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SAFETY AND EFFICACY OF NEW BIOLOGICAL THERAPIES IN INFLAMMATORY BOWEL DISEASE

Prof. Stefan Schreiber, Department for General Internal Medicine and Institute for Clinical Molecular Biology, University Hospital Schleswig-Holstein, Germany
Email s.schreiber@mucosa.de

Chronic inflammatory diseases have become one the major challenges of both modern medicine and health-care economies. The incidence of inflammatory bowel diseases (Crohn's disease, ulcerative colitis) has strongly increased in industrialised nations. Tumor necrosis factor (TNF) has been identified as the major cytokine in disease pathophysiology. With a series of important discoveries in the underlying disease genetics a vastly deepened understanding of early events in patho-physiology will result in new targets for future therapeutic developments.

The primary goal of therapy in inflammatory bowel disease is the long-term maintenance of a sufficient health state. A meaningful clinical benefit is the induction and long-term maintenance of remission as defined in ulcerative colitis by a clinical activity index (CAI) below 4 and in Crohn's disease by a Crohn's disease activity index (CDAI) of less than 150 points, both accompanied by mucosal healing. The ideal therapy does not lead to a large burden of side effects.

However, reality is far away from this. At any given time, almost 50% of the patient population are active despite therapies in cross-sectional, population-based studies. Glucocorticoids, which are still the most frequently used therapy for active episodes of inflammatory bowel disease (IBD), induce remission only in 50% of cases. The others become steroid-dependent or develop steroid refractory disease. The use of anti-metabolite drugs has greatly improved the shortcomings of glucocorticoid therapy but has not solved the problem by any means. Despite vastly increased use of antimetabolites, operation rates in IBD patients have not changed over the past two decades.

The introduction of anti-TNF therapy is the most important single innovation in IBD therapy. With introduction of infliximab in 1996 high efficacy was shown in various, therapy refractory rheumatic and inflammatory barrier disorders, including Crohn disease, ulcerative colitis and psoriasis. New anti-TNF antibody constructs (i.e. adalimumab, certolizumab pegol and golimumab) have been brought into clinical develop-ment with adalimumab being now introduced into prescription use.

The different anti-TNF therapies appear to result in similar efficacies with about 30–40% of mostly therapy refractory patients in clinical trials showing a full primary response (i.e. remission) and up to 70% developing a clinically significant response. Less than 50% of these initial successes can be maintained over extended time frames (i.e. measured in years). While this is a large achievement in therapy refractory IBD, it does not solve the unmet need in therapy.

However, the introduction of anti-TNF therapies in the present therapeutic scenario is late in the chronic development of disease. The fear of side effects largely dictates the late use of anti-TNF therapies. The right time point to introduce this therapy is presently re-evaluated. If side effects permit, the early use of anti-TNF therapy holds the promise of having a large impact on the long-term outcome in patients with IBD. The SONIC trial of infliximab in immunosuppressant-naive patients with Crohn's disease and posthoc analyses of 'early' Crohn's disease patients in trials of adalimumab and certolizumab pegol suggest that efficacy rate for remission induction and maintenance could be far higher in less complicated patients. It is hoped that the early use of anti-TNF therapy changes the natural course of disease (i.e. avoiding the transition form an inflammatory to a penetrating or structuring phenotype). The rights place of anti-TNF therapies will be eventually determined by the outcome of larger clinical trials in terms of the balance between efficacy and side effects.

While one explanation for the only partial success of anti-TNF therapies in the long-term treatment of complex Crohn's disease could be too late an introduction in the course of the disease, another explanation could be an escape mechanism. With the intent to offer complementary therapies addressing different key targets in patho-physiology, several other compounds are being developed, including anti-integrin molecules, anti-cytokine antibodies (e.g. anti Il-6), antibody constructs blocking the T-cell accessory pathway (CTLA4/CD28) and antibodies eliminating either activated T- or B-cells. Some of these drugs have reached the approval stage in the US (e.g. natalizumab, which shows excellent efficacy in Crohn's disease but is restricted due to rare and severe side effects and therefore not approved in Europe) or have undergone primary development in other immunopathies from which they presently are extended through studies in IBD (e.g. abatacept and rituximab).

The future will offer many interesting opportunities for patients. The correct placement of the different therapies is an enormous challenge for clinical researchers in the field. With anti-TNF therapies 10 years after introduction into the market not having found their ideal place in the

treatment algoithms for patients with IBD structural changes in the existing cooperative research patterns are required to promote the organized generation of knowledge necessary to fulfil this task.

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SEEING THROUGH A GLASS, DARKLY: IS THERE A WAY FORWARD IN ALCOHOLIC HEPATITIS?

Dr Ewan Forrest, Consultant Gastroenterologist, Glasgow Royal Infirmary, Glasgow, UK
Email ewan. forrest@northglasgow.scot.nhs.uk

Alcoholic hepatitis is the most florid manifestation of alcoholic liver disease, but there is little consensus upon its diagnosis, with similar pathological features being found in patients with mild and those with severe disease. However, a clinical diagnosis of alcoholic hepatitis can be made with a minimum threshold of bilirubin (80 µmol/L), appropriate biochemistry and the exclusion of other liver disease. The discriminant function is used to assess severity, however this has been found wanting on recent re-analysis. More recently, the Glasgow Alcoholic Hepatitis Score (GAHS) has proven itself to be more accurate than the discriminant function. The model for end-stage liver disease (MELD) score has been advocated but has yet to be validated in this context.

The use of corticosteroids in alcoholic hepatitis is controversial. The change in bilirubin after one week of corticosteroid treatment indicates responsiveness. Pentoxifylline has also been used with an apparent reduction in hepato-renal failure. However, pentoxifylline does not seem to benefit patients who have not responded to initial corticosteroid therapy. Nutritional support is vital for these patients, but there is not enough evidence to suggest that nutritional therapy is an alternative to drug treatment. After some initial positive studies, a randomised control trial of infliximab showed a higher mortality in the treated group. On balance, corticosteroids probably remain the most effective treatment for alcoholic hepatitis in patients with severe disease (GAHS ≥ 9).

Long-term abstinence after an admission with alcoholic liver disease is a realistic possibility and is more likely in patients with more severe disease.

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BILIARY TRACT DISEASE

Dr Stephen Pereira, Consultant Gastroenterologist, University College London, London, UK
Email stephen.pereira@ucl.ac.uk

Biliary tract cancer (BTC: cholangiocarcinoma and the less common cancer of the gallbladder) typically affects older individuals (two-thirds of patients are more than 65 years of age) and is usually detected at a late stage with abdominal pain, weight loss and jaundice. In the UK, more than 1,500 men and women die from this cancer each year (compared with 7,000 deaths each year from pancreatic cancer), and the death rate appears to be increasing at a faster rate than any other gastrointestinal malignancy. The prognosis of BTC is usually poor because most patients present with advanced, inoperable disease and respond poorly to palliative oncological treatments such as chemotherapy. In addition, diagnosis is extremely difficult because of the lack of reliable tumour markers, radiological similarities with benign hepatobiliary diseases and tumour location making access to diagnostic tissue difficult. Relief of biliary obstruction and palliative chemotherapy are the mainstays of therapy but, even of the 10% of cases where surgery is feasible, few patients survive beyond three years. To address the lack of randomised trial data with which to guide treatment, an international phase III study of photodynamic therapy (PDT, a technique for inducing localised tumour necrosis by light after prior administration of a photosensitising agent) is currently under way (http://www.ncrn.org.uk).

Diagnosis of strictures is often reliant on bile and brush cytology acquired at endoscopic retrograde cholangiopancreatography (ERCP), with reported sensitivities of 6–32% and 15–65%, respectively. The most commonly used serum biomarker (CA19-9) has a median sensitivity and specificity for the diagnosis of BTC of at most 70–80% across a range of studies, which is inadequate for either screening or diagnostic purposes. Making a pathological diagnosis is important, as non-malignant diseases such as primary sclerosing cholangitis and autoimmune pancreatitis may cause similar strictures but have radically different management. Consequently, the need for further investigations (such as ultrasound- or CT-guided percutaneous biopsy, endoscopic ultrasound-guided fine needle aspiration or repeat ERCP) may lead to delays and uncertainty for patients, and an increased burden of cost to the health service.

Recent advances in ERCP techniques include a novel peroral cholangioscope with four-way deflected steering that provides an opportunity to directly visualise biliary strictures and takes targeted biopsies for histological analysis. In the assessment of strictures in 53 patients with PSC (who have an incidence of cholangiocarcinoma of 0.6–1.5% per year and a lifetime risk of up to 20%), the reported sensitivity and specificity of biopsies for detection of malignancy were 92% and 93%, respectively (Tischendorf JJ, Krüger M, Trautwein C et al. Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis. *Endoscopy* 2006; 38:665–9). In a non-randomised multi-centre study of 60 patients with indeterminate biliary strictures or intraductal filling defects who underwent ERCP followed by

cholangioscopy and targeted biopsy, the sensitivity and specificity of biopsies were 78% and 100% respectively (Pleskow D, Parsi MA, Chen YK et al. Biopsy of indeterminate biliary strictures – does direct visualization help? – a multicenter experience. *Gastrointest Endosc* 2008; 67:AB103). Molecular markers such as the presence of aneuploidy in biliary brushings or Kirsten rat sarcoma gene (KRAS) and p53 in bile have also been evaluated but are not sufficiently sensitive nor specific to be useful as screening or diagnostic tests. There is an ongoing need for better diagnostic techniques in biliary tract disease.

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IS DIAGNOSTIC COLONOSCOPY OBSOLETE?

Prof. Owen Epstein, Professor of Gastroenterology, Centre for Gastroenterology, Royal Free Hampstead NHS Trust, London, UK
Email o.epstein@medsch.ucl.ac.uk

In 1966, Overholt reported the first successful total colonoscopy using the 'fiberoptic coloscope'.[1] By the turn of the millennium, optical colonoscopy (OC) was established as the gold standard for imaging the colonic mucosa. Optical colonoscopy is a difficult skill to master. The procedure may be painful, almost always requiring intravenous pre-medication with a combination of opiate analgesia and benzodiazepine sedation. Caecal intubation rates are variable and complications of diagnostic colonoscopy include over-sedation, perforation and procedure related death.[2,3] These factors weigh heavily when considering that most patients undergoing colonoscopy have either a normal study or diverticulosis.

Computerised tomographic (CT) examination of the inflated air or CO_2-filled colon is an attractive alternative. The procedure does not require sedation or analgesia, and a complete examination is almost always possible even in the presence of stenosing cancers. Perforation is extremely rare and the examination provides simultaneous images of the extracolonic organs. Where a CT study revealed an indication for OC, this could be immediately followed by a pre-planned, targeted diagnostic or therapeutic procedure, without the need to visualise the entire organ.

The Viatronix workstation (V3D) is the first to display a virtual reality 3D image of the entire colonic lumen as the primary imaging modality with 2D images only used for problem solving. This is the reverse of current CT colonography where 2D greyscale imaging is used as the primary image with short 3D segments only reconstructed for 2D problem solving. The primary 3D display closely resembles the image seen on OC and studies indicate that unlike conventional CT colonography, V3D is as sensitive as OC for uncovering cancer, adenomatous polyps greater than 5 mm in diameter and diverticulosis.[4,5] Given the ease, safety and sensitivity of V3D, it is likely that 3D virtual reality colonoscopy will become the primary imaging modality for polyp and cancer screening as well as the investigation of patients presenting with colonic-type symptoms.

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TURNING THE TIDE OF ALCOHOLIC LIVER DISEASE IN THE UK

Dr Nicholas Sheron, Consultant Hepatologist and Senior Lecturer, University of Southampton, Southampton, UK
Email nick.sheron@southampton.ac.uk

In 2005 there were 25,213 deaths from non-malignant diseases of the digestive tract in England and Wales, of which 27% (6,889) were due to intrinsic liver disease. Of all these deaths, 6,888 people were under the age of 65 and of these 68% (4,702) died of liver disease.

Over the past 30 years liver deaths have increased by around eight times in the UK; in most other EU countries they have fallen dramatically. Underlying reasons for increases in liver mortality in the UK will be explored alongside the evidence base for strategies that could reduce deaths in the future.

The majority of liver deaths (around 80–90%) are due to alcohol-related liver disease, and there are a number of key areas where deaths can be reduced. Firstly and most importantly measures could be taken to reduce overall alcohol consumption at a population level, secondly specific intervention can be used to reduce individual risk and detect liver disease at an earlier stage, thirdly it may be possible to reduce acute in hospital mortality through improved provision of liver services and finally much more needs to be done to specifically address the alcohol issue in these patients.

Further reading

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HOW I MANAGE UPPER GASTROINTESTINAL BLEEDING

Dr Nicholas Church, Consultant Gastroenterologist, Queen Margaret Hospital, Dunfermline, UK
Email nickchurch100@hotmail.com

Significant upper GI bleeding requiring endoscopic intervention is caused by peptic ulcer in 30–50% of cases and varices in 2–12%. Bleeding resulting from other pathologies generally settles with conservative therapy. This lecture will cover pre-endoscopy treatment, timing and type of endoscopic therapy and management strategies following endoscopy.

Pre-endoscopy treatment

Initial decisions regarding management are based on factors in the patient's history which give clues as to the aetiology of bleeding, and vital signs to determine the severity of the bleed. Resuscitation is the mainstay of primary therapy. The Rockall scoring system may be useful to stratify patients according to their risk of death. There is some evidence that management is best undertaken in specialised bleeding units. Evidence to suggest that use of intravenous proton pump inhibitors is beneficial prior to endoscopy is weak, but in suspected variceal bleeding terlipressin and antibiotics should be commenced early.

Timing of endoscopy

Resuscitation should be complete before endoscopy to minimise cardiovascular complications. Endoscopy should be performed within 24 hours of the bleed, but the majority of patients can wait until the next available list. In the selected group of patients who remain unstable despite resuscitation, or in those suspected to have significant variceal bleeding, more urgent endoscopy may be required.

Endoscopic therapy for peptic ulcer bleeding

Injection, thermal and mechanical methods are effective but no single approach has been proven to be superior to the others. Adrenaline injection is effective and larger volumes have been shown to be safe. The heater probe or bipolar probe (BICAP) works by coaptive coagulation. Mechanical clips compress the bleeding vessel. The evidence now suggests that adrenaline injection should not be used alone, but combined with either a thermal or mechanical method.

Endoscopic therapy for variceal bleeding

For oesophageal varices band ligation is superior to injection sclerotherapy, but the latter may be required if banding is not technically possible. Bleeding gastric varices should be treated by injection of cyanoacrylate or thrombin.

Post endoscopy management

Patients who have required endoscopic therapy for bleeding peptic ulcer should be treated with high dose IV proton pump inhibitors for 72 hours. *H. Pylori* should be eradicated and ulcerogenic medication discontinued if possible. In the case of variceal bleeding, vasoactive drug therapy should continue for 2–5 days after banding. Secondary prophylaxis with banding and beta blockade is beneficial.

Management of failed endoscopic therapy for varices

Balloon tamponade is an effective rescue therapy which will stabilise patients to allow them to be transferred to a centre where insertion of a transjugular intrahepatic portosystemic shunt can be considered.

Management of failed endoscopic therapy for peptic ulcer

Repeat endoscopy and therapy may be appropriate. Transcatheter arterial embolisation appears to be a viable alternative to surgery in selected patients.

Recommended reading

- Scottish Intercollegiate Guidelines Network. *Management of acute upper and lower gastrointestinal bleeding: a national clinical guideline.* Edinburgh: SIGN; 2008. Available from: http://www.sign.ac.uk

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HOW I MANAGE ABNORMAL LIVER FUNCTION TESTS

Dr Stephen D Ryder, Consultant Hepatologist, Nottingham Digestive Disease Centre and Biomedical Research Unit, Nottingham, UK
Email stephen.ryder@mail.qmcuh-tr.trent.nhs.uk

Liver function tests (LFTs) are a core part of the investigative pathway for patients presenting with a wide range of symptoms. There is clear evidence that medical interventions such as statin prescribing are increasing the frequency with which liver enzyme levels are requested. Despite this there is widespread misunderstanding of the implications of abnormal results, particularly where the patient has no symptoms or signs suggesting overt liver disease and where tests of liver synthetic function are normal.

There are two large studies investigating the clinical significance of abnormal liver enzymes in different patient populations in both primary and secondary care. These studies suggest that unexplained abnormal liver biochemistry has a significant yield.

In a primary care setting, an audit of 873 abnormal liver enzyme results in a single laboratory over a six-month period, 157 (18%) on review of the case records, required further investigation. Of these, no further tests had been requested in 91 (58%) and in seven a diagnostic follow-up test had been carried out but a significant positive result not acted on. Overall, 97 (62%) of patients had a diagnosis made when appropriate follow-up was undertaken (alcoholic liver disease n=42, non-alcoholic fatty liver disease n=26, autoimmune liver disease n=7, haemochromatosis n=4, viral hepatitis n=8, other n=10). Retesting after an interval shows that 25% of abnormal transaminases normalise and can probably be ignored. In those with persistent abnormality screening with ultrasound scan, hepatitis B and C serology, auto-antibodies, immunoglobulins and coeliac serology plus screening for alpha-1-antitrypsin deficiency and Wilson's disease in selected patients will often yield a diagnosis.

In secondary care the situation is different, with most patients referred for outpatient investigation having an appropriate set of serological investigations if abnormal liver enzymes are noted. In this setting of abnormal liver enzymes in the absence of diagnostic serology, the yield of significant pathology on liver biopsy in a study of 354 patients was high, with 26% having fibrotic liver disease and 6% cirrhosis. The most common finding in this group of patients was one of the fatty liver variants, approximately 66% having either pure fatty liver of non-alcoholic steatohepatitis. Other potentially treatable liver disorders were found in this patient group and management was altered directly by the liver histology findings in 18%. Serum fibrosis markers and fibroscan may alter the management algorithm in the future, but now if weight loss and exercise do not normalise LFTs, biopsy should be considered.

Routine measurement of liver enzymes is a good screening tool for the detection of many forms of liver disease, both in primary and secondary care. Appropriate further investigation of asymptomatic liver enzyme abnormalities in primary care yields a significant diagnosis in more than 60%. In secondary care, non-alcoholic fatty liver disease accounts for the majority of cases.

Further reading

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