ABSTRACT FROM CURRENT LITERATURE

Trial of Cinpanemab in Early Parkinson's Disease

Lang AE, Siderow AD, Macklin EA, et al
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Background: Aggregated a-synuclein plays an important role in Parkinson`s pathogesis. Cinpanemab, a human-derived monoclonal antibody that binds to A-synucclein, is being evaluated as a disease-modifying treatment for Parkinson's disease .

Methods: In a 52 –week, multicenter, double-blind, phase 2 trial , We randomly assigned, in a 2:1:2:2 ratio, participants with early Parkinson`s disease to receive intravenous infusions of placebo (control) or cinpanemab at a dose of 250 mg, 1250 mg, or 3500 mg every 4 weeks, followed by an active-treatment dose-blinded extension period for up to 112 weeks. The primary end points were the changes from baseline in the movement Disorder Society-sponsored revision of the Unified Parkinson`s Disease Rating Scale (MDS-UPDRS) total score (range, 0 to 236, with higher scores indicating worse performance) at weeks 52 and 72. Secondary end points included MDS-UPDRS subscale scores and striatal binding as assessed on dopamine transporter single-photon- emssion computed tomography (DaT-SPECT).

Results: Of the 357 enrolled participants, 100 were assinged to the control group, 55 to the 250-mg cinpanemab gruop, 102 to the 1250 –mg group, and 100 to the 3500-mg group. The trial was stopped after the week 72 interin analysis owing to lack of efficacy. The change to week 52 in the MDS-UPDRS score was 10.8 points in the control group. 10.5 points in the 250-mg group, 11.3 points in the 1250-mg group and 10.9 points in the 3500-mg group (adjusted mean difference vs. control, - 0.3 points [95% confidence interval {CL} , -4.9 to 4.3], P=0.90; 0.5 points [95% CI, -3.3 to 4.3], P=0.80; and 0.1 point [95% confidence intervals -3.8 to 4.0] p=0.97, respectively). The adjusted mean difference at 72 weeks between participants who received cinpanemab through 72 weeks and the pooled group of those who started cinpanemab at 52 weeks was -0.9 points (95% CI, -5.6 to 3.8) for the 250-mg dose; 0.6 points (95% CI, -3.3 to 4.4) for the 1250-mg dose, and -0.8 points (95% CI, -4.6 to 3.0) for the 3500-mg dose. Results for secondary end points were similar to those for the primary end points. Da T- SPECT imaging at week 52 showed no diffences between the control group and any cinpanemab group. The most adverse events with cinpanemab were headache, naspharygitis, and falls.

Conclusions: In participants with early Parkinson`s disease, the effects of cinpanemab on clinical measures of disease progression and changes in Da T- SPECT imaging did not differ from those of placebo over a 52-week period (Funded by Biogen; SPARK Clinical Trials gov number.

Albuterol-Budesonide fixed-dose combination rescue inhaler for asthma

Papi A, Chipps BE, Beasley R, et al
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Background : As asthma symptoms worsen, patients typically rely on short-acting ß-agonist (SABA) rescue therapy, but SABAs do not address worsening inflammation, which leaves patients at risk for severe asthma exacerbations. The use of a fixed-dose combination of albuterol and budesonide, as compared with albuterol alone, as rescue medication might reduce the risk of severe asthma exacerbation.

Methods: We conducted a multinational, phase 3, double-blind, randomized, event-driven trial to evaluate the efficacy and safety of albuterol-budesonide, as compared with albuterol alone, as rescue medication in patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid- containing maintenance therapies, which were continued throughout the trial. Adults and adolescents (≥12 years of age) were randomly assigned in a 1:1:1 ratio to one of three trial groups: a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide (with each dose consisting of two actuations of 90 µg and 80 µg, respectively [the higher-dose combination group]), a fixed-dose combination of 180 µg of albuterol and 80 µg of budesonide (with each dose consisting of two actuations of 90 µg and 40 µg, respectively [the lower-dose combination group]), or 180 µg of albuterol (with each dose consisting of two actuations of 90 µg [the albuterol-alone group]).

Children 4 to 11 years of age were randomly assigned to only the lower-dose combination group or the albuterol-alone group. The primary efficacy end point was the first event of severe asthma exacerbation in a time-to-event analysis, which was performed in the intention-to-treat population.

Results: A total of 3132 patients underwent randomization, among whom 97% were 12 years of age or older. The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P=0.001). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P=0.052). The incidence of adverse events was similar in the three trial groups.

Conclusions: The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies. (Funded by Avillion; MANDALA Clinical Trials.gov number, NCT03769090.)

Thrombectomy for anterior circulation stroke beyond 6 h from time last known well (AURORA): a systematic review and individual patient data meta-analysis

Jovin TG, Nogueira RG, Lansberg MG, et al
THE LANCET 2022; 399: 249-258

Background: Trials examining the benefit of thrombectomy in anterior circulation proximal large vessel occlusion stroke have enrolled patients considered to have salvageable brain tissue, who were randomly assigned beyond 6 h and (depending on study protocol) up to 24 h from time last seen well. We aimed to estimate the benefit of thrombectomy overall and in prespecified subgroups through individual patient data meta-analysis.

Methods: We did a systematic review and individual patient data meta-analysis between Jan 1, 2010, and March 1, 2021, of randomised controlled trials of endovascular stroke therapy. In the Analysis Of Pooled Data From Randomized Studies Of Thrombectomy More Than 6 Hours After Last Known Well (AURORA) collaboration, the primary outcome was disability on the modified Rankin Scale (mRS) at 90 days, analysed by ordinal logistic regression. Key safety outcomes were symptomatic intracerebral haemorrhage and mortality within 90 days.

Findings: Patient level data from 505 individuals (n=266 intervention, n=239 control; mean age 68-6 years [SD 13-7], 259 [51.3%] women) were included from six trials that met inclusion criteria of 17 screened published randomised trials. Primary outcome analysis showed a benefit of thrombectomy with an unadjusted common odds ratio (OR) of 2-42 (95% CI 1.76-3-33; p<0•0001) and an adjusted common OR (for age, gender, baseline stroke severity, extent of infarction on baseline head CT, and time from onset to random assignment) of 2.54 (1.83-3-54; p<0.0001). Thrombectomy was associated with higher rates of independence in activities of daily living (mRS 0-2) than best medical therapy alone (122 [45.9%] of 266 vs 46 [19.3%] of 238; p<0.0001). No significant difference between intervention and control groups was found when analysing either 90-day mortality (44 [16.5%] of 266 vs 46 [19.3%] of 238) or symptomatic intracerebral haemorrhage (14 [5.3%] of 266 vs eight [3.3%] of 239). No heterogeneity of treatment effect was noted across subgroups defined by age, gender, baseline stroke severity, vessel occlusion site, baseline Alberta Stroke Program Early CT Score, and mode of presentation; treatment effect was stronger in patients randomly assigned within 12-24 h (common OR 5.86 [95% CI 3.14-10.94]) than those randomly assigned within 6-12 h (1.76 [1-18-2-62]; Pinteraction =0•0087).

Interpretation: These findings strengthen the evidence for benefit of endovascular thrombectomy in patients with evidence of reversible cerebral ischaemia across the 6-24 h time window and are relevant to clinical practice. Our findings suggest that in these patients, thrombectomy should not be withheld on the basis of mode of presentation or of the point in time of presentation within the 6-24 h time window.

Paediatric pneumonia: deriving a model to identify severe disease

Haggie S, Barnes EH, Selvadurai H, et al
Archives of Disease in Childhood 2022; 107: 486-491

Background: Community acquired paeumonia (CAP) is a leading cause of childhood hospitalisation. Limited data exist on factors predicting severe disease with no paediatric-specific predictive tools.

Methods: Retrospective cohort (2011-2016) of hospitalised CAP cases. We analysed clinical variables collected at hospital presentation against outcomes. Stratified outcomes were mild (hospitalised), moderate (invaseve dainage procedure, intensive care) or severe (mechanical ventilation, vasopressors, death).

Results: We report 3330 CAP cases, median age 2.0 years (IQR 1-5 years), with 2950 (88.5%) mild, 305 (9.2%) modate and 75 (2.3%) severe outcomes. Moderate-severe outcomes were associated with hypoxia (SaO2 <90%; OR 6.6, 95% CI 5.1 to 8.5), increased work of breathing (severe vs normal OR 5.8, 95% CI 4.2 to 8.0) comorbidities (4+ comorbidities vs nil: OR 8.8, 95% CI 5.5 to 14) and being indigenous (OR 4.7, 95% C1 2.6 to 8.4) Febrile children were less likely than afebrile children to have moderate-severe outcomes (OR 0.57 95% CI 0.44 to 0.74). The full model receiver operating characteristic (ROC) area under the curve (AUC) was 0.78 Sensitivity analyses showed similar results with clinical or radiological CAP definitions. We derived a clinical tool to stratify low, intermediate or high likelihood of severe disease (AUC 0.72) High scores (>5) had nearly eight times higher odds of moderate-severe disease than those with a low (<1) score (OR 7.7 95% CI 5.6 to 10.5)

Conclusions: A clinical risk prediction tool is needed for child CAP. We have identified risk factors and derived a simple clinical tool using clinical variables at hospital presentation to determine a child's risk of invasive or intensive care treatment with an ROC AUC comparable with adult pneumonia tools.

DIAgnostic iMaging or Observation in early equivocal appeNDicitis (DIAMOND): open-label, randomized clinical trial

Lastunen KS and others

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Background: Mild appendicitis may resolve spontaneously. The use of CT may lead to an overdiagnosis of uncomplicated appendicitis. The aims of this study were to examine whether early imaging results in more patients being diagnosed with acute appendicitis than initial observation, and to study the safety and feasibility of score-based observation compared with imaging in patients with equivocal signs of appendicitis.

Methods: Patients with suspected appendicitis with symptoms for fewer than 24 h and an Adult Appendicitis Score of 11-15 were eligible for this trial. After exclusions, patients were randomized openly into two equal-sized groups: imaging and observation. Patients in the imaging group had ultrasound imaging followed by CT when necessary, whereas those in the observation group were reassessed after 6-8 h with repeated scoring and managed accordingly. The primary outcome was the number of patients requiring treatment for acute appendicitis within 30 days.

Results: Ninety-three patients were randomized to imaging and 92 to observation; after exclusions, 93 and 88 patients respectively were analysed. In the imaging group, more patients underwent treatment for acute appendicitis than in the observation group: 72 versus 57 per cent (difference 15 (95 per cent c.i. 1 to 29) per cent). This suggests that patients with spontaneously resolving appendicitis were not diagnosed or treated in the observation group. Some 55 per cent of patients in the observation group did not need diagnostic imaging within 30 days after randomization. There was no difference in the number of patients diagnosed with complicated appendicitis (4 versus 2 per cent) or negative appendicectomies (1 versus 1 per cent) in the imaging and observation groups.

Conclusion: Score-based observation of patients with early equivocal appendicitis results in fewer patients requiring treatment for appendicitis. Registration number: NCT02742402

Watch and wait after a clinical complete response in rectal cancer patients younger than 50 years

Bahadoer RR and others

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Background: Young-onset rectal cancer, in patients less than 50 years, is expected to increase in the coming years. A watch-and-wait strategy is nowadays increasingly practised in patients with a clinical complete response (CCR) after neoadjuvant treatment. Nevertheless, there may be reluctance to offer organ preservation treatment to young patients owing to a potentially higher oncological risk. This study compared patients aged less than 50 years with those aged 50 years or more to identify possible differences in oncological outcomes of watch and wait.

Methods: The study analysed data from patients with a CCR after neoadjuvant therapy in whom surgery was omitted, registered in the retrospective- prospective, multicentre International Watch & Wait Database (IWWD).

Results: In the IWWD, 1552 patients met the inclusion criteria, of whom 199 (12.8 per cent) were aged less than 50 years. Patients younger than 50 years had a higher T category of disease at diagnosis (P=0.011). The disease-specific survival rate at 3 years was 98 (95 per cent c.i. 93 to 99) per cent in this group, compared with 97 (95 to 98) per cent in patients aged over 50 years (hazard ratio (HR) 1.67, 95 per cent c.i. 0.76 to 3.64; P=0.199). The cumulative probability of local

regrowth at 3 years was 24 (95 per cent c.i. 18 to 31) per cent in patients less than 50 years and 26 (23 to 29) per cent among those aged 50 years or more (HR 1.09, 0.79 to 1.49; P=0.603). Both groups had a cumulative probability of distant metastases of 10 per cent at 3 years (HR 1.00, 0.62 to 1.62; P=0.998).

Conclusion: There is no additional oncological risk in young patients compared with their older counterparts when following a watch-and-wait strategy after a cCR. In light of a shared decision-making process, watch and wait should be also be discussed with young patients who have a CCR after neoadjuvant treatment.

Adult lifetime body mass index trajectories and endometrial cancer risk

Dalmartello M, Vermunt J, Negri E, et al
BJOG 2022; 129: 1521-1529

Objective: To identify body mass index (BMI) trajectories in adult life and to examine their association with endometrial cancer (EC) risk, also exploring whether relations differ by hormonal replacement therapy use.

Design: Pooled analysis of two case-control studies.

Setting: Italy and Switzerland.

Population: A total of 458 EC cases and 782 controls.

Methods: We performed a latent class growth model to identify homogeneous BMI trajectories over six decades of age, with a polynomial function of age. Odds ratios (ORs) and the corresponding 95% CI for EC risk were derived through a multiple logistic regression model, correcting for classification error.

Main outcome measures: The relation of BMI trajectories with endometrial cancer.

Results: We identified five BMI trajectories. Compared with women in the 'Normal weight-stable' trajectory, a reduction by about 50% in the risk of EC emerged for those in the 'Underweight increasing to normal weight' (95% CI 0.28-0.99). The 'Normal weight increasing to overweight' and the 'Overweight-stable' trajectories were associated with, respectively, an excess of 3% (95% CI 0.66-1.60) and of 71% (95% CI 1.12-2.59) in cancer risk. The OR associated to the trajectory 'Overweight increasing to obese' was 2.03 (95% CI 1.31-3.13). Stronger effects emerged among hormonal replacement therapy never users (OR 2.19 for the 'Overweight-stable' trajectory and OR 2.49 for the 'Overweight increasing to obese' trajectory).

Conclusions: Our study suggests that longer exposure to overweight and obesity across a lifetime is associated with an increased risk of endometrial cancer. Weight during adulthood also appears to play an important role.

The project appropriate birth and a reduction in caesarean section rates: an analysis using the Robson classification system

Marin DFD, Wernke AR, Dannehl D, et. al
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Objective: The objective of this study was to assess caesarean section (CS) rates before and after the implementation of the Project Appropriate Birth (PPA), based on the Robson ten group classification system.

Design: A before-and-after study.

Setting: Maternity hospital in South Brazil.

Population: All pregnant women attending from April 2016 to April 2017 (period 1, pre-implementation of PPA) and from June 2017 to June 2018 (period 2, post-implementation of PPA).

Methods: Maternal and obstetric characteristics were evaluated, including Robson's classification, based on the characteristics of pregnancy and childbirth. A chi-square test and crude and adjusted relative rates were used to analyse the study variables. The significance level was set at 5%.

Main outcome measures: The CS rate for each group, their contribution to the overall CS rate and the differences in these contributions before and after PPA implementation.

Results: The CS rates decreased from 62.4 to 55.6%, which represented a 10.9% reduction after the implementation of the PPA. Pregnant women in Robson classification groups 1-4 had a 21.4% reduction in CS rates, ranging from 49.1 to 38.6%. The greatest contributors to the overall CS rates were group 5 and group 2, accounting for more than 60% of the CS deliveries. Conclusion: The study results suggest that Project Appropriate Birth had an impact on the reduction of CS rates, especially in Robson classification groups 1 through 4, which indicates that providing mothers with evidence-based interventions for labour and childbirth assistance contributed to reduce CS rates.