Daclizumab-induced encephalitis in multiple sclerosis

Editorial

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Daclizumab is a humanized monoclonal antibody directed towards CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R). The immunological effect of daclizumab has been associated to: (i) the blockage of T-cell activation, expansion, and survival\textsuperscript{1,2}, (ii) the upregulation of CD56\textsuperscript{bright} natural killer (NK) cells\textsuperscript{1,2}, (iii) the reversible decrease in circulating regulatory T-cells (T\textsubscript{reg}), whose expansion is dependent on IL-2\textsuperscript{1,2}, and (iv) the reduction of pro-inflammatory lymphoid tissue inducers, which are thought to contribute to cortical lesion formation\textsuperscript{1}.

Phase II (SELECT) and III (DECIDE) clinical trials in relapsing multiple sclerosis (RMS) demonstrated the efficacy of daclizumab in reducing: (i) the annualized relapse rate by 50–54% versus placebo and 45% versus intramuscular IFN-β-1a, and (ii) the development of new or enlarging T2 lesions by 70% versus placebo and 54% versus intramuscular IFN-β-1a\textsuperscript{1,2}. In 2016 the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the subcutaneous formulation of daclizumab for the treatment of RMS. The adverse events (AEs) reported during these clinical trials were infections and autoimmune disorders (e.g., hepatitis, associated with raised levels of liver enzymes, skin rash, and autoimmune thyroiditis\textsuperscript{2,3}); the cumulative incidence of autoimmune disorders was 1.4%, and the risk of serious autoimmune AEs was 0.4\%\textsuperscript{3}.

In March 2018, the EMA recommended the immediate suspension of daclizumab following twelve reports of serious inflammatory brain disorders, including encephalitis and meningoencephalitis. Three of the cases were fatal\textsuperscript{4}. One of these twelve patients developed glial fibrillary acidic protein (GFAP)\textalpha immunoglobulin G-associated encephalitis, which presented 8 months after initiating treatment with daclizumab\textsuperscript{5}. In May 2018, the EMA’s Pharmacovigilance Risk Assessment Committee confirmed that the drug-related risk of serious and potentially fatal immune AEs
involving the brain, liver and other organs, outweighed the benefits of the drug. After a few days, the marketing authorisation was withdrawn.

In this issue of *Multiple Sclerosis Journal*, Stork et al. have reviewed the clinical, laboratory, radiological, and histological findings of seven out of the twelve cases of daclizumab-associated meningo-/encephalitis. The patients had received between two and seven cycles of daclizumab before the clinical onset of meningo-/encephalitis. Six patients were on treatment with daclizumab at symptom onset, while one patient developed a meningoencephalitis 4 months after discontinuing daclizumab.

All patients presented with a severe meningo-/encephalitis. Secondary autoimmune diseases were diagnosed in two patients and all patients developed non-neurological autoimmune symptoms. Blood tests were characterised by leukocytosis, with concurrent lymphopenia in four patients. CD56brightness NK cells was decreased in two patients and in three patients the number of eosinophils was increased. Hepatic enzymes tested normal or mildly/moderately elevated. Severe thrombocytopenia and anaemia were found in one and two patients respectively. Cerebrospinal fluid showed pleocytosis and hyperprotidorrachia in all cases.

Six patients fulfilled the criteria for the diagnosis of DRESS (drug reaction with eosinophilia and systemic symptoms). Brain MRI showed a high inflammatory activity, with multiple and gadolinium-enhancing white matter lesions, and a marked involvement of ependyma, meninges and cranial nerves. In three cases, a vasculitic pattern was seen on MRI, and a small cortical infarct was detected in one case.
In five out of six patients who underwent a brain biopsy, histological findings showed demyelinating lesions characterised by lymphocytic infiltrates, predominantly containing CD4+ and CD8+ T-cells, and plasma cells. Three patients presented with a marked eosinophilic infiltrate. A severe vasculitis-like involvement of vessels was detected.

Immunosuppressive therapies were used with minimal beneficial effects. The disease course was progressive and a severe neurological deterioration was observed in all patients, who needed intensive care treatment; two patients died.

The main messages of this review are: (i) the clinical presentations of daclizumab-induced meningo-/encephalitis are typical for this disorder and atypical for an MS relapse, although in some patients a severe MS relapse was initially diagnosed, (ii) the daclizumab-induced meningo-/encephalitis shows histological and MRI features of vasculitis, and (iii) the development of systemic symptoms and other autoimmune phenomena is common.

Although the mechanism of the daclizumab-associated meningo-/encephalitis is not fully understood, the imbalance between the decrease in T\textsubscript{reg} cells and the increase in of the CD56\textsuperscript{bright} NK cells, which may lead to a paradoxically inhibition of the autoregulatory mechanisms, has been considered the most likely causative mechanism\textsuperscript{1,2}. Unfortunately, this case series did not provide information on circulating CD56\textsuperscript{dim} cells and T\textsubscript{reg} cells. The CD56\textsuperscript{dim} cells act a major role in controlling the activation of anti-self T-cells and have been largely demonstrated to be impaired in MS and
modified by anti-IL-2R treatments\textsuperscript{1,9,10}. Other limitations of this review are its retrospective design, the limited information on clinical symptoms (psychiatric vs. neurological – such as movement-related symptoms) at onset of meningo-/encephalitis, and the fact that some of the cases has been previously reported, as clearly stated by the authors. Additionally, there is some overlap, but also inconsistencies, between the cases described by Stork et al. and those reviewed by Luessi et al\textsuperscript{6}. For example, two patients that Luessi et al. reported as having a positive outcome, were reported by Stork et al. as having a fatal outcome. Stork et al. stated that they obtained the information directly from the treating neurologist and that they reviewed all the patients’ medical records, including their own neuropathological results. A question that remains unanswered is whether some of the relapses which occurred during the trials represent a misclassification and were instead cases of autoimmune meningo-/encephalitis\textsuperscript{8}.

Following the Stork et al’s report, the Medicines and Healthcare Products Regulatory Agency in the UK (https://www.gov.uk/drug-safety-update/daclizumab-beta-zinbryta-risk-of-immune-mediated-encephalitis-some-cases-several-months-after-stopping-treatment) recommended that clinicians remain vigilant for any symptoms suggestive of autoimmune encephalitis. In patients presenting with an atypical MS relapse and neuropsychiatric symptoms, testing for a broad panel of autoantibodies, including anti-NMDA receptor antibody, should be considered up to 12 months following discontinuation of daclizumab.

The main lesson learnt from the daclizumab experience is that post-marketing safety requirements, including monitoring for and reporting of adverse events of new medications, are crucial to ensure patient safety, and, therefore, should be stringent, specific and timely.
References


Declaration of interests

AB has nothing to disclose.

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