The future for metabolism-based therapies looks bright, but further clinical studies are needed to ascertain the effects of ketogenic diets and other metabolism-based therapies, not only on seizures, but also on comorbidities and quality of life.

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Gene therapy for X-linked myotubular myopathy: the challenges

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X-linked myotubular myopathy is a rare congenital myopathy caused by pathogenic variants in the *MTM1* gene. The disease is severe in 80% of affected boys, with profound skeletal muscle weakness, respiratory weakness, and dysphagia at birth.[1] Without intervention, more than 50% of these children will die within the first 18 months of life, and those who survive will often require assisted ventilation.[2]

In *The Lancet Neurology*, Perry B Shieh and colleagues report the results of the ASPIRO trial,[3] which was conducted at seven centres in Canada, France, Germany, and the USA. 24 boys (aged ≤6 years) with X-linked myotubular myopathy who were on mechanical ventilatory support were enrolled in the trial. The intervention was gene therapy with resamirigene bilparvovec, an adeno-associated virus serotype 8 vector delivering human *MTM1* transgene.[3] Participants received either a lower dose ($1{\cdot}33\times10^{14}$ vector genomes [vg]/kg bodyweight) or a higher dose ($3{\cdot}5\times10^{14}$ vg/kg) of resamirigene bilparvovec at baseline or, as a delayed treatment control, at 24 weeks after baseline. The study was initially planned in two parts: a safety phase, and a confirmatory phase with the optimal dose selected from the safety phase. Overall in the trial, seven children were treated with the lower dose, 17 with the higher dose, and 14 untreated children were included in a control group.

The global outcome of the ASPIRO trial is tragic; despite a beneficial effect of resamirigene bilparvovec in some participants, four deaths occurred due to side-effects. Although the higher dose was selected for the confirmatory phase, three (17%) children who received the higher dose died and the trial was placed on clinical hold (after the first death) by the US Food and Drug Administration, eliminating the two-part trial design. The clinical hold was later lifted and treatment with the lower dose continued. However, a fourth death in the lower dose group led to the trial being placed on a second hold, which is still in effect. All deaths were coincident with severe treatment-related cholestatic liver injury with decompensation at the time of death, possibly due to pre-existing, unrecognised cholestatic hepatic disease. In the surviving children, compared with untreated controls, a significant reduction in hours of daily ventilator support was reported at 24 weeks (higher dose cohort, 22·8 percentage point [95% CI 6·15–39·37] greater reduction from baseline compared with controls [p=0·0077]; and lower dose cohort, 77·7 percentage point [40·22–115·24] greater reduction [p=0·0002]). These differences in the estimated reduction between dosed and control participants increased at 48 weeks (62·1 percentage points [47·49–76·61]) and 103·7 percentage points [78·61–128·83], respectively, p<0·0001 for both). Furthermore, 16 of the 20 surviving children who

received resamirigene bilparvovec became ventilator-independent, and dosed participants showed greater improvement of motor milestones and motor function compared with controls.

The development of gene therapy for X-linked myotubular myopathy has been considered a crucial step in the therapeutic landscape for rare, severe congenital myopathies. ASPIRO was preceded by an extensive preclinical development process,[4] with natural history studies contributing to trial readiness, including a prospective 1-year longitudinal study,[5] INCEPTUS,[6] and NatHis-CNM (NCT03351270). INCEPTUS was designed as a run-in for ASPIRO, providing datapoints before dosing and enabling identification of suitable participants and selection of clinically relevant endpoints. However, the deaths of four children in ASPIRO show that, despite careful preparation, blind spots can exist in our understanding of rare inherited myopathies. The tragic outcome of ASPIRO highlights the crucial need to have a detailed overview of the general health status of participants.

During the INCEPTUS run-in trial, 12 (35%) of 34 participants had at least one episode of elevated total or direct bilirubin, including two children who had levels more than five times the upper limit of normal—an observation that, on reflection, could have prompted increased awareness of risks of hepatotoxicity. The four children who died in ASPIRO had clinical evidence consistent with cholestasis before treatment, including intermittent hyperbilirubinaemia, cholestatic hepatitis, or hepatic ultrasounds showing increased echogenicity, suggesting that these participants might have been more susceptible to hepatotoxicity, which in hindsight could have informed the decision to participate. Indeed, the ASPIRO study team suggest that increased monitoring for cholestasis (including serum bile acids testing) should be considered for future studies, in accordance with discussions surrounding hepatoxicity in gene therapy trials in general.[7] Future trial design must consider that neuromuscular conditions due to mutations in genes encoding ubiquitously expressed proteins might be multisystem disorders. A similar consideration is that targeting of gene transfer to skeletal muscle might not prevent disease manifestations in other organs.

Several important lessons should be learnt from the ASPIRO trial. First, promising outcomes in relevant animal models can raise false expectations because the model might not fully reflect the human phenotype. Therefore, all stakeholders should view the transferability of such findings to the clinical setting with extreme caution. Second, the severity of hepatic involvement, and reports of myocarditis in ASPIRO and other gene therapy trials, shows the need to cooperate with a multidisciplinary array of specialists (eg, cardiologists, hepatologists, immunologists, pulmonologists, and intensivists), and should prompt preparation of an emergency protocol for optimal treatment of heart and liver failure, or other extramuscular complications, well before the start of a clinical trial. Third, post-trial in-depth critical analysis of outcomes and suspected unexpected serious adverse reactions (SUSARs) is a pivotal step to accelerate therapeutic progress and reduce future risks in ultra-rare diseases. This process requires that all stakeholders communicate and discuss these sometimes sensitive data openly and constructively in a safe environment.[7] Fourth, it is crucially important that participants and their families are promptly informed about SUSARs by their study team, well before this information becomes available through other channels. Participation of European and North American patient organisations in future trial design would facilitate this process. Finally, a considerable emotional burden was associated with the outcomes of the ASPIRO trial, which not only affected the families of the children who died but also those of the survivors.

The outcomes of ASPIRO have stimulated new preclinical research projects on hepatic features of various mouse models,[8] complemented by a clinical information brochure and an online survey regarding hepatic involvement in X-linked myotubular myopathy, which has been arranged by the international patient community.[9,10] We expect that these efforts will result in novel insights into the underlying mechanisms, prevalence, and severity of hepatic involvement in X-linked myotubular myopathy, and that they will provide crucial information for future trials.

NCV was Principal Investigator of the Unite-CNM trial on Dynacure, and is a member of the scientific advisory board of ZNM Zusammen Stark!. HJ has acted in an advisory capacity for Audentes and Astellas, two companies involved in the development of treatments for X-linked myotubular myopathy. AAR and AF declare no competing interests. All authors are members of the European Reference Network for rare neuromuscular diseases. The authors are grateful to all patients and their families who participated in the natural history studies and the ASPIRO trial, and to the international patient organisations ZNM Zusammen Stark!, the Myotubular Trust, and the MTM-CNM Family Connection.

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Anticoagulation in people with atrial fibrillation after intracranial haemorrhage

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For people with atrial fibrillation, anticoagulation can reduce the risk of stroke by approximately two-thirds. However, their risk of bleeding is high, causing a dilemma for clinicians on whether to prescribe anticoagulants or not when managing these patients after intracranial haemorrhage. Therefore, it is crucial to evaluate risks versus benefits of anticoagulants in these high-risk patients. Fortunately, since the warfarin era, the balance between benefit and risk of bleeding has now improved with the use of direct oral anticoagulants. The risk of a first event of intracranial haemorrhage is reduced by about half in people with atrial fibrillation treated with direct oral anticoagulants, compared with warfarin.[1] However, the safety and efficacy of anticoagulation with direct oral anticoagulants in patients with atrial fibrillation after intracranial haemorrhage is unclear, because these patients are typically excluded from randomised controlled trials.

In *The Lancet Neurology*, Rustam Al-Shahi Salman and colleagues report the results of the prospective COCROACH meta-analysis, in which individual participant data from four randomised trials were used to estimate the safety and efficacy of oral anticoagulation in people with atrial fibrillation who had spontaneous intracranial haemorrhage.[2] They compared data for participants who started long-term oral anticoagulation after the haemorrhage with those who did not. This meta-analysis is a methodological advance from previous meta-analyses, in which either randomised trial data were combined with findings from observational cohort studies or estimates of aggregated treatment effects were used instead of individual participant data. Further advantages of COCROACH are that the methodology for obtaining high-quality data for individual participants was rigorous, and that the meta-analysis adhered to a prespecified protocol and statistical analysis plan. The findings are important because they can be used to guide clinical practice.

The meta-analysis included data from 412 individuals (212 who started oral anticoagulation and 200 who did not) who were enrolled in one of four randomised controlled trials: SoSTART,[3] APACHE-AF,[4] NASPAF-ICH,[5] and ELDERCARE-AF.[6] Direct oral anticoagulants were used by most participants who started anticoagulation, and either antiplatelet agents were used by participants who avoided anticoagulants or no antithrombotic drug was used in that group.