In the news

BREAKTHROUGH NEUROIMMUNOLOGY TRIALS IMPRESS AT AAN MEETING

Three positive phase III trials that could trigger a seismic shift in the therapeutic landscape for neuromyelitis optica spectrum disorder (NMOSD) were presented at the American Academy of Neurology (AAN) Annual Meeting in Philadelphia, USA, at the beginning of May 2019. The three studies were among a number of trials to offer hope to patients with difficult-to-treat neurological diseases.

The first of the NMOSD trials, which has been published in the *New England Journal of Medicine*, was a phase III study of eculizumab, a monoclonal antibody that targets complement component C5 to inhibit complement activation, which is a major component of CNS inflammation in NMOSD. In a total of 143 patients with anti-aquaporin-4 (AQP4) antibodies, eculizumab reduced the risk of relapse by 94.2% relative to placebo. "This was a dramatic result, providing a significant amount of hope for people with this disease," said Sean Pittock, the first author of the trial, at the AAN meeting.

The second NMOSD trial, led by Bruce Cree, was a phase III study of the monoclonal antibody inebilizumab, which targets CD19 and leads to depletion of antibody-producing B cells. Against placebo, the antibody reduced the risk of relapse by 77%. Similarly, in the *SakuraSky* trial of the anti-IL-6 antibody satralizumab, conducted by Takashi Yamamura and colleagues, treatment reduced the risk of relapse by 79% compared with placebo among patients who were anti-AQP4-antibody-positive, and by 34% among patients who were anti-AQP4-antibody-negative.

The antibodies have yet to receive regulatory approval for their clinical use, but the positive results change the outlook for patients with NMOSD dramatically. "How this will play out for patients is difficult to know," commented Pittock, who was also involved in the inebilizumab trial. "We now have three drugs, whereas last year we had none. Hopefully, as we continue to work in this area, we can try to identify which patients will suit which drug."

Continuing the immunological theme was a trial of a novel therapeutic strategy for the treatment of progressive multifocal leukoencephalopathy (PML). This trial, conducted by Irene Cortese and colleagues, involved adoptive transfer of donor-derived T cells that had been engineered to be highly reactive against the JC polyomavirus, which causes PML. A total of 12 patients received T cells, and no serious adverse reactions were seen. Although the study was designed primarily to test the safety of the approach, seven patients survived after the treatment when all were expected to deteriorate rapidly, providing preliminary evidence that the adoptive transfer approach could be effective. Further studies are needed to confirm efficacy, but the results could be a major breakthrough in PML treatment.

Ian Fyfe

ORIGINAL ARTICLE Pittock, S. et al. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa1900866> (2019)

NEURODEVELOPMENTAL DISORDERS

Remyelinating drug to the rescue in a Williams syndrome model

New research in a mouse model of Williams syndrome has uncovered myelination defects that can be rescued with a remyelinating drug. The findings provide new insights into the pathophysiology of this neurodevelopmental disorder and raise the prospect of new therapies.

Williams syndrome is caused by a heterozygous microdeletion of a chromosome 7 region that includes the general transcription factor II-I (*GTF2I*) gene. Loss of function of *GTF2I* has been linked to hypersociability, which is one of the defining characteristics of Williams syndrome. In the new study, Boaz Barak and colleagues investigated the cellular and molecular consequences of *Gtf2i* deletion in a mouse model.

"The *Gtf2i* full knockout is lethal at embryonic day 11," comments Barak. "To overcome this problem,

we utilized the Cre-*loxP* system to induce deletion of *Gtf2i* specifically in excitatory neurons of the forebrain — a brain region that is known to be important for social behaviour."

This conditional knockout model recapitulated several features of Williams syndrome, including fine motor deficits, anxiety and hypersociability. Cortical tissue from the knockout mice showed reduced expression of myelin-associated genes, as well as defects in oligodendrocyte maturation and myelin ultrastructure. Similar myelination defects were observed in post-mortem brain tissue from patients with Williams syndrome.

The antihistamine clemastine, which is known to promote remyelination, rescued both the myelination defect and the behavioural phenotype in the mouse model. Clemastine is already being explored as a treatment for

NEUROMUSCULAR DISEASE

Long-term benefits of nusinersen in later-onset spinal muscular atrophy

Treatment with the antisense oligonucleotide nusinersen benefits patients with spinal muscular atrophy (SMA) type II and type III over 3 years, a new study shows. The results not only demonstrate the potential of nusinersen in older children, but also reveal that improvements continue over time in patients receiving this drug.

SMA is a genetic neuromuscular disorder. The most common form is SMA type I, which has an age of onset <6 months, severely impairs motor development and leads to death. SMA types II and III have later ages of onset (7–18 months and >18 months, respectively), and patients can lose existing motor function over time.

Previous trials have demonstrated that nusinersen slows or halts SMA progression in infantile-onset and later-onset SMA, but follow-up periods

in these trials were limited. "We wanted to find out whether the drug could show benefit and safety in older children with later-onset SMA, up to the age of 15 years at enrolment," explains Darras. "We also wanted to see whether this benefit could be observed for an extended period of time."

In the new study, the researchers analysed the motor function of 11 children with SMA type II and 17 children with SMA type III who received treatment with nusinersen, first as part of a phase Ib/Ia open-label trial and then as part of an extension study. The two studies provided a total follow-up period of ~3 years. Functional outcome measures included scores on the Hammersmith Functional Motor Scale-Expanded, the Upper Limb Module and the 6-Minute Walk Test, and electrophysiological outcome measures included compound muscle