

Inflammatory bowel disease

Risks and benefits of azathioprine therapy

D P B McGovern, D P Jewell

The risk of lymphoma may be increased by about fourfold in patients with inflammatory bowel disease treated with thiopurines. The increased risk could be a result of the medications, the severity of the underlying disease, or a combination of the two

The benefits of the thiopurines, azathioprine (AZA), and 6-mercaptopurine (6-MP) in maintaining remission and corticosteroid sparing in inflammatory bowel disease (IBD) are beyond doubt. However, adverse events as well as benefits should always be considered when the effectiveness of any treatment is being evaluated. The "short term" side effects of thiopurines have been well documented and there have been a number of studies examining the role of thiopurine methyltransferase activity in predicting the risk of these side effects. In this issue of *Gut*, Kandiel and colleagues¹ address the difficult issue of the long term risk of lymphoma associated with thiopurine therapy (see page 1121). Using the technique of meta-analysis of cohort studies, the authors concluded that there was about a fourfold increase in lymphoma in IBD patients treated with thiopurines. The headline from this study will cause alarm among patients and clinicians alike but, as in all studies, closer examination of the limitations (as acknowledged by the authors) of the study is necessary before firm conclusions can be drawn. Meta-analyses have their own particular methodological problems and are only as good as the constituent studies. The authors demonstrated heterogeneity between the studies suggesting that the studies were "different" with respect to study population or methodology. The consistent risk of lymphoma, even after sensitivity analyses (to ensure that rogue studies had not radically influenced the risk), is somewhat reassuring but the negative correlation between size of cohort and risk of lymphoma is of concern.

Association does not prove causation and it is possible that the demonstrated risk is with IBD itself and not with

thiopurines. The authors cite evidence that there is no association between IBD and lymphoma but other data suggest that there may be a significant but small association.^{2,3} The authors address this by demonstrating an increased lymphoma risk in patients treated with thiopurines when compared with IBD patients who had not received thiopurines. Thiopurine use however may simply be a marker for more severe disease which may itself increase the risk of lymphoma. This effect of disease severity may be small and already underpowered studies may have missed such a relationship. The studies included in this analysis were mainly from tertiary referral centres and the largest population based study found no thiopurine-lymphoma association, further raising the possibility of a disease severity bias. Smoking has a deleterious effect on Crohn's disease⁴ and smokers are, in theory at least, more likely to require secondline therapies for Crohn's disease and are also at increased risk of Hodgkin's lymphoma,⁵ thereby adding more complexity to the demonstrated association.

Should thiopurines be used more judiciously or even stopped? Quite the contrary! We believe that the case of thiopurines and lymphoma remains unproven but even if the relationship is proved to be causative, the data suggest that thiopurines are of benefit in IBD. The suggested fourfold risk is likely to be an exaggeration, and risk-benefit model analyses have suggested that a 10-fold risk is necessary for the overall effect of thiopurines in IBD to be detrimental.⁶ The alternatives are not without significant risk. These include uncontrolled inflammation, repeated courses of corticosteroids, alternative immunosuppressants (methotrexate

and infliximab administration have also been associated with an increased risk of lymphoma), and surgery. So what should clinicians tell their patients? The risk of lymphoma in IBD patients receiving thiopurines is small, if there at all, but the benefits far outweigh the risks.

Study data suggest that thiopurines are effective for up to five years⁷ and indeed anecdotal evidence suggests that they may be effective for much longer than that. Vigilance and further large scale studies will be required in the future to ensure that long term thiopurine therapy is not associated with a significant risk of neoplasia. For the present, clinicians should be reassured that, on the whole, these drugs are safe in the long term and are of significant benefit to patients with IBD, and their appropriate use should be actively encouraged.

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5-HT₃

5-HT₃ receptor antagonists ameliorate fatigue: so much potential, so little knowledge!

N M Barnes

There is growing evidence that 5-HT₃ receptor blockade will benefit patients with fatigue. Further research is needed to determine the mechanism underlying this widespread clinically important symptom and therapies may be derived from targeting the 5-HT system

Despite a high prevalence with massive socioeconomic implications, fatigue per se, or as a symptom of a diagnosed condition, remains poorly understood. Much of the evidence available arises from measurement of biochemicals or proteins; alterations in which may be primary or secondary to the symptom, or indeed associated with another aspect of an underlying disease. However, an increasing body of evidence implicates an altered central 5-HT (5-hydroxytryptamine; serotonin) system. Although apparent inconsistencies are evident (for example, see Hartz and colleagues¹), elevated 5-HT neurotransmission appears most likely.²⁻⁵ Numerous distinct receptors have evolved to transduce 5-HT signalling. The majority of these receptors (at least 13) are G protein coupled receptors (GPCRs) but, unusual for monoamine neurotransmitters, an additional receptor, the 5-HT₃ receptor, is a member of the cys-cys loop ligand gated ion channel superfamily; other members being the nicotinic acetylcholine receptor, the GABA_A receptor, and the glycine receptor.⁶ The 5-HT₃ receptor is predominantly expressed by central neurones and peripheral nerves and is known to mediate fast synaptic neurotransmission in the brain.

The clinical availability of 5-HT₃ receptor antagonists offers an opportunity to probe further for roles for this receptor. In this issue of *Gut*, Piche and colleagues⁷ provide further support for the use of 5-HT₃ receptor antagonists to alleviate fatigue, in this case arising from hepatitis C infection (see page 1169). This builds on previous observations where these compounds have reduced fatigue in uncontrolled studies with small numbers of patients.^{8,9} The double blind placebo controlled trial with originally 36 patients demonstrated

that chronic administration of the selective 5-HT₃ receptor antagonist ondansetron (Zofran; a relatively low oral dose of 4 mg twice daily for 30 days) improved the level of fatigue in patients relative to placebo (although a significant positive placebo response was also evident at one of the time points). As acknowledged by the authors, they selected patients with relatively high levels of fatigue, which may have allowed a greater scope for the detection of drug induced effects in this symptom that is notoriously difficult to quantify. Interestingly, depressive symptoms in patients also improved. Given the strong association of fatigue as a symptom of depressed patients, it would be pertinent to investigate whether the ondansetron induced reduction in the two symptoms are interrelated. Of further note, both the reduction in fatigue and depression were also evident 30 days after discontinuation of the drug treatment, suggesting that plastic changes may have occurred, as has been postulated for more traditional antidepressant therapies. It may be relevant, however, that another symptom often associated with hepatic disease, pruritus, also likely to be centrally mediated, appears responsive to 5-HT₃ receptor antagonists.^{10,11}

From their early development in the mid- to late 1980s, the selective 5-HT₃ receptor antagonists have been hailed for their potential clinical utility. Much of the initial impetus for their synthesis and development came from the antiemetic efficacy of metoclopramide. At high dosage, metoclopramide afforded additional protection from the nausea and vomiting associated with aggressive anticancer treatment that appeared to correlate with the relatively low affinity to antagonise 5-HT₃ receptors (for review see Barnes and colleagues¹²). The strategy was vindicated with the substantial antiemetic efficacy of selective 5-HT₃

receptor antagonists such as ondansetron (Zofran), granisetron (Kytril), and tropisetron (Navoban).

Soon after the availability of selective 5-HT₃ receptor antagonists, pioneering work by Costall and Naylor, as well as others, demonstrated that these compounds displayed therapeutic potential in numerous animal models predictive of, for instance, anxiolytic, antipsychotic, and cognitive enhancing actions. The subsequent clinical trials however were largely disappointing and curtailed the development of these compounds for these indications (for reviews see Barnes and Sharp⁶ and Costall and Naylor¹³). Clear reasons for these failures remain to be elucidated. Perhaps the animal models simply did not accurately mimic the human diseases? An often quoted explanation is that the unusual bell shaped dose-response curve often evident with 5-HT₃ receptor antagonists (that is, efficacy is lost at higher dosages) necessitates a wide dose range to prove the negative (that is, to prove that there really is no effect). This phenomenon still awaits a mechanistic rationalisation.

However, perhaps the failure simply reflects the different pattern of forebrain expression in humans compared with laboratory animals. For instance, the human cerebral cortex displays relatively low levels of 5-HT₃ receptor binding sites, unlike rodents.¹⁴⁻¹⁸ In contrast, human extrapyramidal regions such as the caudate nucleus and putamen display relatively high levels of 5-HT₃ receptor binding sites, whereas little corresponding expression is evident in rodents.¹⁴⁻¹⁸ The area is further complicated by the apparent species specific expression of individual 5-HT₃ receptor subunits. Thus central expression of the biophysical 5-HT_{3B} subunit is apparent in human but not rodent brain.¹⁹⁻²² The presence of at least three further purported 5-HT₃ receptor subunits (5-HT_{3C}, 5-HT_{3D}, and 5-HT_{3E} subunits²¹) within the human genome, with no corresponding genes identified in rodents, further highlights interspecies differences in the potential expression of different 5-HT₃ receptor isoforms. This area has received little investigation to date, yet in terms of pharmacology, at least the homomeric 5-HT_{3A} receptor and the heteromeric 5-HT_{3A/3B} receptor appear nearly identical,²³ although major functional differences are apparent—for instance, the differing ionic selectivity of the ion channel integral with the receptor, with homomeric 5-HT_{3A} receptors displaying high permeability to Ca²⁺ relative to the heteromeric 5-HT_{3A/3B} receptor complex. A further difference is the single channel conductance, which is an order of

magnitude higher for heteromeric 5-HT_{3A/3B} receptors relative to homomeric 5-HT_{3A} receptors.^{19,24}

Given these major pattern of expression and functional differences between the human 5-HT₃ receptor isoforms and their rodent counterparts, it is perhaps not surprising that the behavioural consequences of antagonising forebrain 5-HT₃ receptors appear to be species dependent. In terms of investigating clinical utility, clearly this problem is bypassed by direct evaluation of 5-HT₃ receptor function in human volunteers or patients; this strategy identifying the ability of 5-HT₃ receptor antagonists to reduce fatigue.⁷⁻⁹

The growing evidence that 5-HT₃ receptor blockade will benefit patients with fatigue requires support from large multicentre trials. However, the encouraging signs will further promote research to determine the mechanism(s) underlying this widespread clinically important symptom and suggests that further therapies may be derived from targeting the 5-HT system, a strategy that has already reaped rich rewards.²⁵

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Alcoholic hepatitis

Predicting mortality by the Glasgow alcoholic hepatitis score: the long awaited progress?

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The new Glasgow alcoholic hepatitis score may represent a substantial improvement in clinical phenotyping and could catalyse the development of new treatments in severe alcoholic hepatitis

Severe alcoholic hepatitis is associated with a high mortality and the presence of liver failure, manifested by jaundice, coagulopathy, and often encephalopathy. Whereas insights

into the pathophysiology of this devastating disease have improved over the past years, clinical progress in the last two decades has been minor. For more than two decades, steroids have

remained the only moderately effective treatment option. One key confounder to most therapy studies has been the use of the discriminant function to identify patients at highest risk of mortality in the absence of better scoring systems more accurately predicting the outcome of severe alcoholic steatohepatitis. The now reported Glasgow alcoholic hepatitis score might represent a substantial improvement in clinical phenotyping and could catalyse the development of new treatments in this disease.

The appearance of steatohepatitis is an important rate limiting step in the development of progressive alcoholic liver disease. One month mortality rates of 40-50% have been reported in patients hospitalised with acutely decompensated liver disease due to alcohol induced steatohepatitis.¹ Patients with severe alcoholic steatohepatitis typically present with fever, hepatomegaly, jaundice, and anorexia. The presence of liver failure manifested by

coagulopathy, jaundice, and/or encephalopathy is an indicator of poor outcome, usually highlighting the presence of limited hepatic functional reserve. Approximately 40–50% of patients have ascites and tender hepatomegaly is common. Leucocytosis is frequent and correlates with the severity of hepatic injury.² Neutrophilic infiltration is commonly seen on liver biopsy and these cells may play an important role in the hepatic injury. Although the diagnosis can be confirmed by liver biopsy, clinical and laboratory features are often adequate for establishing the diagnosis. Absolute values for serum aspartate and alanine aminotransferases are almost always <400 IU/l and higher concentrations should raise suspicion of concurrent liver injury due to viral or other aetiologies. Combined cirrhosis and alcoholic hepatitis is often associated and has the worst prognosis.³

The severity of this disease is best correlated with serum bilirubin level and prothrombin time after vitamin K administration.⁴ As part of a seminal clinical study on corticosteroid therapy in severe alcoholic hepatitis, the discriminant function (DF) formula (which includes prothrombin time and bilirubin levels) was derived to predict disease severity and individual mortality risk in these patients.⁴ This DF was later modified in the context of a further placebo controlled corticosteroid trial.⁵ A modified discriminant function (mDF) of >32 and/or the presence of encephalopathy in placebo treated patients in this latter study was associated with a 65% 28 day survival. A recent re-analysis confirmed this finding and also demonstrated that patients with a score <32 had a survival of 93%.⁶ Therefore, this cut off value of 32 has been used and recommended as the threshold to consider corticosteroid treatment.⁷ More recently, the MELD score has been applied to alcoholic hepatitis. In a study of 34 patients with a MELD score of >11, there was a 45% 30 day survival while those with a score ≤11 had a survival of 96%.⁸ The MELD score includes creatinine values as both blood urea and creatinine values increase and may reflect severity in severe alcoholic steatohepatitis. They predict the development of the hepatorenal syndrome. A polymorph leucocytosis is found (>15–20×10⁹/l) in proportion to the severity of the disease.⁹

DO WE NEED BETTER SCORING SYSTEMS IN ALCOHOLIC HEPATITIS?

(i) We need a simple test which can be calculated at the bedside

Calculation of mDF relies on the absolute value of the prothrombin time and

there exists significant variation in the absolute values of prothrombin time obtained using different assays in different countries (for example, UK, USA). This may thereby affect the validity of the mDF score in countries such as the UK where a greater severity score will be generated based on the prothrombin time. This creates a definite inaccuracy in the mDF value and limits its translation between different facilities. Furthermore, the presence of encephalopathy has often been included when making a treatment decision, in addition to just calculating the mDF. This is problematic, as encephalopathy is very subjective in its milder forms. Kulkarni and colleagues¹¹ have also shown that addition of encephalopathy displayed a slight increase in sensitivity but a dramatic decrease in specificity compared with the mDF. Therefore, encephalopathy is not an attractive parameter influencing treatment decisions (although this reflects current practice). The MELD score is also difficult to calculate at the bedside and inclusion of creatinine in the MELD may also limit its usefulness as creatinine values will be underestimated in the context of hyperbilirubinaemia unless corrected. In addition, it has been demonstrated that the MELD score is not superior to mDF in this population.⁸ Recently, the MELD score has been demonstrated to be a useful score for a panel of chronic advanced liver diseases, including severe alcoholic hepatitis, albeit it is only equivalent to the Child-Turcotte-Pugh score in predicting survival.¹⁰ Both scoring systems (mDF, MELD) use highly relevant variables in severe alcoholic liver disease but ignore other aspects of this disease, such as inflammatory parameters. Therefore, a score including a more complex panel of clinical variables but which can be easily assessed at the bedside would be highly desired.

(ii) We need a score which identifies as many patients as possible with a high mortality risk

Apart from the positive reports on the relevance of an mDF cut off value of 32,⁶ its accuracy in predicting survival has been repeatedly questioned. Kulkarni *et al* recently reported that patients with a low mDF (≤32) also had significant mortality, approaching 17%.¹¹ In this study, the mDF was only moderately sensitive (66.7%) and specific (61.7%). Considering the considerable mortality in patients with a DF ≤32, it would be reasonable to consider treatment options for these patients also. In addition, even more importantly, re-evaluation of current criteria for assessing disease severity is needed to more

accurately identify patients at risk for short and long term mortality.

Given the relatively poor ability of the mDF to predict short term mortality, a new indicator of mortality and severity was eagerly awaited. Forrest and colleagues¹² report in this issue of *Gut* the derivation of a score termed the Glasgow alcoholic hepatitis score (GAHS) based on a large patient population and its validation using a new and independent set of patients (*see page 1174*). Importantly, overall survival was studied in a large patient population (n=241) until day 84, allowing more accurate judgement about the clinical course and not only short term survival (day 28). In their analysis, mDF was highly sensitive in the prediction of death from alcoholic hepatitis but lacked specificity. This was dramatic as it incorrectly predicted the outcome at 28 days after admission in 51% of cases. By multiple stepwise logistic regression they developed the key factors for later deriving and developing their GAHS. All of these factors (age, white blood cell count, blood urea, prothrombin time ratio, and bilirubin) are well known from other studies to affect mortality but have never been used in combination to calculate survival.^{13–15} In their analysis, patients with an admission mDF ≥32 had a survival of 64% and 52% at days 28 and 84, respectively, whereas patients with a GAHS ≥9 had a survival of 46% and 40% at days 24 and 84, respectively. The GAHS at days 1 and 7 was significantly more accurate in predicting day 24 and 84 outcome than the mDF and had an impressive better overall accuracy. Furthermore, the GAHS was also significantly more accurate than the MELD score in predicting short and long term survival.

(iii) Future developments and aspects which might be considered in further new scores

Whereas the new GAHS for the first time includes an inflammatory parameter (white blood cell count) which is important for such a highly inflammatory disease, other inflammatory and immune parameters may also be helpful for future scoring systems. C reactive protein levels and plasma levels of tumour necrosis factor soluble receptors p55 and p75 have been demonstrated to correlate with short and long term survival.^{16–18} On the other hand, extracellular matrix markers such as laminin might be accurate markers predicting survival in these patients.¹⁹ Apart from immune markers, early changes in bilirubin levels and major changes in portal flow are prognostic factors in

patients with severe alcoholic steatohepatitis treated with corticosteroids.^{20 21}

Treatment of severe alcoholic hepatitis has hardly progressed in recent years. Lack of a scoring system with appropriate overall accuracy may have contributed to this poor situation by confounding clinical studies. Current clinical strategy favours a "watch and wait" strategy awaiting disease progression in those patients incorrectly identified as low risk by a low DF (≤ 32). Such a strategy may be counter-productive in a severe disease with high mortality and is an uncommon strategy in modern medicine. In addition, patients with a DF >32 often have contraindications for steroid treatment and cannot receive this treatment. Therefore, the new score presented here raises hopes of a more accurate clinical tool to predict survival and therefore advance the field, initiating new studies with innovative treatment modalities reflecting current pathophysiology. In conclusion, the new Glasgow alcoholic hepatitis score might indeed be the long awaited progress in this field.

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2nd annual BSG-AGA research meeting "The pathogenesis and prevention of oesophageal and gastric adenocarcinoma"

This meeting will take place in the Medical Sciences Teaching Centre, South Parks Road, Oxford, on 1–2 September 2005. The closing date for applications is Wednesday 10 August 2005. The speakers are leading USA and UK clinicians and scientists in the field. There will also be abstract presentations. The meeting will have a strictly limited number of attendees to ensure a workshop atmosphere and vibrant discussion.

The cost for the meeting, including accommodation at Wadham College for Wednesday 31 August – Thursday 1 September and a dinner at Wadham College on 1 September, is only £140 or \$250.

We encourage people to submit abstracts, although this is not in any way compulsory. Depending on the number submitted, we may be willing to consider late submissions.

For full details, a programme, and an application form please visit the BSG website at www.bsg.org.uk. Alternatively please email: simon.travis@orh.nhs.uk or victoria.mcneile@ndm.ox.uk or phone Simon Travis on +44 (0)1865 224829.