

## Omega-3 Fatty Acids Therapy in Children with Nonalcoholic Fatty Liver Disease: a Randomized Controlled Trial

Janczyk W. *et al.*

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To evaluate the efficacy and safety of omega-3 fatty acid supplementation in children with nonalcoholic fatty liver disease (NAFLD).

Overweight/obese children with NAFLD (n = 76; median age, 13 years; IQR, 11.1–15.2 years) were eligible to participate in the study. The diagnosis of NAFLD was based on elevated alanine aminotransferase (ALT) to  $\geq 30\%$  of the upper limit of normal (ULN) and liver hyperechogenicity on ultrasound. The patients were randomized to receive omega-3 fatty acids (docosahexaenoic acid and eicosapentaenoic acid, 450–1300 mg/day) or placebo (omega-6 sunflower oil). The primary outcome was the number of patients who demonstrated decreased ALT activity by  $\geq 0.3$  times the ULN. Secondary outcomes included alterations in liver function tests, liver hyperechogenicity, insulin resistance, and other metabolic markers after 6 months of intervention.

Out of 76 enrolled patients, 64 completed the trial and were analyzed. After 6 months, no significant differences were found between the omega-3 and placebo groups in the number of patients with decreased ALT by  $\geq 0.3$  times, liver hyperechogenicity, insulin resistance, or serum lipid levels. However, patients in the omega-3 group had lower levels of aspartate aminotransferase and gamma-glutamyl transpeptidase ( $P = 0.04$ ), and significantly higher levels of adiponectin.

Omega-3 fatty acid supplementation did not increase the number of patients with decreased ALT levels and did not affect liver steatosis on ultrasound, but it improved aspartate aminotransferase and gamma-glutamyl transpeptidase levels in children with NAFLD compared with placebo.

## Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

Saver JL. *et al.*

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Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfusion rates and may improve long-term functional outcome.

Eligible patients with stroke were randomly assigned into two groups: those who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 h after symptom onset (intervention group). The patients had confirmed occlusions in the proximal anterior intracranial circulation and absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin scale.

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The study was stopped early because of efficacy. At 39 centers, 196 patients underwent randomization (98 patients in each group). In the intervention group, the median time from qualifying imaging to groin puncture was 57 minutes, and the rate of substantial reperfusion at the end of the procedure was 88%. Thrombectomy with the stent retriever plus intravenous t-PA reduced disability at 90 days over the entire range of scores on the modified Rankin scale ( $P < 0.001$ ). The rate of functional independence was higher in the intervention group than in the control group (60% vs. 35%,  $P < 0.001$ ). No significant between-group differences were reported in 90-day mortality (9% vs. 12%,  $P = 0.50$ ) or symptomatic intracranial hemorrhage (0% vs. 3%,  $P = 0.12$ ).

In patients receiving intravenous t-PA for acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, thrombectomy with a stent retriever within 6 h after onset improved functional outcomes at 90 days.

## Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke

Jovin TG. *et al.*

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During a 2-year period at four centers in Catalonia, Spain, 206 patients, who could be treated within 8 h after the onset of symptoms of acute ischemic stroke were randomly assigned to receive either medical therapy (including intravenous alteplase when eligible) and endovascular therapy with the Solitaire stent retriever (thrombectomy group) or medical therapy alone (control group). All patients had confirmed proximal anterior circulation occlusion and the absence of a large infarct on neuroimaging. In all patients, the use of alteplase either did not achieve revascularization or was contraindicated. The primary outcome was the severity of global disability at 90 days, as measured on the modified Rankin scale (ranging from 0 [no symptoms] to 6 [death]). Although the maximum planned sample size was 690, enrollment was halted early because of loss of equipoise after positive results for thrombectomy were reported from other similar trials.

Thrombectomy reduced the severity of disability over the range of the modified Rankin scale (adjusted odds ratio for improvement of 1 point, 1.7; 95% confidence interval [CI], 1.05–2.8) and led to higher rates of functional independence (a score of 0–2) at 90 days (43.7% vs. 28.2%; adjusted odds ratio, 2.1; 95% CI, 1.1–4.0).

Among patients with anterior circulation stroke who could be treated within 8 h after symptom onset, stent retriever thrombectomy reduced the severity of post-stroke disability and increased the rate of functional independence.

## Corticosteroids and Pneumonia: Time to Change Practice

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Pneumonia is characterized by lung inflammation, with fluid filling the alveoli and preventing adequate oxygenation of the body, and can be acquired in the community or in hospital. In 2013, about one million children died from pneumonia, which was the leading cause of death in children aged 5 years or younger. Annually, 15 adults per 1000 visit a doctor for symptoms of community-acquired pneumonia. In 2013, lower respiratory tract infections caused 2.7 million deaths. Although the epidemiological burden of community-acquired pneumonia is highest in patients aged 65 years or older, the disease incurs substantial morbidity and health-care costs in working-age adults.

## Adjunct Prednisone Therapy for Patients with Community-acquired Pneumonia: a Multicenter, Double-blind, Randomized, Placebo-controlled Trial

Blum CA. *et al.*

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Clinical trials yielded conflicting data about the benefit of adding systemic corticosteroids for the treatment of community-acquired pneumonia. The study assessed whether short-term corticosteroid treatment reduces time to clinical stability in patients admitted to hospital for community-acquired pneumonia.

In this double-blind, multicenter, randomized, placebo-controlled trial, patients aged 18 years or older with community-acquired pneumonia were recruited from seven tertiary care hospitals in Switzerland within 24 h of presentation. The patients were randomly assigned (1:1 ratio) to receive either prednisone 50 mg daily for 7 days or placebo. The computer-generated randomization was done with variable block sizes of four to six and stratified by study center. The primary endpoint was time to clinical stability defined as time (days) until stable vital signs for at least 24 h, and analyzed by intention to treat.

From December 1, 2009, to May 21, 2014, of 2911 patients assessed for eligibility, 785 patients were randomly assigned to either the prednisone group (n = 392) or the placebo group (n = 393). Median time to clinical stability was shorter in the prednisone group (3.0 days, IQR 2.5–3.4) than in the placebo group (4.4 days, 4.0–5.0; hazard ratio [HR] 1.33, 95% CI 1.15–1.50, P < 0.0001). Pneumonia-associated complications until day 30 did not differ between groups (11 [3%] in the prednisone group and 22 [6%] in the placebo group; odds ratio [OR] 0.49, 95% CI 0.23–1.02, P = 0.056). The prednisone group had a higher incidence of in-hospital hyperglycemia needing insulin treatment (76 [19%] vs. 43 [11%]; OR 1.96, 95% CI 1.31–2.93, P = 0.0010). Other adverse events compatible with corticosteroid use were rare and similar in both the groups.

Prednisone treatment for 7 days in patients with community-acquired pneumonia admitted to hospital shortens time to clinical stability without an increase in complications. This finding is relevant from a patient perspective and an important determinant of hospital costs and efficiency.

## Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

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Apolipoprotein C-III (APOC3) is a key regulator of plasma triglyceride levels. Elevated triglyceride levels are associated with a risk of adverse cardiovascular events and pancreatitis. ISIS 304801 is a second-generation antisense inhibitor of APOC3 synthesis.

A randomized, double-blind, placebo-controlled, dose-ranging, phase 2 study was conducted to evaluate ISIS 304801 in untreated patients with fasting triglyceride levels between 350 mg per deciliter and 2000 mg per deciliter (ISIS 304801 monotherapy cohort), as well as in patients receiving stable fibrate therapy who had fasting triglyceride levels between 225 mg per deciliter and 2000 mg per deciliter (ISIS 304801 fibrate cohort). Eligible patients were randomly assigned to receive either ISIS 304801, at doses ranging from 100 to 300 mg, or placebo, once weekly for 13 weeks. The primary outcome was the percentage change in APOC3 level from baseline.

A total of 57 patients were treated in the ISIS 304801 monotherapy cohort (41 received active agent and 16 received placebo), and 28 patients were treated in the ISIS 304801 fibrate cohort (20 received active agent and 8 received placebo). The mean ( $\pm$ SD) baseline triglyceride levels in the two cohorts were  $581 \pm 291$  mg per deciliter and  $376 \pm 188$  mg per deciliter, respectively. Treatment with ISIS 304801 resulted in dose-dependent and prolonged decreases in plasma APOC3 levels when the drug was administered as a single agent (decreases of  $40.0 \pm 32.0\%$  in the 100-mg group,  $63.8 \pm 22.3\%$  in the 200-mg group, and  $79.6 \pm 9.3\%$  in the 300-mg group, vs. an increase of  $4.2 \pm 41.7\%$  in the placebo group) and when it was administered as an add-on to fibrates (decreases of  $60.2 \pm 12.5\%$  in the 200-mg group and  $70.9 \pm 13.0\%$  in the 300-mg group, vs. a decrease of  $2.2 \pm 25.2\%$  in the placebo group). Concordant reductions of 31.3–70.9% were observed in triglyceride levels. No safety concerns were identified in this short-term study.

It was found that treatment with ISIS 304801 was associated with significant lowering of triglyceride levels, among patients with a broad range of baseline levels, through selective antisense inhibition of APOC3 synthesis.

## GMOs, Herbicides, and Public Health

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Genetically modified organisms (GMOs) are not high on most physicians' worry lists. If we think at all about biotechnology, most of us probably focus on direct threats to human health, such as prospects for converting pathogens to biologic weapons or the implications of new technologies for editing the human germline. But while those debates simmer, the application of biotechnology to agriculture has been rapid and aggressive. The vast majority of the corn and soybeans grown in the United States are now genetically engineered. Foods produced from GM crops have become ubiquitous.

Two recent developments are dramatically changing the GMO landscape. First, sharp increases have been noted in the amounts and numbers of chemical herbicides applied to GM crops. Second, the International Agency for Research on Cancer (IARC) has classified glyphosate, the herbicide most widely used on GM crops, as a "probable human carcinogen," and a second herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D), as a "possible human carcinogen."

The application of genetic engineering to agriculture builds on the ancient practice of selective breeding. But unlike traditional selective breeding, genetic engineering vastly expands the range of traits that can be moved into plants and enables breeders to import DNA from virtually anywhere in the biosphere. Depending on the traits selected, genetically engineered crops can increase yields, thrive when irrigated with salty water, or produce fruits and vegetables resistant to mold and rot.

The National Academy of Sciences has twice reviewed the safety of GM crops—in 2000 and 2004. Those reviews, which focused almost entirely on the genetic aspects of biotechnology, concluded that GM crops pose no unique hazards to human health. They noted that genetic transformation has the potential to produce unanticipated allergens or toxins and might alter the nutritional quality of food. Both reports recommended the development of new risk-assessment tools and postmarketing surveillance. These recommendations have largely gone unheeded.

Herbicide resistance is the main characteristic that the biotechnology industry has chosen to introduce into plants. Corn and soybeans with genetically engineered tolerance to glyphosate were first introduced in the mid-1990s. These "Roundup-Ready" crops now account for more than 90% of the corn and soybeans planted in the United States. Their

advantage, especially in the first years after introduction, is that they greatly simplify weed management. Farmers can spray herbicide both before and during the growing season, leaving their crops unharmed.

However, widespread adoption of herbicide-resistant crops has led to overreliance on herbicides and, in particular, on glyphosate. The first of the two developments that raise fresh concerns about the safety of GM crops is a 2014 decision by the Environmental Protection Agency (EPA) to approve Enlist Duo, a new combination herbicide comprising glyphosate plus 2,4-D. Enlist Duo was formulated to combat herbicide resistance. It will be marketed in tandem with newly approved seeds genetically engineered to resist glyphosate, 2,4-D, and multiple other herbicides. The EPA anticipates that a 3- to 7-fold increase in 2,4-D use will result.

It is presumed that the science and the risk assessment supporting the Enlist Duo decision are flawed. These studies predated current knowledge of low-dose, endocrine-mediated, epigenetic effects and were not designed to detect them. The risk assessment gave little consideration to potential health effects in infants and children, thus contravening federal pesticide law. It failed to consider ecological impact, such as effects on the monarch butterfly and other pollinators. It considered only pure glyphosate, despite studies showing that formulated glyphosate that contains surfactants and adjuvants is more toxic than the pure compound.

It is believed that the time has therefore come to thoroughly reconsider all aspects of the safety of plant biotechnology.

It is hoped, in light of this new information, that the FDA will reconsider labeling of GM foods and couple it with adequately funded, long-term postmarketing surveillance.

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## Community-Acquired Pneumonia Requiring Hospitalization among US Adults

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Community-acquired pneumonia is a leading infectious cause of hospitalization and death among US adults.

A study was conducted on active population-based surveillance for community-acquired pneumonia requiring hospitalization among adults 18 years of age or older in five hospitals in Chicago and Nashville. The patients with recent hospitalization or severe immunosuppression were excluded. Blood, urine, and respiratory specimens were systematically collected for culture, serologic testing, antigen detection, and radiographs. Population-based incidence rates were of community-acquired pneumonia requiring hospitalization according to age and pathogen.

From January 2010 through June 2012, 2488 of 3634 eligible adults were enrolled (68%). Among 2320 adults with radiographic evidence of pneumonia (93%), the median age of the patients was 57 years; 498 patients (21%) required intensive care, and 52 (2%) died. Among 2259 patients who had radiographic evidence of pneumonia and specimens available for both bacterial and viral testing, a pathogen was detected in 853 (38%): one or more viruses in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and a fungal or mycobacterial pathogen in 17 (1%). The most common pathogens were human rhinovirus (in 9% of patients), influenza virus (in 6%), and *Streptococcus pneumoniae* (in 5%). The annual incidence of pneumonia was 24.8 cases, with the highest rates among adults 65–79 years of age and those 80 years of age or older (164.3 cases per 10,000 adults). For each pathogen, the incidence increased with age.

The incidence of community-acquired pneumonia requiring hospitalization was highest among the oldest adults. Despite current diagnostic tests, no pathogen was detected in the majority of patients. Respiratory viruses were detected more frequently than bacteria.

## A Phase 3 Trial of Sebelipase Alfa in Lysosomal Acid Lipase Deficiency

Burton BK. *et al.*

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Lysosomal acid lipase is an essential lipid-metabolizing enzyme that breaks down endocytosed lipid particles and regulates lipid metabolism. A phase 3 trial of enzyme-replacement therapy in children and adults with lysosomal acid lipase deficiency, an underappreciated cause of cirrhosis and severe dyslipidemia, was conducted.

In this multicenter, randomized, double-blind, placebo-controlled study involving 66 patients, the safety and effectiveness of enzyme-replacement therapy with sebelipase alfa (administered intravenously at a dose of 1 mg per kilogram of body weight every other week) were evaluated with the placebo-controlled phase of the study, 20 weeks long, followed by open-label treatment for all patients. The primary endpoint was normalization of the alanine aminotransferase level. Secondary endpoints included additional disease-related efficacy assessments, safety, and side-effect profile.

Substantial disease burden at baseline included a very high level of low-density lipoprotein cholesterol ( $\geq 190$  mg per deciliter) in 38 of 66 patients (58%) and cirrhosis in 10 of 32 patients (31%) who underwent biopsy. A total of 65 of the 66 patients who underwent randomization completed the double-blind portion of the trial and continued with open-label treatment. At 20 weeks, the alanine aminotransferase level was normal in 11 of 36 patients (31%) in the sebelipase alfa group and in 2 of 30 (7%) in the placebo group ( $P = 0.03$ ). With respect to prespecified key secondary efficacy endpoints, improvements in lipid levels and reduction in hepatic fat content were reported ( $P < 0.001$  was observed for all comparisons, except  $P = 0.04$  for triglycerides). The number of patients with adverse events was similar in the two groups; most events were mild and considered by the investigator to be unrelated to treatment.

Sebelipase alfa therapy resulted in a reduction in multiple disease-related hepatic and lipid abnormalities in children and adults with lysosomal acid lipase deficiency.

## Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component

Richards DB. *et al.*

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The amyloid fibril deposits that cause systemic amyloidosis always contain the nonfibrillar normal plasma protein, serum amyloid P component (SAP). The drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) efficiently depletes SAP from the plasma but leaves some SAP in amyloid deposits that can be specifically targeted by therapeutic IgG anti-SAP antibodies. In murine amyloid A type amyloidosis, the binding of these antibodies to the residual SAP in amyloid deposits activates complement and triggers the rapid clearance of amyloid by macrophage-derived multinucleated giant cells.

An open-label, single-dose-escalation, phase 1 trial was conducted involving 15 patients with systemic amyloidosis. After using CPHPC to deplete circulating SAP, a fully humanized monoclonal IgG1 anti-SAP antibody was infused. Patients with clinical evidence of cardiac involvement were not included for safety reasons. Organ function, inflammatory markers, and amyloid load were monitored.

No serious adverse events were reported. Infusion reactions occurred in some of the initial recipients of larger doses of the antibody; reactions were reduced by slowing the infusion rate for later patients. At 6 weeks, patients who had received

a sufficient dose of the antibody in relation to their amyloid load had decreased liver stiffness, as measured with the use of transient elastography. These patients also had improvements in liver function in association with a substantial reduction in hepatic amyloid load, as shown by means of SAP scintigraphy and measurement of extracellular volume by magnetic resonance imaging. A reduction in kidney amyloid load and shrinkage of an amyloid-laden lymph node were also observed.

Treatment with CPHPC followed by an anti-SAP antibody safely triggered clearance of amyloid deposits from the liver and some other tissues.

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## A Randomized Trial of Phototherapy with Filtered Sunlight in African Neonates

Slusher TM. *et al.*

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Sequelae of severe neonatal hyperbilirubinemia constitute a substantial disease burden in areas where effective conventional phototherapy is unavailable. It was previously found that the use of filtered sunlight for the purpose of phototherapy is a safe and efficacious method for reducing total bilirubin. However, its relative safety and efficacy as compared with conventional phototherapy are unknown.

A randomized, controlled noninferiority trial was conducted in which filtered sunlight was compared with conventional phototherapy for the treatment of hyperbilirubinemia in term and late-preterm neonates in a large, urban Nigerian maternity hospital. The primary endpoint was efficacy, which was defined as a rate of increase in total serum bilirubin of less than 0.2 mg per deciliter per hour for infants up to 72 h of age or a decrease in total serum bilirubin for infants older than 72 h of age who received at least 5 h of phototherapy; a noninferiority margin of 10% was pre-specified for the difference in efficacy rates between groups. The need for an exchange transfusion was a secondary endpoint. The safety was also assessed, which was defined as the absence of the need to withdraw therapy because of hyperthermia, hypothermia, dehydration, or sunburn.

A total of 447 infants were enrolled; 224 were randomly assigned to filtered sunlight and 223 to conventional phototherapy. Filtered sunlight was efficacious on 93% of treatment days that could be evaluated, as compared with 90% for conventional phototherapy, and had a higher mean level of irradiance (40 vs. 17  $\mu\text{W}$  per square centimeter per nanometer,  $P < 0.001$ ). Temperatures higher than 38.0°C occurred in 5% of the infants receiving filtered sunlight and in 1% of those receiving conventional phototherapy ( $P < 0.001$ ), but no infant met the criteria for withdrawal from the study for reasons of safety or required an exchange transfusion.

Filtered sunlight was noninferior to conventional phototherapy for the treatment of neonatal hyperbilirubinemia and did not result in any study withdrawals for reasons of safety.