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Gastro-intestinal system



Outcome following infliximab therapy in children with ulcerative colitis

Infliximab is effective in treating moderate/severe ulcerative colitis (UC) in adults. The aim of this study was to determine the outcome after treatment with infliximab in paediatric UC.

This was a multicentre cohort study of 332 paediatric patients with UC enrolled in the US Paediatric Inflammatory Bowel Disease Collaborative Research Group Registry. Children ≤ 16 years of age and newly diagnosed with UC are enrolled in the registry. Disease and medication information are collected prospectively from the treating physician at diagnosis, 30 days, and quarterly thereafter. No interventions were specified, per protocol.

Of 332 patients, 52 (16%) received infliximab (23% < 3 months from diagnosis, 38% 3–12 months, 38% > 12 months). Mean age at infliximab initiation was 13.3 ± 2.6 (range 6–17) years; 87% of patients had pancolitis. Median follow-up was 30 months. Continuous maintenance (CM) therapy was given in 65%, episodic in 21%, episodic converted to CM in 6%, and insufficient data in 8% of patients. Sixty-three percent of patients were corticosteroid refractory, and 35% were corticosteroid dependent. Concomitant medications at first infliximab infusion included corticosteroids (87%), thiopurines (63%), and 5-aminosalicylates (51%). Corticosteroid-free inactive disease by physician global assessment was noted in 12/44 (27%), 15/39 (38%), and 6/28 (21%) patients at 6, 12, and 24 months, respectively. Kaplan–Meier analysis showed that the likelihood of remaining colectomy free after treatment with infliximab was 75% at 6 months, 72% at 12 months, and 61% at 2 years.

In this cohort of children with UC receiving infliximab, corticosteroid-free inactive disease was observed in 38 and 21% of patients at 12 and 24 months, respectively. By 24 months, 61% of patients had avoided colectomy.

Jeffrey S Hyams MD, et al for the Paediatric Inflammatory Bowel Disease Collaborative Research Group Am J Gastroenterol 105: 1430-1436



Unintended effects of statins

A prospective open cohort study using routinely collected data from 368 general practices in England and Wales to quantify the unintended effects of statins according to type, dose, and duration of use.

The QResearch database includes 2 004 692 patients aged 30-84 years of whom 225 922 (10.7%) were new users of statins: 159 790 (70.7%) were prescribed simvastatin, 50 328 (22.3%) atorvastatin, 8103 (3.6%) pravastatin, 4497 (1.9%) rosuvastatin, and 3204 (1.4%) fluvastatin.

Cox proportional hazards models were used to estimate effects of statin type, dose, and duration of use. The number needed to treat (NNT) or number needed to harm (NNH) was calculated and numbers of additional or fewer cases estimated for 10 000 treated patients.

Outcome measures were first recorded occurrence of cardiovascular disease, moderate or serious myopathic events, moderate or serious liver dysfunction, acute renal failure, venous thromboembolism, Parkinson's disease, dementia, rheumatoid arthritis, cataract, osteoporotic fracture, gastric cancer, oesophageal cancer, colon cancer, lung cancer, melanoma, renal cancer, breast cancer, or prostate cancer.

Individual statins were not significantly associated with risk of Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, colon cancer, lung cancer, melanoma, renal cancer, breast cancer, or prostate cancer. Statin use was associated with decreased risks of oesophageal cancer but increased risks of moderate or serious liver dysfunction, acute renal failure, moderate or serious myopathy, and cataract. Adverse effects were similar across statin types for each outcome except liver dysfunction where risks were highest for fluvastatin. A dose-response effect was apparent for acute renal failure and liver dysfunction. All increased risks persisted during treatment and were highest in the first year. After stopping treatment the risk of cataract returned to normal within a year in men and women. Risk of oesophageal cancer returned to normal within a year in women and within 1-3 years in men. Risk of acute renal failure returned to normal within 1-3 years in men and women, and liver dysfunction within 1-3 years in women and from three years in men. Based on the 20% threshold for cardiovascular risk, for women the NNT with any statin to prevent one case of cardiovascular disease over five years was 37 (95% CI 27 to 64) and for oesophageal cancer was 1266 (850 to 3460) and for men the respective values were 33 (24 to 57) and 1082 (711 to 2807). In women the NNH for an additional case of acute renal failure over five years was 434 (284 to 783), of moderate or severe myopathy was 259 (186 to 375), of moderate or severe liver dysfunction was 136 (109 to 175), and of cataract was 33 (28 to 38). Overall, the NNHs and NNTs for men were similar to those for women, except for myopathy where the NNH was 91 (74 to 112).

Claims of unintended benefits of statins, except for oesophageal cancer, remain unsubstantiated, although potential adverse effects at population level were confirmed and quantified. Further studies are needed to develop utilities to individualise the risks so that patients at highest risk of adverse events can be monitored closely.

Julia Hippisley-Cox, Carol Coupland *BMJ* 2010;340:c2197

Spironolactone use and renal toxicity

A Scottish population based longitudinal analysis using a record linkage database to determine the safety of spironolactone prescribing.

All patients who received one or more dispensed prescriptions for spironolactone between 1994 and 2007 were included. Rates of prescribing for spironolactone, hospital admissions for hyperkalaemia, and hyperkalaemia and renal function without admission, before and after the publication of results from the Randomised Aldactone Evaluation Study (RALES) were analysed.

Prescriptions for spironolactone and measurements of serum creatinine and serum potassium all increased in parallel in Tayside after the release of the RALES results in 1999 (from 2847, 5345, and 5246 in the first half of 1999 to 6582, 10 753, and 10 534 by the second half of 2001, and to 8619, 17 844, and 17 649 by 2007). These increases occurred in patients with and without heart failure. Few hospital admissions for hyperkalaemia occurred over this time: three in the first quarter of 1995, two in the last quarter of 2001, and three in 2007. Among patients who were taking ACE inhibitors and who had recently been admitted to hospital for heart failure, the rate of spironolactone use was 19.8 per 100 patients in early 1999 rising to 70.1 per 100 patients by late 2001 ($P < 0.01$) and 61.3 by 2007. The rate of outpatient measured hyperkalaemia (serum $K^+ > 6$ mmol/l) did not increase over time (9.9 per 100 patients in early 1999, 6.9 per 100 patients in late 2001, and 2.9 per 100 patients in 2007) despite the increased use of spironolactone.

Despite a marked increase in the use of spironolactone in patients with and without heart failure, no increase was seen in hospital admissions for hyperkalaemia and outpatient hyperkalaemia actually fell. Careful monitoring of patients prescribed spironolactone seems to have been associated with no increase in risk of hyperkalaemia.

Li Wei, et al *BMJ* 2010;340:c1768



Respiratory system



Efficacy of a long-acting inhaled β_2 -agonist indacaterol versus formoterol in COPD

Indacaterol is a long-acting inhaled β_2 -agonist (LABA) for the treatment of chronic obstructive pulmonary disease (COPD). In previous studies, indacaterol provided 24h bronchodilation on once-daily dosing with a fast onset of action. This study compared the efficacy and safety of indacaterol with the twice-daily LABA formoterol and placebo over 1 year.

Patients with moderate to severe COPD were randomised to receive once-daily indacaterol 300 μ g (n=437) or 600 μ g (n=428), twice-daily formoterol 12 μ g (n=435) or placebo (n=432) for 52 weeks in a double-blind double-dummy parallel group study. The primary efficacy variable was forced expiratory volume in 1s (FEV1) measured 24h postdose after 12 weeks (indacaterol vs placebo). Other outcomes included dyspnoea (transition dyspnoea index, TDI), use of as-needed salbutamol, symptom-based measures recorded on diary cards, exacerbations, health status (St George's Respiratory Questionnaire), BODE index (body mass index, obstruction, dyspnoea, exercise), safety and tolerability.

Indacaterol increased 24h postdose FEV1 after 12 weeks by 170ml (both doses) versus placebo and by 100ml versus formoterol (all $p < 0.001$). These differences were maintained at 52 weeks. Symptomatic outcomes were improved compared with placebo with all active treatments, and indacaterol was more effective than formoterol in improving TDI score and reducing the need for as-needed salbutamol. Indacaterol was well tolerated and had a good overall safety profile, including minimal impact on QTc interval and systemic β_2 -mediated events.

Ronald Dahl, et al Thorax 2010;65:473-479



Central nervous system



Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts

Some heroin addicts persistently fail to benefit from conventional treatments. This study aimed to compare the effectiveness of supervised injectable treatment with medicinal diamorphine or supervised injectable methadone versus optimised oral methadone for chronic heroin addiction.

In this multisite, open-label, randomised controlled trial, chronic heroin addicts who were receiving conventional oral treatment (≥ 6 months), but continued to inject street heroin regularly ($\geq 50\%$ of days in preceding 3 months) were enrolled. Randomisation by minimisation was used to assign patients to receive supervised injectable methadone, supervised injectable diamorphine, or optimised oral methadone. Treatment was provided for 26 weeks in three supervised injecting clinics in England. Primary outcome was 50% or more of negative specimens for street heroin on weekly urinalysis during weeks 14–26. Primary analysis was by intention to treat; data were adjusted for centre, regular crack use at baseline, and treatment with optimised oral methadone at baseline.

Of 301 patients screened, 127 were enrolled and randomly allocated to receive injectable methadone (n=42 patients), injectable diamorphine (n=43), or oral methadone (n=42); all patients were included in the primary analysis. At 26 weeks, 80% (n=101) patients remained in assigned treatment: 81% (n=34) on injectable methadone, 88% (n=38) on injectable diamorphine, and 69% (n=29) on oral methadone. Patients on injectable diamorphine were significantly more likely to have achieved the primary outcome (72% [n=31]) than were those on oral methadone (27% [n=11], OR 7.42, 95% CI 2.69–20.46, $p < 0.0001$; adjusted: 66% [n=28] vs 19% [n=8], 8.17, 2.88–23.16, $p < 0.0001$), with number needed to treat of 2.17 (95% CI 1.60–3.97). For injectable methadone (39% [n=16]; adjusted: 30% [n=14]) versus oral methadone, the difference was not significant (OR 1.74, 95% CI 0.66–4.60, $p = 0.264$; adjusted: 1.79, 0.67–4.82, $p = 0.249$). For injectable diamorphine versus injectable methadone, a significant difference was recorded (4.26, 1.63–11.14, $p = 0.003$; adjusted: 4.57, 1.71–12.19, $p = 0.002$), but the study was not powered for this comparison. Differences were evident within the first 6 weeks of treatment.

Treatment with supervised injectable diamorphine leads to significantly lower use of street heroin than does supervised injectable methadone or optimised oral methadone. The authors argue that UK Government proposals should be rolled out to support the positive response that can be achieved with heroin maintenance treatment for previously unresponsive chronic heroin addicts.

John Strang, et al Lancet 2010; 375: 1885-1895

Efficacy of atypical v. typical antipsychotics for early psychosis: meta-analysis

There is an ongoing debate about the use of atypical antipsychotics as a first-line treatment for first-episode psychosis. This meta-analysis of randomised controlled trials in the early phase of psychosis examined the evidence base for this recommendation, looking at long-term discontinuation rates, short-term symptom changes, weight gain and extrapyramidal side-effects. Trials were identified using a combination of electronic (Cochrane Central, EMBASE, MEDLINE and PsycINFO) and manual searches.

Fifteen randomised controlled trials with a total of 2522 participants were included. No significant differences between atypical and typical drugs were found for discontinuation rates (odds ratio (OR) = 0.7, 95% CI 0.4 to 1.2) or effect on symptoms (standardised mean difference (SMD) = -0.1, 95% CI -0.2 to 0.02). Participants on atypical antipsychotics gained 2.1 kg (95% CI 0.1 to 4.1) more weight than those on typicals, whereas those on typicals experienced more extrapyramidal side-effects (SMD = -0.4, 95% CI -0.5 to -0.2).

There was no evidence for differences in efficacy between atypical and typical antipsychotics, but there was a clear difference in the side-effect profile.

Nicolas A. Crossley, et al Br J Psychiatry 196: 434-439



Endocrine system



Long term treatment with metformin and risk of vitamin B-12 deficiency

A multicentre randomised placebo controlled trial in outpatient clinics of three hospitals in the Netherlands.

A total of 390 patients with type 2 diabetes receiving treatment with insulin were randomised to 850 mg metformin or placebo three times a day for 4.3 years.

The main outcome measures were percentage change in vitamin B-12, folate, and homocysteine concentrations from baseline at 4, 17, 30, 43, and 52 months.

Compared with placebo, metformin treatment was associated with a mean decrease in vitamin B-12 concentration of -19% (95% CI -24% to -14%; $P < 0.001$) and in folate concentration of -5% (95% CI -10% to -0.4%; $P = 0.033$), and an increase in homocysteine concentration of 5% (95% CI -1% to 11%; $P = 0.091$). After adjustment for body mass index and smoking, no significant effect of metformin on folate concentrations was found. The absolute risk of vitamin B-12 deficiency (<150 pmol/l) at study end was 7.2 percentage points higher in the metformin group than in the placebo group (95% CI 2.3 to 12.1; $P = 0.004$), with a number needed to harm of 13.8 per 4.3 years (95% CI 4.3 to 8.3). The absolute risk of low vitamin B-12 concentration (150-220 pmol/l) at study end was 11.2 percentage points higher in the metformin group (95% CI 4.6 to 17.9; $P = 0.001$), with a number needed to harm of 8.9 per 4.3 years (95% CI 2.7 to 5.6). Patients with vitamin B-12 deficiency at study end had a mean homocysteine level of 23.7 $\mu\text{mol/l}$ (95% CI 18.8 to 30.0 $\mu\text{mol/l}$), compared with a mean homocysteine level of 18.1 $\mu\text{mol/l}$ (95% CI 16.7 to 19.6 $\mu\text{mol/l}$; $P = 0.003$) for patients with a low vitamin B-12 concentration and 14.9 $\mu\text{mol/l}$ (95% CI 14.3 to 15.5 $\mu\text{mol/l}$; $P < 0.001$) compared with vitamin B-12 deficiency; $P = 0.005$ compared with low vitamin B-12) for patients with a normal vitamin B-12 concentration (>220 pmol/l).

Long term treatment with metformin increased the risk of vitamin B-12 deficiency, which results in raised homocysteine concentrations. Vitamin B-12 deficiency is preventable; therefore, the authors suggest that regular measurement of vitamin B-12 concentrations during long term metformin treatment should be strongly considered.

Jolien de Jager, et al BMJ 2010;340:c2181, doi: 10.1136/bmj.c2181 (Published 20 May 2010)



Nutrition and blood



Effect of folic acid, with or without other B vitamins, on cognitive decline: Meta-Analysis

This meta-analysis aimed to quantify the effect of folic acid supplementation on the prevention of cognitive decline. Nine placebo-controlled randomized trials (2835 participants, median duration 6 months) assessing effect of folic acid, with or without other B vitamins, on cognitive function were included. Standardized mean differences in cognitive function test scores were calculated between folic acid and placebo-treated groups.

The standardized mean difference in cognitive function test scores was 0.01 (95% CI, -0.08 to 0.10), or an increase of 1% (95% CI, -8% to 10%) of 1 standard deviation. The results were similar within each of the 4 categories of cognitive function (memory, speed, language, and executive function); standardized mean differences were 0.01 (95% CI, -0.08 to 0.09), -0.01 (95% CI, -0.10 to 0.13), -0.05 (95% CI, -0.15 to 0.04), and 0.03 (95% CI, -0.13 to 0.19), respectively.

Randomized trials show no effect of folic acid, with or without other B vitamins, on cognitive function within 3 years of the start of treatment. Trials of longer duration, recording the incidence of dementia, as well as cognitive decline, are needed.

David S. Wald, Anuradhani Kasturiratne, Mark Simmonds AM J Med 2010; 123: 522-527.e2



A practical guide to vaccinating the inflammatory bowel disease patient

The increasing use of corticosteroids, immune modulators, and biologics as a mainstay of therapy in certain Crohn's disease and ulcerative colitis patients have placed these inflammatory bowel disease (IBD) patients at increased risk for a variety of infections, many of which are preventable by prior vaccination. This article provides a review of the issues surrounding immunizations in the IBD patient and a practical guide for clinicians regarding the appropriate vaccinations to administer both before and during immunosuppressive therapy.

Sharmeel K Wasan et al Am J Gastroenterol 105: 1231-1238

Efficacy of sweet solutions for analgesia post-immunisation in infants: a systematic review

A systematic review to compare the efficacy of oral sweet solutions to water or no treatment in infants aged 1–12 months during immunisation.

Randomised controlled trials (RCTs) were retrieved through internet searches or manual searches of reference lists. Search terms included newborn, infant, pain, sucrose and alternative names for sweet solutions. Summary estimates with 95% CIs were calculated and included relative risk (RR), risk difference (RD) and number needed to treat to benefit (NNTB) for dichotomous outcomes, and weighted mean differences (WMD) for continuous outcomes. Where pooling of results was not possible, a narrative summary of study results is presented.

Of the 695 studies identified, 14 RCTs with 1674 injections met the inclusion criteria. Sucrose or glucose, compared to water or no treatment decreased crying during or following immunisation in 13 of the 14 studies. Infants receiving 30% glucose (three trials, 243 infants) had a decreased RR in crying incidence following immunisation (typical RR 0.80, 95% CI 0.69 to 0.93; RD -0.17, 95% CI -0.29 to -0.05; NNTB 6, 95% CI 3 to 20). With sucrose or glucose, there was a 10% WMD reduction in proportion of crying time (95% CI -18 to -2) and a 12s reduction in crying duration (95% CI -23 to -0.7 s). An optimal dose of sucrose or glucose could not be ascertained due to the varied volumes and concentrations used.

Infants aged 1–12 months administered sucrose or glucose before immunisation had moderately reduced incidence and duration of crying.

Denise Harrison, et al Arch Dis Child 2010;95:406-413

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