

ABSTRACT FROM CURRENT LITERATURE

Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial

*Papp K, Cather JC, Rosoph L et al
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Background : Apremilast, a small-molecule inhibitor of phosphodiesterase 4, works intracellularly to modulate proinflammatory and anti-inflammatory mediator production, and doses of 20 mg twice daily have shown efficacy in the treatment of moderate to severe plaque psoriasis in a 12-week phase 2 study. We assessed the clinical efficacy and safety of different doses of apremilast in the treatment of patients with moderate to severe plaque psoriasis.

Methods : In this phase 2b, multicentre, randomised, placebo-controlled, dose-ranging study, patients (aged >18 years), with moderate to severe psoriasis were randomly assigned (in a 1:1:1:1 ratio) to receive oral placebo or apremilast 10, 20 or 30 mg twice daily at 35 US and Canadian sites between Sept 24, 2008, and Oct 21, 2009. At week 16, patients in the placebo group were assigned apremilast 20 or 30 mg twice daily until week 24. Randomisation was generated with a permuted-block randomisation list via interactive voice response system. For the first 16 weeks, treatment assignment was concealed from both investigators and participants. During weeks 16-24, investigators and participants all knew that treatment was active, but the dose was concealed. The primary endpoint was the proportion of patients achieving at least 75% reduction from baseline psoriasis area and severity index (PASI-75) at week 16. Analyses were by intention to treat; missing values were imputed by last-observation-carried-forward. This trial is registered with ClinicalTrials.gov, number NCT00773734.

Findings : 89 patients were randomly assigned apremilast 10 mg, 87 apremilast 20 mg, and 88 apremilast 30 mg twice daily 88 were assigned placebo. At week 16, PASI-75 was achieved in five patients (6%) assigned placebo, ten (11%) assigned apremilast 10 mg, 25 (29%) assigned 20 mg, and 36 (41%) assigned 30 mg. Apremilast 10 mg did not differ significantly from placebo in achievement of the endpoint (odds ratio 2-10; 95% CI 0-69-6-42); for both apremilast 20 mg (6-69; 2.43-18.5; $p<0.0001$) and apremilast 30 mg (11-5; 4.24-31.2; $p<0.0001$), the differences from placebo were significant. Most adverse events (96%) were mild or moderate; at least 5% of patients had nausea, upper respiratory tract infection, diarrhoea, nasopharyngitis, headache, arthralgia (placebo), gastroenteritis, or dyspepsia. Eight serious adverse events occurred (three each,

placebo and apremilast 20 mg; two, apremilast 30 mg); none were judged to be related to apremilast. Apremilast had no apparent effect on the results of haematological, urinalysis, immunological or inflammation, serum chemistry, or electrocardiographic tests.

Interpretation Apremilast, given orally at 20 or 30 mg twice daily, seems to be efficacious, safe, and tolerable for patients with moderate to severe plaque psoriasis. Our results support continuing, longer-term studies.

Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial)

*Davaos A, Sabin JA, Castillo J et al
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Background : Citicoline is approved in some countries for the treatment of acute ischaemic stroke. The drug has shown some evidence of efficacy in a pooled analysis. We sought to confirm the efficacy of citicoline in a larger trial.

Methods : We undertook a randomised, placebo-controlled, sequential trial in patients with moderate-to-severe acute ischaemic stroke admitted at university hospitals in Germany, Portugal, and Spain. Using a centralised minimisation process, patients were randomly assigned in a 1:1 ratio to receive citicoline or placebo within 24 h after the onset of symptoms (1000 mg every 12 h intravenously during the first 3 days and orally thereafter for a total of 6 weeks [2x500 mg oral tablets given every 12 h]). All study participants were masked. The primary outcome was recovery at 90 days measured by a global test combining three measures of success: National Institutes of Health Stroke Scale < 1 modified Rankin score <1, and Barthel Index >95. Safety endpoints included symptomatic intracranial haemorrhage in patients treated with recombinant tissue plasminogen activator, neurological deterioration, and mortality. This trial is registered, NCT'00331890.

Results : 2298 patients were enrolled into the study from Nov 26, 2006, to Oct 27, 2011. 37 centres in Spain, 11 in Portugal, and 11 in Germany recruited patients. Of the 2298 patients who gave informed consent and underwent randomisation, 1148 were assigned to citicoline and 1150 to placebo. The trial was stopped for futility at the third interim analysis on the basis of complete data from 2078 patients. The final randomised analysis was based on data for 2298 patients: 1148 in citicoline group and 1150 in placebo group. Global recovery was similar in both groups (odds ratio 1.03, 95% CI 0.86-1.25; $p=0.364$). No

significant differences were reported in the safety variables nor in the rate adverse events.

Interpretation: Under the circumstances of the ICTUS trial, citicoline is not efficacious in the treatment of moderate-to severe acute ischaemic stroke.

Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis

*Cadeira D, Alarcao J, Carneior AV et al
BMJ 2012; 345 : e4260*

Objective: To systematically review longitudinal studies evaluating use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and risk of pneumonia.

Design Systematic review and meta-analysis.

Data sources: Medline through PubMed, Web of Science with conference proceedings (inception to June 2011), and US Food and Drug Administration website (June 2011). Systematic reviews and references of retrieved articles were also searched.

Study selection: Two reviewers independently selected randomised controlled trials and cohort and case-control studies evaluating the use of ACE inhibitors or ARBs and risk of pneumonia and retrieved characteristics of the studies and data estimates.

Data synthesis: The primary outcome was incidence of pneumonia and the secondary outcome was pneumonia related mortality. Subgroup analyses were carried according to baseline morbidities (stroke, heart failure, and chronic kidney disease) and patients' characteristics (Asian and non-Asian). Pooled estimates of odds ratios and 95% confidence intervals were derived by random effects meta-analysis. Adjusted frequentist indirect comparisons between ACE inhibitors and ARBs were estimated and combined with direct evidence whenever available. Heterogeneity was assessed using the I² test.

Results: 37 eligible studies were included. ACE inhibitors were associated with a significantly reduced risk of pneumonia compared with control treatment (19 studies: odds ratio 0.66, 95% confidence interval 0.55 to 0.80; I²=79%) and ARBs (combined direct and indirect odds ratio estimate

0.69, 0.56 to 0.85). In patients with stroke, the risk of pneumonia was also lower in those treated with ACE inhibitors compared with control treatment (odds ratio 0.46, 0.34 to 0.62) and ARBs (0.42, 0.22 to 0.80). ACE inhibitors were associated with a significantly reduced risk of pneumonia among Asian patients (0.43, 0.34 to 0.54) compared with non-Asian patients (0.82, 0.67 to 1.00; P<0.001). Compared with control treatments, both ACE inhibitors (seven studies: odds ratio 0.73, 0.58 to 0.92; I²=51 %) and ARBs (one randomised controlled trial: 0.63, 0.40 to 1.00) were associated with

a decrease in pneumonia related mortality, without differences between interventions.

Conclusion: The best evidence available points towards a putative protective role of ACE inhibitors but not ARBs in risk of pneumonia. Patient populations that may benefit most are those with previous stroke and Asian patients. ACE inhibitors were also associated with a decrease in pneumonia related mortality, but the data lacked strength.

Weight gain in smokers after quitting cigarettes: meta-analysis

*Aubin HJ, Farley A, Lycett D et al
BMJ 2012; 345: e4439*

Objective: To describe weight gain and its variation in smokers who achieve prolonged abstinence for up to 12 months and who quit without treatment or use drugs to assist cessation.

Design: Meta-analysis.

Data sources: We searched the Central Register of Controlled Trials (CENTRAL) and trials listed in Cochrane reviews of smoking cessation interventions (nicotine replacement therapy, nicotinic partial agonists, antidepressants, and exercise) for randomised trials of first line treatments (nicotine replacement therapy, bupropion, and varenicline) and exercise that reported weight change. We also searched CENTRAL for trials of interventions for weight gain after cessation.

Review methods: Trials were included if they recorded weight change from baseline to follow-up in abstinent smokers. We used a random effects inverse variance model to calculate the mean and 95% confidence intervals and the mean of the standard deviation for weight change from baseline to one, two, three, six, and 12 months after quitting. We explored subgroup differences using random effects meta-regression.

Results: 62 studies were included. In untreated quitters, mean weight gain was 1.12 kg (95% confidence interval 0.76 to 1.47), 2.26 kg (1.98 to 2.54), 2.85 kg (2.42 to 3.28), 4.23 kg (3.69 to 4.77), and 4.67 kg (3.96 to 5.38) at one, two, three, six, and 12 months after quitting, respectively. Using the means and weighted standard deviations, we calculated that at 12 months after cessation, 16%, 37%, 34%, and 13% of untreated quitters lost weight, and gained less than 5 kg, gained 5-10 kg, and gained more than 10 kg, respectively. Estimates of weight gain were similar for people using different pharmacotherapies to support cessation. Estimates were also similar between people especially concerned about weight gain and those not concerned.

Conclusion: Smoking cessation is associated with a mean increase of 4-5 kg in body weight after 12 months of abstinence, and most weight gain occurs within three months of quitting. Variation in weight

change is large, with about 16% of quitters losing weight and 13% gaining more than 10 kg.

Spinal tuberculosis in children

*Eisen S, Honywood L, Shingadia D et al
Arch Dis Child 2012; 97: 724-729*

Objectives: To review our experience of spinal tuberculosis (TB) at a major UK paediatric tertiary referral centre.

Methods: The authors performed a retrospective case survey of 21 patients admitted to Great Ormond Street Hospital over a 15-year period (1995-2010) with confirmed or presumed spinal TB. Data were collected concerning demographics, clinical, laboratory and radiological characteristics, treatment and clinical outcome.

Results: Only one patient was of Caucasian origin. Four (19%) had a previous diagnosis of TB, 11 (52%) a known contact, 10 (48%) had received BCG vaccine and none were HIV-positive. Clinical presentations included systemic symptoms (18 patients), back pain (16 patients), deformity (five patients) and neurological deficits (12 patients). Mycobacterium tuberculosis was isolated from 14 patients (67%) including one multidrug resistant strain. Spinal cord compression or critical stenosis was demonstrated in eight patients (38%).

All received TB treatment for at least 12 months; six patients received treatment for a longer period. Seven (33%) underwent surgical intervention. Seventy-five per cent showed clinical and radiological resolution after treatment. No patients died or suffered long-term neurological deficit.

Conclusion: Spinal TB in children needs a high index of suspicion for diagnosis. Early referral to an expert centre allows a multidisciplinary approach to management.

The authors recommend that treatment should be individually tailored and may need to exceed 12 months in cases of poor adherence, extensive disease or drug resistance.

Anemia, apnea of prematurity and blood transfusions

*Zagol K, Lake DE, Vergales B et al
J Pediatr 2012; 161: 417-21*

Objective: To compare the frequency and severity of apneic events in very low birth weight (VLBW) infants before and after blood transfusions using continuous electronic waveform analysis.

Study design: We continuously collected waveform, heart rate, and oxygen saturation data from patients in all 45 neonatal intensive care unit beds at the University of Virginia for 120 weeks. Central apneas were detected using continuous computer processing

of chest impedance, electrocardiographic, and oximetry signals. Apnea was defined as respiratory pauses of >10, >20, and >30 seconds when accompanied by bradycardia (<100 beats per minute) and hypoxemia (<80% oxyhemoglobin saturation as detected by pulse oximetry). Times of packed red blood cell transfusions were determined from bedside charts. Two cohorts were analyzed. In the transfusion cohort, waveforms were analyzed for 3 days before and after the transfusion for all VLBW infants who received a blood transfusion while also breathing spontaneously. Mean apnea rates for the previous 12 hours were quantified and differences for 12 hours before and after transfusion were compared. In the hematocrit cohort, 1453 hematocrit values from all VLBW infants admitted and breathing spontaneously during the time period were retrieved, and the association of hematocrit and apnea in the next 12 hours was tested using logistic regression.

Results : Sixty-seven infants had 110 blood transfusions during times when complete monitoring data were available. Transfusion was associated with fewer computer-detected apneic events ($P < .01$). Probability of future apnea occurring within 12 hours increased with decreasing hematocrit values ($P < .001$). **Conclusion:** Blood transfusions are associated with decreased apnea in VLBW infants, and apneas are less frequent at higher hematocrits.

Artery-first approaches to pancreatoduodenectomy

*Sanjay P, Takaori K, Govil S et al
British Journal of Surgery 2012; 99 : 1027-1035*

Background: The technique of pancreatoduodenectomy (PD) has evolved. Previously, non-resectability was determined by involvement of the portal vein-superior mesenteric vein. Because venous resection can be achieved safely and with greater awareness of the prognostic significance of the status of the posteromedial resection margin, non-resectability is now determined by involvement of the superior mesenteric artery (SMA). This change, with a need for early determination of resectability before an irreversible step, has promoted the development of an 'artery-first' approach. The aim of this study was to review and illustrate this approach.

Methods: An electronic search was performed on MEDLINE, Embase and Pub. Med databases from 1960 to 2011 using both medical subject headings and truncated word searches to identify all published articles that related to this topic.

Results: The search revealed six different surgical approaches that can be considered as 'artery first'. These involved approaching the SMA from the retroperitoneum (posterior approach), the uncinate process (medial uncinate approach), the infracolic

region medial to the duodenojejunal flexure (inferior infracolic or mesenteric approach), the infracolic retroperitoneum lateral to the duodenojejunal flexure (left posterior approach), the supracolic region (inferior supracolic approach) and through the lesser sac (superior approach).

Conclusion: The six approaches described provide a range of options for the early determination of arterial involvement, depending on the location and size of the tumour, and before the 'point of no return'. Whether these approaches will achieve an increase in the proportion of patients with negative margins, improve locoregional control and increase long term survival has yet to be determined.

Long-term cerebral imaging after pre-eclampsia

*Aukes AM, Groot DG, Wiegman MJ et al
BJOG 2012; 119 : 117-1122*

Objective: Formerly eclamptic women demonstrate cerebral white matter lesions (WMLs) several years following the index pregnancy. The pathophysiology is unclear and may be related to the predisposition for cerebrovascular /cardiovascular disease in such women and/or the occurrence of posterior reversible encephalopathy syndrome whilst pregnant. The aim of this study was to assess the presence and severity of WMLs and their relationship with the severity of the neurological symptoms during the index pregnancy and several current cardiovascular risk factors in formerly pre-eclamptic women.

Design: This was a retrospective cohort study.

Setting: The Neuroimaging Centre at the School for Behavioural and Cognitive Neurosciences, Groningen, the Netherlands.

Population: Seventy-three formerly pre-eclamptic women were matched for age (37 ± 6 years) and elapsed time since index pregnancy (5.1 ± 3.7 years) with parous control women.

Methods: Cerebral magnetic resonance imaging scans were performed on cases and controls. Scans were rated by a neuroradiologist blind to the patient category.

Main outcome measures: The presence and severity of cerebral WMLs.

Results: Formerly pre-eclamptic women had WMLs significantly more often (37%) and more severely (mean, 0.11; median, 0.00; range, 0-2.34 tnl) than controls (21%, $P = 0.04$; mean, 0.015; median, 0.00; range, 0-0.13 ml; $P = 0.02$). Current hypertension and a history of early-onset pre-eclampsia (07 weeks) were independently associated with the presence of WMLs ($B = 1.34$, $1' = 0.02$ and $B = 1.73$, $p = 0.01$, respectively).

Conclusions: Our findings indicate that pre-eclampsia might be a risk marker for early cerebrovascular damage. The predisposition of formerly pre-eclamptic women to later cardiovascular and cerebrovascular disease may be an important factor for the development of cerebral WMLs. Whether a history of posterior reversible encephalopathy syndrome may be an additive risk factor for the development of these lesions remains unknown.