but that it is also abundantly present in the terminal ileum and ileocaecal fold where gut associated lymphoid tissue is present in large amounts. The whole of the gastrointestinal tract was positive for PrPSc from the duodenum to the rectum. Both gut associated lymphoid tissue and the autonomic nerve supply were highly involved, including nerve fibres lying just below the mucosal boundary. The authors suggested that the possible risk of transmitting vCJD via endoscopic procedures might be currently underestimated as the detection of PrPSc is the best marker for infectivity in prion diseases.

This new information should help to inform gastroenterologists that the risk of transmitting vCJD via an endoscopic procedure remains a distinct possibility and the advice of two years ago remains as relevant today as it was then. All patients undergoing gastrointestinal endoscopy should be considered potential carriers of vCJD in the context that the majority of the UK population is likely to have had dietary exposure to the BSE agent during the 1980s. Perhaps the most important aspect of this new information is the increasing realisation that any biopsy from anywhere in the gastrointestinal tract is as “high risk” as a biopsy of the terminal ileum. It is not logical to reserve disposable biopsy forceps for this one area; it seems more appropriate for endoscopy units to move entirely into using disposable forceps for all procedures and phase out the use of re-usable equipment that might be difficult to trace or decontaminate. This advice should only be performed where this is likely to influence clinical management.

Although one recent case of vCJD has been associated with blood transfusion,2 no case of vCJD has so far been attributed to an endoscopic procedure. However, we would urge all staff involved in endosкопic decontamination to remain vigilant and adhere strictly to guidelines already issued by the BSG2 in order to minimise this risk.

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References

Is mesalazine really safe for use in breastfeeding mothers?

Mesalazine containing preparations are commonly used for the treatment and maintenance of remission of inflammatory bowel disease. The young age of many inflammatory bowel disease sufferers means that the issue of whether to continue therapy in nursing mothers often arises.

We report a small study that was instigated after a nursing mother with Crohn’s disease approached us concerned about the safety of continuing to breastfeed while taking mesalazine. She had a cracked bleeding nipple and was worried about the dose of the drug that her baby would be receiving. We agreed to undertake a simple analysis to measure the drug levels in milk from two non-related breastfeeding mothers. It is thought that maternal use of 5-ASA medication is safe for the breastfed infant although bloody diarrhoea in an infant being breast fed by a woman taking sulphasalazine has been reported,3 as has watery diarrhoea in the infant of a woman using 5-ASA suppositories.4 There has in fact been little research into excretion of 5-ASA and its metabolite (N-ac-ASA) in breast milk.

We obtained breast milk samples from four breastfeeding mothers with inflammatory bowel disease who were taking a 5-ASA preparation. Ethics approval for the study was obtained from the local ethics committee. Breast milk analysis was carried out using high performance liquid chromatography. Concentrations of 5-ASA in the breast milk of 5-ASA treated patients were 4.40 ng/ml while those of N-ac-5-ASA were 5.0–14.9 ng/ml (some 1000 times higher). These results are similar to levels found by other investigators.5,6

Based on an average intake of a breastfeeding infant of 150 ml of milk/kg of body weight/day, concentrations of 5-ASA found in breast milk samples equate to a dosage of 0.0006–0.006 mg/kg. This falls well below 10% of the standardised therapeutic dose, and therefore by this conventional criteria the use of 5-ASA on the contrary may be considered clinically unimportant. However, our finding of high levels of metabolite (N-ac-5-ASA) in breast milk suggests that the metabolite is greatly enriched in breast milk. Differences in the physical properties of 5-ASA and N-ac-5-ASA may well account in part for some difference in their rate of transfer into breast milk. But it is more likely that the findings reflect the result of active metabolism of 5-ASA taking place within the glandular cells of the breast.

We have shown that the concentration of 5-ASA in the breast milk of patients receiving 5-ASA therapy is low. It is therefore interesting to speculate whether the low levels of 5-ASA may, in part, be due to metabolism of 5-ASA to N-ac-5-ASA by breast tissue as a
mechanism to prevent high levels of active 5-ASA from accumulating in milk. N-Ac-5-ASA is a relatively inactive metabolite and is therefore unlikely to have a toxic effect on the infant, although to our knowledge the effect of N-Ac-5-ASA on infants has not been studied. We therefore cautiously support the view that 5-ASA containing medication is safe for breastfeeding mothers with inflammatory bowel disease. In addition to our specific findings relating to 5-ASA, the discovery of active drug metabolism in the breast has potentially wider implications. Based on our findings we would recommend that future studies looking at breast milk drug levels explore the possible effects of metabolism by breast tissue and the potential toxic effects of any metabolites produced.

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References

Duodenal adenoma and cancer in FAP
We congratulate the authors (Gut 2004; 53:381–6) on gathering this large cohort of patients in this important area in familial adenomatous polyposis (FAP) but would like to express some reservations concerning their results. Our first concern relates to the means of endoscopic assessment. Standard forward viewing endoscopy was used, whereas in clinical practice side view endoscopy is recommended as duodenal polyposis in FAP is more severe in the periampullary region and this is likely to be missed with standard endoscopy. This will therefore underestimate both adenoma staging and frequency. This matter is raised in their discussion where they describe side viewing endoscopy as unrealistic. We however feel this is unreasonable in an era where ERCP services are available in most hospitals, at least in the UK.

Furthermore, the need for appropriate endoscopy technique and biopsy protocols has been highlighted in a recent study" which reveals that side effects of duodenal disease when comparing biopsy specimens and resected specimens, in addition to the finding of invasive cancer in a number of specimens resected for “severe duodenal adenomatosis” (that is, Spigelman stage 3 with high grade dysplasia or stage 4). The need to operate before biopsy proven carcinoma is demonstrated by the high mortality rates from metastatic disease in those with duodenal carcinoma. Accurate staging and assessment for endoscopic or surgical intervention is, in our opinion, not possible by standard forward viewing endoscopy.

Our other concern relates to the quoted cancer incidence, which we feel must be biased. The cohort was not followed up from a young age and a proportion of the cohort at first endoscopy was 20–81 years. Both the authors’ own data and others have shown that there is an increased risk of stage 4 disease and cancer with increasing age. As such, older patients in this group we would expect to be self selected and to have less severe disease. Those who were destined to develop severe duodenal disease or cancer may well have developed it prior to screening. Of note, the median age of those developing cancer was 52 years (range 26–58).

In addition, those 12 patients undergoing open duodenotomy and polyectomy are likely to be those with most advanced disease and a highest risk of malignant transformation, thus again biasing the likely natural incidence of duodenal carcinoma.

There are also few details with regard to medical intervention which may affect duodenal staging and disease progression. In the discussion, the authors mention that a few patients may have been on periodic surveillance but feel that this would have a negligible impact on their analysis. In the present era of selective COX-2 inhibition, our current clinical practice is to consider celecoxib treatment in those with stage 3 or 4 disease as well as those who have undergone surgical intervention. If this practice were followed using sulindac in the centres involved in this trial, then up to 91 (24%) patients in this cohort could have been exposed to non-steroidal anti-inflammatory drugs.

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References

Treatment of recurrent gastrointestinal haemorrhage in a patient with von Willebrand’s disease with octreotide LAR and propranolol
Von Willebrand’s disease (vWD) is the most common inherited bleeding disorder and is caused by quantitative deficiency or qualitative abnormalities of von Willebrand factor (vWF). Until recently, treatment of bleeding from the gastrointestinal tract in patients with vWD included administration of tranexamic acid or clotting factor products such as fresh frozen plasma, cryoprecipitate, or partially purified vWF concentrates, or preparations that contain vWF and factor VIII. Desmopressin, beta blocking drugs, and hormonal therapy with oestrogen and/or progesterone have also been used.

We report a patient with vWD who had suffered recurrent and life threatening bleeding from the gastrointestinal tract in whom, despite an extensive investigation, no apparent cause of haemorrhage was identified. He was successfully treated with combined administration of octreotide LAR (long active released) and propranolol. This is the first report on the use of octreotide LAR in a patient with vWD.

A 55 year old man presented to our department because of recurring episodes of melaena, which first appeared five years previously. He had a history of epistaxis during his childhood. During investigation of his bleeding diathesis, he was found to have type I vWD. His niece was also diagnosed with type I vWD whereas his father, brother, and grandmother suffered from bleeding diathesis but no extensive investigation had been undertaken. Laboratory investigation was compatible with the diagnosis of vWD, with prolonged bleeding time (15 minutes), moderate prolongation of activated partial thromboplastin time (41 seconds), mild deficiency of factor VIII (42%; normal range 50–160%), and a moderate decrease in vWF antigen (33%; normal range 50–160%). Platelet count and prothrombin time were within normal limits and the extensive laboratory investigation excluded the presence of concomitant disorders.

Over a period of 17 months, the patient had been admitted 14 times for recurrent episodes of melaena with an overall hospitalisation time of 98 days and consequent sick leave from his job. On two occasions, haemoglobin concentration on admission was 6 g/dl. He required 40 red cell transfusions and 22 000 IU of purified vWF. During this period, upper endoscopy was performed five times, small bowel series radiography twice, and colonoscopy three times; computed tomography of the abdomen, radionuclide scanning with 99mTc pertechnetate labelled autologous red blood cells, angiography of the superior mesenteric artery, and exploratory surgery with intraoperative enteroscopy were also performed, but the source of bleeding could not be localised. He had received intranasal desmopressin for three months with no effect and a therapeutic regimen the bleeding stopped completely. Haemoglobin values stabilised at normal levels (13.2 g/dl), and no treatment related complications were observed. During a follow up period of eight months, bleeding did not recur and the patient has returned to his work. Repeated evaluation of vWF revealed that vWF levels did not rise (28%), although vWF induced platelet aggregation was completely normal, and propranolol remained absent, and activated partial thromboplastin time and bleeding time prolongations remained unchanged.

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Antiviral treatment initiation costs in chronic hepatitis C

We thank Dr Paynord for his comments highlighting the role of pretreatment evaluation costs prior to antiviral treatment of patients with chronic hepatitis C (Gut 2003;52:1352). The rate of fibrosis progression varies greatly in chronic hepatitis C, so liver biopsy can identify those with advanced disease who are at greatest risk for progressing to decompensated cirrhosis when therapeutic options are limited. Other testing, such as genotyping and viral load, can help estimate the likelihood of antiviral response or determine the duration of therapy, and still others are obtained for baseline values to monitor for potential side effects from therapy.

In our cost effectiveness analyses of antiviral treatment strategies for chronic hepatitis C, treatment initiation costs included those related to procedures performed before the beginning of antiviral therapy: pregnancy test, quantitative hepatitis C virus (HCV)-RNA testing, HCV genotyping, thyroid stimulating hormone, thyroxine, and liver biopsy, as well as partial inpatient costs for initiation of antiviral treatment. Previously published cost effectiveness studies have applied different biopsy costs depending on the country and health care system.14–17 The costs in our study are based on the German Hepatitis C Database and reflect the German health care system. However, there are different options for defining these costs. Liver biopsy can be performed as an inpatient or outpatient procedure. The German Uniform Assessment Standard (Einheitlicher Bewertungsmaßstab, EBM), which is the fee for service coding system in social health insurance for outpatient care in Germany,18 assigns a total of 1450–1630 score points to the performance of outpatient liver biopsy. This includes ultrasound guidance (530 points), biopsy (700 points), and histology (220–400 points), and translates to a cost between €49 and €55. The German Hepatitis C Model Clinical Expert Panel (n=14) estimated that inpatient liver biopsy requires an average hospital stay of one day or less. Based on administrative per diem costs, a one day hospital stay in Germany costs €234.19 To bias our analysis against antiviral treatment, we conservatively estimated the cost effectiveness of antiviral treatment, we applied a full hospital day for all patients undergoing liver biopsy in our base case analysis. When we performed sensitivity analyses on all cost parameters, we found little variation in the incremental cost effectiveness ratios of antiviral treatment compared with no antiviral treatment. When comparing combination therapy to pegylated interferon plus weight based ribavirin with a combination of standard interferon plus ribavirin, pretreatment costs do not alter the incremental cost effectiveness ratio. However, if treatment costs occur for all antiviral treatment strategies, they cancel each other out when we calculate the incremental cost of antiviral treatment (that is, the difference in treatment costs between antiviral treatment strategies).

This is not however the case when combination therapy with pegylated interferon plus weight based ribavirin is compared with no antiviral treatment. In response to Dr Paynord’s comment, if the cost of liver biopsy were €1000, the discounted incremental cost effectiveness ratio of treatment with pegylated interferon and ribavirin fell to €3760 per QALY gained. Varying biopsy related mortality from 0 to 5 per 10 000 did not affect the incremental cost effectiveness ratios when rounded to two significant figures, but clearly had an impact on the individual basis for those affected. To bias our results against no antiviral treatment, our analysis did not consider periodic repeat liver biopsy, in which case disease related costs and morbidity and mortality from liver biopsy would be higher.11 In such an analysis, the use of non-invasive biochemical markers would have a greater effect on hepatitis C related morbidity, mortality, and costs.

These additional analyses suggest that even for countries with substantially higher initial pretherapeutic costs than exist in Germany, the expected long term clinical benefits and cost savings from antiviral treatment induced prevention of future advanced liver disease outweighs the initial pretherapeutic and antiviral treatment costs in patients with chronic hepatitis C. If inexpensive and accurate fibrosis markers replaced liver biopsy, the cost effectiveness of antiviral treatment would improve even further.

References
Adherence to BSG adenoma surveillance guidelines will reduce colonoscopic workload

There is an ever increasing demand for colonoscopy nationally which will increase further when colorectal cancer screening is rolled out nationally. To accommodate this, a marked improvement in the efficiency of endoscopy units is required. One simple way of reducing demand is to reduce the number of repeat procedures performed. We have found that by following the British Society of Gastroenterology (BSG) polyp follow up guidelines, our unit could prevent a significant number of unnecessary colonoscopies.

Our unit’s three month retrospective audit found that 79 of 528 patients undergoing colonoscopy had colonic polyps; 130 polyps in total were detected of which 65 were histologically confirmed adenomas (45 tubular, 18 tubulovillous, and two villous). Over two thirds were in the rectum/sigmoid.

By classifying patients with polyps according to BSG guidelines:

- 32 were low risk, of which 16 had too short a follow up interval and 16 had correct follow up (of the 16 with too short a follow up, 10 had no follow up and six had a five year follow up);
- 13 were intermediate risk, with three having correct follow up, six too short a follow up interval, one too long a follow up, and three had no follow up;
- one patient was high risk and received too long a follow up interval;
- 11 had incomplete polyp removal of which four received appropriately rapid follow up, two had late follow up, and five received no follow up;
- of 22 patients with non-adenomatous polyps, only eight had an unnecessary repeat procedure arranged.

Strict adherence to the BSG guidelines would have added eight apparently over-looked procedures but could have saved up to 30 other surveillance procedures (if a policy of no follow up for low risk polyps was used), resulting in a net reduction of 22 procedures. This is equivalent to a 47% reduction in surveillance colonoscopies.

The simple measure of reviewing repeat requests for surveillance procedures to ensure they adhere to BSG guidelines should reduce the number of unnecessary procedures performed, creating additional capacity within our endoscopy unit and reducing the exposure of patients to unnecessary risk.

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Reference


Correction

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In the Editor’s quiz: G1 snapshot entitled “An unusual treatment for a colon polyp” (Gut 2004;53(7):1000, 1019) the last two authors were listed incorrectly. The correct order is M Crobu and then MG Porpora.