

Below Are Selected Good Abstracts from Digestive Disease Week 2006 Meeting  
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<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1859999/?tool=pmcentrez>

### **Can erythropoietin treatment during antiviral drug treatment for hepatitis C be cost effective?**

**Introduction:** Sustained viral response (SVR) of hepatitis C to antiviral drug treatment with ribavirin and PEG interferon is dose dependent. Dose reduction is required in up to 45% of patients. Erythropoietin (Epo) treatment reduces ribavirin induced anaemia and therefore should reduce the need for dose reduction and thus increase the SVR rates.

**Aims:** Our aims were twofold: (1) to prevent dose reduction of ribavirin by intervening with Epo therapy when a ribavirin dose reduction would otherwise be indicated and (2) to determine the cost of such intervention and the potential cost effectiveness.

**Methods:** Twenty three patients with chronic hepatitis C (9 with genotype 1, 14 genotypes 2/3) commenced treatment with ribavirin and PEG - interferon (in keeping with manufacturer's guidelines) between June 2004 to February 2005. If the haemoglobin fell below 10g/dl or dropped by 3g/dl below the pretreatment value with symptoms, subcutaneous Epo was commenced. The dose was increased as necessary until the haemoglobin was sustained at or above 10g/dl. Standard NHS drug costs were used in the calculations.

**Results:** (1) Dosing: 13/23 patients required Epo therapy (7/9 genotype 1 and 6/14 genotypes 2 and 3), all but one within eight weeks of beginning antiviral therapy. Genotype 1 patients required higher doses of Epo, with 6/7 needing dose increases, and three needing doses in excess of 7500iU twice weekly. For genotype 2 and 3 patients, a dose of 2000iU twice weekly was sufficient in 4/6. Ribavirin dose was reduced due to anaemia in two (9%) patients. (2) Costs: The cost of full dose PEG - interferon and ribavirin is £11,500 for genotype 1 and £5000 for genotypes 2 and 3. The mean additional cost of Epo was £4700 for genotype 1 and £864 for genotypes 2 and 3.

**Conclusions:** Epo treatment sustained 91% of patients at optimal ribavirin dose. This intervention increased the drug costs by 40.9% for genotype 1 and 17.3% for genotypes 2 and 3. To achieve cost effectiveness, Epo would thus need to increase the SVR by 40.9% for genotype 1 and by 17.3% for genotypes 2 and 3. Using previous trial data this would mean increasing the SVR from 42% to 59.2% for genotype 1 and from 80% to 93.8% for genotypes 2 and 3.

## **Are all mesalazines equal? A meta - analysis of PH7 - dependent versus controlled release mesalazine in the maintenance of medically induced remission of inactive Crohn's disease**

**Background:** Research indicates that the maintenance of quiescent Crohn's disease with oral mesalazines is most frequently observed following surgical rather than medically induced remission. Studies assessing the effectiveness of mesalazine in treating patients with medically induced remission have yielded inconsistent results. It is possible that these inconsistencies arise from differences in the formulation of mesalazine administered.

**Methods:** A meta - analysis was undertaken to evaluate the efficacy of pH7 dependent and controlled release mesalazine in maintaining medically induced remission of Crohn's disease. A MEDLINE literature search identified six relevant (two pH7 dependent, four controlled release) randomised controlled trials (RCTs), involving a total of 683 patients (191 pH7 v 492 controlled release). The crude rate of symptomatic relapse (CDAI >150 or an increase in baseline from 60 to 100 points) for both treatment and control groups was extracted for each RCT using the intention - to - treat method. The Mantel - Haenszel approach was used to derive a pooled estimate of odds ratio (OR) and the number needed to treat (NNT) calculated.

**Results:** Treatment with pH7 dependent mesalazine significantly reduced the risk of symptomatic relapse (pooled OR 0.430; 95% CI 0.229 to 0.809) but not with controlled release mesalazine (pooled OR 0.888; 95% CI 0.603 to 1.307) when compared with placebo. There were also differences in treatment effectiveness by NNT, 5 and 36 for pH7 dependent and controlled - release mesalazine trials, respectively.

**Conclusion:** The results of this meta - analysis, although involving only a small number of studies, suggest that differences in mesalazine delivery may partially account for inconsistencies in the literature. Moreover, pH7 dependent mesalazine may offer an effective treatment for maintaining medically induced remission of Crohn's disease.

## **Cancer risk in Barrett's oesophagus: a meta - analysis**

**Background:** The risk of cancer in Barrett's oesophagus (BO) is uncertain with studies showing a variable annual incidence (from 1/52 to 1/450). Recent reports have suggested regional variations in cancer incidence in the west.<sup>1</sup> However no formal meta - analysis has been performed.

**Aims and Methods:** We aimed to determine by meta - analysis the incidence of oesophageal cancer in patients undergoing surveillance for BO and to examine geographical variation. A MEDLINE, EMBASE, and PubMed search of all English articles from 1966 to 2004, using the key words "Barrett's oesophagus", "Oesophageal cancer", "surveillance", "short segment Barrett's" (SSBO) was done. References in retrieved papers and relevant review articles were scrutinised to identify papers missed on the initial search. Studies with patients who had histological confirmation of BO on surveillance, documented follow up data, and cancer as the outcome measure were included. Heterogeneity statistic (Q value) between studies was significant ( $p < 0.05$ ); hence a random effects model of meta - analysis was used. Conventional BO was defined as length of  $> 3$  cm.

**Results:** Forty two articles were included in the analysis for conventional BO and an additional seven articles were included for SSBO. The overall incidence rate for cancer was 8/1000 person - years duration of follow up (pyd) (95% CI 6 to 10). There was some geographical variation, with the incidence rate in UK being 9/1000 pyd (95% CI 4 to 17), USA 10/1000 pyd (95% CI 7 to 15), Europe 10/1000 pyd (95% CI 7 to 15), and others (Canada, Australia, New Zealand) 5/1000 pyd (95% CI 1 to 25). The overall cancer incidence in SSBO was 5/1000 pyd (95% CI 2 to 12). There was a non - significant increase in cancer risk in conventional BO compared to SSBO (OR 1.6, 95% CI 0.56 to 4.91,  $p = 0.30$ ).

**Conclusion:** We found less geographical variation in BO cancer risk than previously suggested between US and UK and a non - significant increase in the risk of cancer in conventional BO versus SSBO.

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### **Low incidence of oesophageal adenocarcinoma following optimal regimen of aminolaevulinic acid photofrin photodynamic therapy for high grade dysplasia in Barrett's oesophagus**

**Introduction:** Photofrin photodynamic therapy (PDT) has recently been licensed to treat high grade dysplasia (HGD) for the prevention of adenocarcinoma in Barrett's oesophagus. Aminolaevulinic acid (ALA) PDT is a potentially attractive alternative because of the short light photosensitivity (24 hours) and lack of oesophageal stricture formation. Many different ALA regimens have been suggested in the literature for the eradication of dysplasia in Barrett's oesophagus including varying light dose, drug dose and wavelength of the activating light. The optimal regimen of ALA PDT remains unknown.

**Aims & Methods:** Seventy two patients were treated for high grade dysplasia with different parameters of ALA PDT to determine the optimal regimen. All patients were hydrated with intravenous fluids prior to the oral administration of ALA to prevent systemic hypotension. Three groups of patients were studied: Group A: high dose ALA (60mg/kg) activated by high dose red light (1000J/cm), Group B: high dose ALA activated by lower doses of red light (500–750J/cm), and Group C: low dose ALA (30mg/kg) activated by high light dose. Additionally, 24 patients in groups A and C were randomised to either red (1000J/cm) or green laser light (1000J/cm) activation. Success was determined by regular endoscopic follow - up and quadrantic biopsies every 2 cm through the treated area. The primary outcome was development of adenocarcinoma.

**Results:** One patient was lost to follow - up. Kaplan Meier analysis demonstrated that patients treated in group A, with high red light and high drug dose, had a very significant decrease in cancer risk at 36 months at 3% compared with 34% in those treated with other regimens (Log rank statistic = 0.002). In patients randomised to either red or green light activation the difference in adenocarcinoma rates were also significantly different in favour of red light at 8% versus 45% (p value <0.05). No patients suffered photosensitivity reactions or developed oesophageal strictures.

**Conclusion:** This case series of 72 patients demonstrates a statistically significant difference in the cancer rates between ALA regimens. The adenocarcinoma incidence rate following ALA PDT with the most effective regimen was low at 3% compared to the other regimens at 34%. This data compare favourably to the cancer rates in the randomised trial of PPI versus photofrin PDT at 28% and 14% respectively at two years' follow - up. These data would support the use of the optimal regimen of ALA in a randomised controlled trial of ALA versus photofrin PDT.

## **Laser and radical chemoradiotherapy for oesophageal carcinoma**

**Introduction:** The incidence of oesophageal carcinoma is rising with rates in the UK the highest in the EU. Most patients present with locally advanced disease and 5 - year survival rates are poor. The median survival even after neoadjuvant chemotherapy and surgery is only 17 months. Further, most patients are elderly, present with dysphagia and may be unfit for surgery. Minimally invasive approaches are needed.

**Aims & Methods:** To determine whether endoscopic laser followed by radical chemoradiotherapy resulted in acceptable survival and morbidity. We retrospectively reviewed the notes of all patients with oesophageal carcinoma treated with laser followed by radical chemoradiotherapy at UCH between January 1999 and November 2004. All patients had palliation of dysphagia before starting chemoradiation. Mitomycin C and 5 - fluorouracil were then administered during weeks 1 and 4 of external beam radiotherapy (median 55 Gy, range 45–60 Gy) which was given in divided daily doses over 6 weeks.

**Results:** Thirty one patients, (21 male, 10 female), median age 69 (range 51–88) were treated. 19 patients had squamous cell carcinoma and 12, adenocarcinoma. Two patients had stage T2N1, 12 had T3 disease and 15, T3/4 or T4 disease. Dysphagia was adequately palliated in all apart from 4 who had a PEG placed. 28 of 31 patients completed treatment. Overall median survival was 15 months which did not change after exclusion of patients who had had less than 50 Gy radiotherapy. Median survival among patients with adenocarcinoma was 22 months compared with 12 months for squamous cell carcinoma. Early toxicity was mild with radiation - associated dysphagia in only 4 patients. Late toxicity included a benign oesophageal stricture in 50% which responded to dilatation. Local recurrence occurred in at least 50% of patients.

**Conclusion:** Laser followed by radical chemoradiotherapy appears to be a viable treatment for locally advanced oesophageal carcinoma which causes minimal morbidity compared to surgery. It is generally well - tolerated and provides a median survival similar to neoadjuvant chemotherapy followed by resection. A randomised controlled trial comparing these approaches is warranted.

## **Natalizumab maintains corticosteroid - free remission for 2 years in patients with moderately to severely active Crohn's disease and in those with prior infliximab exposure: results from an open - label extension study**

**Introduction:** Natalizumab has been demonstrated as effective therapy for moderately to severely active Crohn's disease (CD) in both induction and long - term maintenance trials. Fifty five per cent of patients who responded to natalizumab induction therapy were in remission (Crohn's Disease Activity Index (CDAI) score <150) after 15 months of continuous natalizumab therapy in the ENACT trials, compared with 22% in the placebo group ( $p < 0.001$ ). This analysis was undertaken to assess the ability of natalizumab to maintain long - term corticosteroid - free remission.

**Aims & Methods:** Patients who completed the ENACT 2 trial were eligible to enroll in an open-label extension (OLE) study. The primary objective of this 2-year study was to examine the long-term safety and tolerability of natalizumab. Secondary efficacy endpoints included evaluation of the ability of natalizumab to maintain remission. This analysis includes patients who were in remission after 15 months of continuous natalizumab therapy in the ENACT trials who enrolled in the OLE study and received an additional 12 months of natalizumab therapy. Eighty seven patients met the criteria for analysis, 22 of whom had previous exposure to, and 11 of whom had previously failed therapy with, infliximab. Remission rates were calculated using last observation carried forward.

**Results:** Ninety three per cent (81/87) of patients who were in remission at Month 12 of ENACT - 2 were in remission following 6 additional natalizumab infusions in the OLE study. After 12 additional infusions, 86% (75/87) were in remission. 91% (73/80) of the patients who were corticosteroid - free and in remission on entry maintained corticosteroid - free remission after 6 additional natalizumab infusions in the OLE, and 85% (68/80) did so after 12 additional infusions. In the subpopulation of patients with prior exposure to infliximab, 85% (17/20) and 90% (18/20) were in corticosteroid - free remission after an additional 6 and 12 infusions of natalizumab in the OLE study. Similarly, 80% (8/10) who had previously failed therapy with infliximab were in corticosteroid - free remission at the same timepoints.

**Conclusion:** Natalizumab maintained remission for >2 years (27 months) when administered as continuous therapy. Patients who entered remission with natalizumab induction therapy were highly likely to maintain long - term corticosteroid - free remission, including patients who had previously failed therapy with infliximab.

## **The place of minimal access surgery among people with gastro - oesophageal reflux disease: the reflux trial**

**Introduction:** The two principal approaches routinely used in the NHS to treat patients with uncomplicated symptoms of confirmed gastro - oesophageal reflux disease (GORD) are medication and surgery. At present, it is uncertain which is the better, and for whom.

**Aims & Methods:** The REFLUX study, funded by the NHS HTA Programme, was a multicentre trial to evaluate the clinical effectiveness, cost effectiveness, and safety of a policy of relatively early laparoscopic surgery compared with continued medical management among people with GORD judged suitable for both policies. Patients with documented evidence of GORD (endoscopy and/or manometry/24h pH monitoring) and with symptoms for longer than 12 months were identified, either retrospectively or prospectively, by participating clinicians in 21 UK hospitals. Of the 810 eligible patients who consented to participate, 357 were recruited to a randomised comparison: 178 allocated to surgical management and 179 to optimised medical management. The other 453 were recruited to parallel non - randomised preference groups: 261 choosing surgical management and 192 choosing optimised medical management. This presentation will concentrate on the randomised comparison. Outcome data were collected from self-completed postal questionnaire containing a disease - specific outcome - measure (The Reflux questionnaire), SF - 36, and EQ - 5D, all at participant - specific time intervals, equivalent to approximately 3 and 12 months after surgery. Primary analyses used the intention to treat (ITT) principle; secondary "per protocol" (PP) analyses were conducted amongst those who actually received their allocated management.

**Results:** The two randomised groups had similar baseline characteristics. Participants were on average 46 years old and 64% were men. 111 (62%) allocated surgery had fundoplication—either total or partial wrap—with a median length of stay of 2 days; complications were rare, with no re - operations within 12 months. At 3 months follow - up there were substantive differences across all measures, with the surgical group having the better scores. Differences persisted at 12 months although they were somewhat less marked in: Reflux questionnaire score 11.2 (95% CI 6.4 to 16.0;  $p < 0.001$ ); SF36 General Health 4.8 (95% CI 2.7 to 6.8;  $p < 0.001$ ); and EQ - 5D 0.047 (95% CI -0.004 to 0.097;  $p = 0.07$ ). PP analyses, as expected, generated larger differences. 38% allocated surgery (PP 14%) compared with 90% (PP 93%) allocated medical management were taking some reflux related drug at 12 months.

**Conclusion:** Surgical management in patients requiring long - term medication to control their reflux symptoms significantly increases general and reflux - specific quality of life measures. Surgical complications in this study were rare.