In the news

TRIALS TAKE MS TREATMENT FORWARD

The raft of disease-modifying therapies for multiple sclerosis (MS) looks set to expand further in light of phase III trial results presented at the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress in September 2019. The most notable trials were the OPTIMUM study of the sphingosine-1-phosphate (S1P) receptor 1 (S1P1) inhibitor ponesimod and the ASCLEPIOS I and II trials of the monoclonal antibody ofatumumab.

Ludwig Kappos presented results of the OPTIMUM study, in which ponesimod was compared with teriflunomide for the treatment of relapsing–remitting MS in 1,113 patients. Ponesimod reduced the annualized relapse rate (ARR) by 30.5% and active MRI lesions by 56% compared with teriflunomide. No significant effect was seen on disability progression over 6 months. Fatigue also stabilized with ponesimod but worsened over time with teriflunomide. This trial was the first in which fatigue was a secondary end point.

Ponesimod is selective for S1P1, in contrast to fingolimod and siponimod, which also affect other S1P receptors. Ponesimod also has few active metabolites. These characteristics did not benefit the safety profile, but Kappos says the new drug offers a cleaner pharmacological approach, meaning that ponesimod could be a better candidate than the other S1P1 inhibitors for combination therapies.

In the ASCLEPIOS I and II trials, which were identical in design, ofatumumab was compared with teriflunomide for the treatment of relapsing–remitting MS. Ofatumumab reduced the ARR by 50.5% and 58.5% in the two trials, and reduced active MRI lesions by 82.0–97.5%. Disability worsening was also reduced by >30%. Ofatumumab depletes B cells via the same mechanism as ocrelizumab. Stephen Hauser, who presented the results, said that the efficacies of the two antibodies seem similar, but ofatumumab is a fully human, rather than humanized, antibody and can be administered via subcutaneous injection rather than intravenous infusion, giving it considerable clinical advantages.

Perhaps the most scientifically exciting aspect of the ASCLEPIOS trials was the use of serum levels of neurofilament light (sNfL) as a secondary end point. Ofatumumab reduced sNfL to a significantly greater extent than did teriflunomide, indicating that sNfL will be a useful measure of treatment response in future trials. However, rates of whole-brain atrophy did not differ between the two treatments, raising questions about what biological processes whole-brain atrophy and sNfL are measuring.

Another study of neurofilament created waves at the ECTRIMS meeting by demonstrating that sNfL is increased up to 6 years before clinical onset of MS. This finding indicates that MS has a prodromal phase that lasts several years, and that neuronal damage is already occurring at this stage. The study, by Bjornevik et al., is now published in *JAMA Neurology*.

Ian Fyfe

ORIGINAL ARTICLE Bjornevik, K. et al. Serum neurofilament light chain levels in patients with presymptomatic multiple sclerosis. *JAMA Neurol.* https://doi.org/10.1001/jamaneurol.2019.3238 (2019)

MULTIPLE SCLEROSIS

Intrathecal immunoglobulin M predicts conversion from CIS to MS

Intrathecally produced immunoglobulin M (IgM) is a strong risk factor for progression from clinically isolated syndrome (CIS) to multiple sclerosis (MS), according to a new study published in *Neurology*. The finding could contribute to the development of a standardized risk score to help guide treatment decisions.

MS is an inflammatory demyelinating disease, the most common form of which is characterized by periods of relapse and remission. An episode of MS-like symptoms in a patient with no previous episodes is referred to as CIS, and predicting whether and when CIS will convert into MS is important for deciding how to treat the condition. Some evidence has suggested that intrathecal production of IgM antibodies is an indicator of conversion, but findings have been conflicting.

In the new study, Klemens Ruprecht, Johanna Oechtering and colleagues aimed to clarify this issue by comparing intrathecal IgM production with established MS risk factors, such as the presence of IgG oligoclonal bands in cerebrospinal fluid (CSF) and the number of CNS lesions visible with MRI.

"A number of previous studies of patients with CIS looked at risk factors for conversion to MS," points out Ruprecht. "However, few studies have investigated the role of intrathecal IgM production."

The team analysed CSF samples from 110 patients with CIS to calculate whether intrathecal IgM production was taking place. Approximately 20% of patients with CIS exhibited intrathecal IgM production. These individuals had a lower age of symptom onset and a higher frequency of infratentorial lesions on MRI than people who

NEURO-ONCOLOGY

Compound kills chemotherapy-resistant glioblastoma cells

High-throughput screening has identified a compound that can kill glioblastoma-initiating cells (GICs) but has a favourable toxicity profile. The findings, published in *Neuro-Oncology*, could lead to therapies that prevent tumour recurrence.

Glioblastoma is a malignant brain tumour that often recurs despite surgery, chemotherapy and radiotherapy. Recurrence has been attributed to cancer stem cells known as GICs, which are resistant to existing therapies. A previous study identified several compounds that killed GICs but were toxic in mice. The new study, led by Toru Kondo, used high-throughput screening to look for compounds that could kill GICs without causing adverse effects.

Kondo and colleagues grew human GICs, neural stem cells (NSCs) and astrocytes in separate cultures and measured the degree of cell death induced by 10,560 individual compounds. One compound that killed GICs but was fairly safe for NSCs and astrocytes was selected for further analysis. This compound inhibited dihydroorotate dehydrogenase (DHODH), an enzyme involved in the de novo pyrimidine synthesis pathway.

To find a more metabolically stable version of the compound to test in vivo, the team screened compounds with a similar structure. A compound known as 10580 was sufficiently stable in blood, inhibited DHODH and killed GICs.

The researchers transplanted GICs into mice and allowed the resulting tumours to grow to 100 mm^3 before beginning oral administration of 10580 or saline. 10580 cannot cross the blood–brain barrier (BBB), so the tumours were grown in the hip. After 11 days of treatment, tumours from 10580-treated mice were significantly smaller