findings and patients with MRI-negative findings (area under the receiver operating characteristic curve 0·852, 95% CI 0·781–0·923).

These results are promising but, as the investigators acknowledge, are some distance from suggesting that GFAP assays should become part of current emergency department management of patients with TBI and negative CT scans. The clinical significance of the positive MRI findings is unknown; data on patient symptom severity at 2 weeks or later follow-up were not reported in the study. If the frequencies of disabling concussion symptoms do not differ in the MRI-positive and MRI-negative cohorts during follow-up, it is hard to argue that either GFAP or the MRI scans are providing key information to guide further management. Nearly half of the TRACK-TBI patients with negative CT scans did not have MRI as part of their follow-up, and because their characteristics are not reported, it is difficult to assess the potential for selection bias. The frequency of self-reported previous TBI was 9% higher in the MRI-positive cohort than in the MRI-negative cohort. The GFAP assay performed best at 9–16 h post injury and blood sampling occurred at a mean of 12 h after injury. Worldwide, many patients with TBI will have had a negative CT brain scan and been discharged from the emergency department before the period of optimal performance of GFAP in this study.

These issues are all shortcomings, but not necessarily fatal flaws. Through the International Initiative for Traumatic Brain Injury Research, the EU-funded Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study has used a similar observational approach for the detailed assessment of European patients with TBI.[7] If these findings from the TRACK-TBI study can be replicated—and their clinical significance demonstrated—then TBI characterisation with GFAP could lead to improved patient outcomes.

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Do we have equipoise when it comes to how we treat active multiple sclerosis?

The management and treatment of multiple sclerosis has been transformed by disease-modifying therapies (DMTs). The clinical effectiveness of the injectable DMTs interferon beta and glatiramer acetate are relatively modest.[1] However, emerging real-life data show clear inflection points in 2000 and 2006 in terms of patients diagnosed in these more recent periods after reaching or surviving longer to to an Expanded Disability Status Score (EDSS) of 6 (ie, needing a walking stick to walk 100 m). In a cohort study in Italy,[2] patients diagnosed with multiple sclerosis in 1991–95 had a similar likelihood of reaching an EDSS of 6 compared with patients diagnosed in 1980–90 and 1996–2000. However, the hazard ratio of progression to EDSS 6 was reduced by 37% in patients diagnosed in 2001–05 and by 46% in patients diagnosed in 2006–10;[2] these latest epochs were characterised by the wide use of the injectables and the introduction of the first highly active DMTs natalizumab and mitoxantrone.

Efficacy or relative efficacy of individual DMTs becomes somewhat less important than the average efficacy of

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See **Personal View** page 973

DMTs in the context of a treatment strategy if the goal is to achieve no evidence of disease activity (NEDA). Choice of a DMT with a low efficacy rate (ie, low NEDA rate) simply means that a high proportion of treated patients will need to be switched onto higher efficacy therapies over time to achieve NEDA. By comparison, patients choosing high-efficacy therapies will have an improved chance of achieving NEDA with their initial choice of therapy.

Do patients treated with the step-care approach do worse than those offered rapid escalations or high-efficacy DMTs first line? In *The Lancet Neurology*, Ontaneda and colleagues[3] describe two clinical trials that will compare these treatment approaches rather than specific DMTs. In the DELIVER-MS study (NCT03535298), participants will be randomised to either an escalation approach or an early high-efficacy treatment approach (ie, flipping the pyramid). By comparison, the TREAT-MS study (NCT03500328) will evaluate patients with high and low risks of disability accumulation to address whether an escalation approach or early highly effective therapy will influence the risk of disability.[3] The TREAT-MS study will also compare the disability risk between individuals who switch from a first-line medication to a highly effective medication (escalation) versus those who switch to another first-line therapy (horizontal switching or cycling).[3]

Whether these trials have equipoise is debatable. In phase 3 studies of alemtuzumab,[4-6] ocrelizumab,[7,8] and daclizumab,[8] patients randomised to 2 years of interferon beta-1a therapy had poorer outcomes than those receiving highly active therapy from the outset.

Real-life data show that patients initially treated with glatiramer acetate or interferon beta have a lower hazard of conversion to secondary progressive multiple sclerosis than propensity-matched untreated patients.[9] However, the hazard was lowest with the high efficacy DMTs fingolimod, natalizumab, and alemtuzumab.[9] These data could be regarded as definitive and in keeping with phase 3 trials showing the high-efficacy DMTs to be superior to the lower efficacy injectable DMTs.

In relation to the conventional step-care paradigm, patients switching horizontally in terms of efficacy from interferon beta to glatiramer acetate, or vice-versa (ie, from one low-efficacy DMT to another moderate-efficacy DMT), do less well compared with patients switching vertically to fingolimod[10] or natalizumab.[11] Many neurologists are reluctant to switch horizontally or cycle their patients on DMTs with lower efficacy than their current DMT. Based on these and other observations, I would question the equipoise of the DELIVER-MS and TREAT-MS trials.

What determines the efficacy level of a DMT that is deemed appropriate for an individual patient depends on many factors specific to that patient, such as the baseline prognostic profile, family planning considerations, local or national treatment guidelines, socioeconomic and employment issues, comorbidities, cognitive impairment, the ability to adhere to treatment, the monitoring burden, risk aversion, and other lifestyle issues. These patient-specific factors make pragmatic studies, such as the DELIVER-MS and TREAT-MS trials, very difficult because all the treatments being evaluated are licensed and available under routine care.

The real litmus test for the investigators of the DELIVER-MS and TREAT-MS trials is the question they should all ask themselves: "If I had multiple sclerosis, how would I want to be treated?" Given the evidence, patients deserve the choice of being treated with a high-efficacy DMT first-line.

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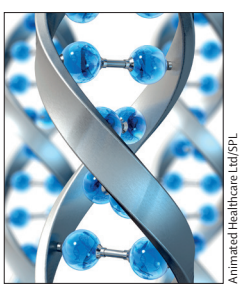
Antisense oligonucleotides might change the therapeutic landscape for Huntington's disease

Huntington's disease is an autosomal dominant neurodegenerative disease that typically presents in midlife with a triad of motor, cognitive, and psychiatric symptoms. Huntington's disease is due to a cytosine-adenine-guanine repeat expansion that results in selective death of the medium spiny neurons in the striatum and associated cortical atrophy. No treatments exist to delay the disease onset and approved treatments are limited to reduction of chorea severity.[1,2]

Hailed by some as the most notable advance since the discovery of the *HTT* gene, Tabrizi and colleagues[3] reported findings of a phase 1–2a trial of the antisense oligonucleotide, HTTRx. The trial randomly assigned 46 patients with early Huntington's disease in a 3:1 ratio to receive either ascending doses (10–120 mg) of HTTRx (n=34) or placebo (n=12) as an intrathecal bolus administration every 4 weeks for four doses. The trial was done at nine centres in the UK, Germany, and Canada and the open-label extension of the administration of 120 mg continues.

Safety, which was the primary endpoint, included physical, neurological, and psychiatric examinations, laboratory assessments, vital signs, electrocardiograms, and neuroimaging sequences as well as open-ended queries about health status. All participants completed the study, and the incidence of adverse events was similar among the groups. Nearly all (98%) participants reported having mild or moderate adverse events. Hospital admission of one patient in the placebo group for headache observation was the only severe adverse event reported. The most commonly reported adverse events were procedural pain and postdural-puncture headache; all resolved spontaneously, and no blood patches were used.

The study was well designed and done rigorously. Dose-dependent decreases in the concentration of mutant huntingtin in CSF were observed. Indeed, this report is the first to suggest that an experimental treatment can lower the presence of mutant huntingtin in CSF with no significant adverse events. Huntingtin might enter the CSF as neurons die and increasing concentrations would therefore reflect more cell death. Although these findings are promising, further work will be needed to replicate these findings.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Increases in neurofilament light chain and enlarged ventricular volumes were associated with treatment. Although these changes are not generally considered efficacious, the authors suggest that an inflammatory response to the intervention might underlie the association. Replication of these findings and further longitudinal data both from mutation carriers and patients with the disease will be crucial. As expected, no clinical correlates of treatment effect were identified, since the preclinical phase of Huntington's disease lasts about 35 years.[4,5] Appropriately, a phase 3 trial is being done at 90 worldwide sites in 660 people with early manifest Huntington's disease to investigate the safety and efficacy of an antisense oligonucleotide (NCT03761849). Encouraging news from the American Academy of Neurology meeting showed that open-label extension data from the study by Tabrizi and colleagues[3] could support the phase 3 study, which will compare three treatment groups: a placebo group, a group given an antisense oligonucletoide every 2 months, and another given an antisense oligonucletoide every 4 months. Health-care visits for drug injections three times per year, instead of 12, will substantially improve clinical care guidelines for practitioners and patients, if eventually approved.

Unsurprisingly, Huntington's disease specialty centres report being flooded with individuals requesting to receive the antisense oligonucleotide intervention. Notably, another two antisense oligonucleotide clinical trials in humans are ongoing (allele-specific; NCT03225833 and NCT03225846) and a patent has been granted for single-treatment AAV5 gene therapy planned to begin