Immune-mediated encephalitis with daclizumab – the final nail.

With the exponential growth in treatment options for active multiple sclerosis (MS) comes the need for diligent post-marketing surveillance for adverse effects. This is highlighted in this issue by Devlin *et al*, who provide the first clinico-pathological report of immune-mediated encephalitis on daclizumab.

Clinical trials identify many safety concerns, but can only provide limited exposure of the drug to a highly selected and controlled cohort. Most MS treatments carry a black triangle status from the European Medicines Agency (EMA), requiring additional monitoring during the initial period of real-world, post-marketing experience. Greater patient exposure occurs in a more diverse patient group, with more potential for drug-drug and drug-other condition interactions. The MS community is all too familiar with this following the initial FDA approval and subsequent temporary suspension of natalizumab as progressive multifocal leukoencephalopathy cases were recognised.

Daclizumab was authorised in 2016, following consideration of clinical trial data from 2,236 exposed patients. Elevated liver enzymes were common, and there was one death due to autoimmune hepatitis, but no cases of encephalitis were identified in any studies[1]. Post-marketing surveillance, however, has critically swung the risk-benefit balance in favour of product withdrawal.

Despite risk minimisation approaches, a further case of fatal autoimmune hepatitis was reported to the EMA pharmacovigilence committee in June 2017, resulting in a licencing restriction to those who have tried two previous disease modifying therapies and are unsuitable for any others[2]. In March 2018, however, the EMA recommended the immediate suspension of daclizumab following 12 reports of meningoencephalitis, 3 of which were fatal.[3]

The report by Devlin *et al* of such a case of immune-mediated encephalitis provides a fascinating insight into the complexity of immune modification in MS. It should also serve as a reminder to all of those prescribing disease modifying therapies as to the importance of their duty to report adverse events as they arise.

1. European Medicines Agency, Assessment report - Zinbryta. (2016). www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003862/WC500210601.pdf
2. European Medicines Agency, Assessment report - Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data - Zinbryta. (2017). www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/003862/WC500241256.pdf
3. European Medicines Agency. EMA urgently reviewing multiple sclerosis medicine Zinbryta following cases of inflammatory brain disorders. **44,** (2018). www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/03/WC500244890.pdf