*What is new in 2013?**

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

Karl Swedberg, M.D., Ph.D., et al.

N Engl J Med 2013; 368:1210-1219

Since patients with systolic heart failure and anemia have worse symptoms, functional capacity, and outcomes than those without anemia, the effects of darbepoetin alfa on clinical outcomes in patients with systolic heart failure and anemia was evaluated.

2278 patients with systolic heart failure and mild-to-moderate anemia (hemoglobin level, 9.0 to 12.0 g per deciliter) receive either darbepoetin alfa (to achieve a hemoglobin target of 13 g per deciliter) or placebo. The primary outcome was a composite of death from any cause or hospitalization for worsening heart failure.

The primary outcome occurred in 576 of 1136 patients (50.7%) in the darbepoetin alfa group and 565 of 1142 patients (49.5%) in the placebo group (hazard ratio in the darbepoetin alfa group, 1.01; 95% confidence interval, 0.90 to 1.13; P=0.87). There was no significant between-group difference in any of the secondary outcomes. The neutral effect of darbepoetin alfa was consistent across all prespecified subgroups. Fatal or nonfatal stroke occurred in 42 patients (3.7%) in the darbepoetin alfa group and 31 patients (2.7%) in the placebo group (P=0.23). Thromboembolic adverse events were reported in 153 patients (13.5%) in the darbepoetin alfa group and 114 patients (10.0%) in the placebo group (P=0.01). Cancer-related adverse events were similar in the two study groups.

Although treatment with darbepoetin alfa raised the hemoglobin level, did not improve clinical outcomes in patients with systolic heart failure and mild-to-moderate anemia. The results do not support the use of darbepoetin alfa in these patients (most likely due of increase of visiosity).

Treatment of Hepatit C virus Infection by Targeting MicroRNA

Harry L.A. Janssen, M.D., Ph.D., et al.

N Engl J Med 2013 (May 2); 368:1685-1694.

Since the stability and propagation of hepatitis C virus (HCV) is dependent on a functional interaction between the HCV genome and liver-expressed microRNA-122, (miR-122). Miravirsen (nucleic acid–modified DNA phosphorothioate antisense oligonuc-leotide that sequesters mature miR-122) a highly stable heteroduplex, thereby inhibiting its function was used fort he treatment.

The safety and efficacy of miravirsen in 36 patients with chronic HCV genotype 1 infection were evaluated. The patients were randomly assigned to receive five weekly subcutaneous injections of miravirsen at doses of 3 mg, 5 mg, or 7 mg per kilogram of body weight or placebo over a 29-day period, and were followed 18 weeks after randomization.

Miravirsen resulted in a dose-dependent reduction in HCV RNA levels that endured beyond the end of active therapy. In the miravirsen groups, the mean maximum reduction in HCV RNA level (log10 IU per milliliter) from baseline was 1.2 (P=0.01) for patients receiving 3 mg per kilogram, 2.9 (P=0.003) for those receiving 5 mg per kilogram, and 3.0 (P=0.002) for those receiving 7 mg per kilogram, as compared with a reduction of 0.4 in the placebo group. During 14 weeks of follow-up after treatment, HCV RNA was not detected in one patient in the 5-mg group and in four patients in the 7-mg group. No dose-limiting adverse events and no escape mutations in the miR-122 binding sites of the HCV genome were observed.

The use of miravirsen in patients with chronic HCV genotype 1 infection showed prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance.

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Analysis of Circulating Tumor DNA to Monitor Metastatic Breast Cancer

Sarah-Jane Dawson, F.R.A.C.P., Ph.D., et al.

N Engl J Med 2013; 368:1199-1209

The management of metastatic breast cancer requires monitoring of the tumor burden to determine the response to treatment, and improved biomarkers are needed. Biomarkers such as cancer antigen 15-3 (CA 15-3) and circulating tumor cells have been widely studied. However, circulating cell-free DNA carrying tumor-specific alterations (circulating tumor DNA) has not been extensively investigated or compared with other circulating biomarkers in breast cancer.

Therefore the radiographic imaging of tumors with the assay of circulating tumor DNA, CA 15-3, and circulating tumor cells in 30 women with metastatic breast cancer who were receiving systemic therapy were compared.

Circulating tumor DNA was successfully detected in 29 of the 30 women (97%) in whom somatic genomic alterations were identified; CA 15-3 and circulating tumor cells were detected in 21 of 27 women (78%) and 26 of 30 women (87%), respectively. Circulating tumor DNA levels showed a greater dynamic range, and greater correlation with changes in tumor burden, than did CA 15-3 or circulating tumor cells. Among the measures tested, circulating tumor DNA provided the earliest measure of treatment response in 10 of 19 women (53%).

This proof-of-concept analysis showed that circulating tumor DNA is an informative, inherently specific, and highly sensitive biomarker of metastatic breast cancer.

A Randomized Trial of Glutamine and Antioxidants in Critically Ill Patients

Daren Heyland, M.D., et al.

N Engl J Med 2013; 368:1489-1497

Critically ill patients have considerable oxidative stress. Glutamine and antioxidant supplementation may offer therapeutic benefit, although current data are conflicting.

In this blinded 2-by-2 factorial trial, we randomly assigned 1223 critically ill adults in 40 intensive care units (ICUs) in Canada, the United States, and Europe who had multiorgan failure and were receiving mechanical ventilation to receive supplements of glutamine, antioxidants, both, or placebo. Supplements were started within 24 hours after admission to the ICU and were provided both intravenously and enterally. The primary outcome was 28-day mortality. Because of the interim-analysis plan, a P value of less than 0.044 at the final analysis was considered to indicate statistical significance.

There was a trend toward increased mortality at 28 days among patients who received glutamine as compared with those who did not receive glutamine (32.4% vs. 27.2%; adjusted odds ratio, 1.28; 95% confidence interval [CI], 1.00 to 1.64; P=0.05). In-hospital mortality and mortality at 6 months were significantly higher among those who received glutamine than among those who did not. Glutamine had no effect on rates of organ failure or infectious complications. Antioxidants had no effect on 28-day mortality (30.8%, vs. 28.8% with no antioxidants; adjusted odds ratio, 1.09; 95% CI, 0.86 to 1.40; P=0.48) or any other secondary end point. There were no differences among the groups with respect to serious adverse events (P=0.83).

Early provision of glutamine or antioxidants did not improve clinical outcomes, and glutamine was associated with an increase in mortality among critically ill patients with multiorgan failure.

Serum Macromoleculer Creatine Kinase Type 1 as a diagnostic clue in inflammatory bowel disease

Hoffman K.M. et al.

European Journal of Pediatrics 2013

In two patients (13 year old girl and 12 year old boy) with inflamatory bowel disease with diarha and weight loss were initially diagnosed as Crohn's disease. During flare-ups the diagnosis was changed to ulcerative colaitis with colonoscopic examination, biopsy and the demonstration of macromoleculer creatine kinase type 1. As in adults it seems that the presence of macro-moleculer kinase type 1 corresponds to diagnosis of ulcerative colaitis during flare-up period.

*What is new in 2013?**

In very low birth weight neonates a blood pressure less than 30 mmHg do not decrease cerebral oxygenation

Özlem Bozkurt MD, H.Gözde Kanmaz Kutman MD

Up to %40 of very low birthweight neonates are treated for hypotension and hypotension is associated with poor neurological outcome. Most often treatment of hypotension is based solely on blood pressure measurement. But it is uncertain whether treatment improves cerebral blood flow. Published by Arch Dis Child Fetal Neonatal Ed. Ganer SR *et al.* showed that treatment of hypotension in VLBW neonates basel solely on a blood pressure less than 30 mmHg, while increasing blood pressure, may not increase cerebral oxygenation.

Noninvasive ventilation, surfactant administration and prevention of chronic lung disease in preterm infants

Dargaville PA et al.,

Neonatology 2013;104:8-14

(DOI:10.1159/000346460)

Preterm infants <32 weeks' gestation are increasingly being managed on continuous positive airway pressure (CPAP), without prior intubation and surfactant therapy. Some infants treated in this way ultimately fail on CPAP and require intubation and ventilation. The authors aimed to define the incidence, predictors and consequences of CPAP failure in preterm infants managed with CPAP from the outset. Preterm infants 25-32 weeks' gestation were included in the study if inborn and managed with CPAP as the initial respiratory support, with division into two gestation ranges and grouping according to whether they were successfully managed on CPAP (CPAP-S) or failed on CPAP and required intubation <72 h (CPAP-F). Predictors of CPAP failure were sought, and outcomes compared between the groups. During the study period, 297 infants received CPAP, of which 65 (22%) failed, with CPAP failure being more likely at lower gestational age. Most infants failing CPAP had moderate or severe respiratory distress syndrome radiologically. In multivariate analysis, CPAP failure was found to be predicted by the highest FiO_2 in the first hours of life. CPAP-F infants had a prolonged need for respiratory support and oxygen therapy, and a higher risk of death or bronchopulmonary dysplasia at 25-28 weeks' gestation (CPAP-F 53% vs. CPAP-S 14%, relative risk 3.8, 95% CI 1.6, 9.3) and a substantially higher risk of pneumothorax at 29-32 weeks. The authors concluded that CPAP failure in preterm infants usually occurs because of unremitting respiratory distress syndrome, is predicted by an FiO2 >0.3 in the first hours of life, and is associated with adverse outcomes.

Allergy testing in atopic dermatitis: often unnecessary

Atopic dermatitis (AD) is a chronic inflammatory skin disease from which many children and adults suffer. In Europe, the majority of patients with AD are treated in the primary health care setting. There is no clear consensus about whether or not to conduct allergy testing in patients with AD. Determining sensitization to inhalant allergens in children with AD has no consequences for its treatment and course and is therefore not necessary. Allergy testing is useful if the child is suspected of having allergic asthma or allergic related diseases. Determining sensitization to food allergens in children with AD without a positive history of acute allergic reactions to food has no therapeutic consequences and could result in the unnecessary prescription or following of elimination diets. Similarly, determining sensitization to inhalant and food allergens has no influence on the treatment regimen for adults with AD. This type of testing is therefore not useful, unless the medical history reveals indications for the occurrence of acute allergic reactions to certain allergens.

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