Immune checkpoint-blocking antibodies bind to inhibitory molecules expressed on immune cells, allowing the immune system to fight the JC virus infection. The checkpoint-blocking antibodies pembrolizumab and nivolumab bind to the PD-1 molecule, a negative immune regulator that is upregulated on activated T cells.[6] PD-1 has two physiological ligands, PD-1 ligand 1 (PD-L1) and PD-L2, which are displayed on a variety of cell types, including antigen-presenting cells and some tumors. When PD-1 binds to its ligands, the T cell expressing PD-1 progressively loses function and eventually can become permanently exhausted. The proportion of cytotoxic T cells that express PD-1 and are JC virus-specific is elevated in patients with PML, indicating that T-cell exhaustion can contribute to the pathogenesis of PML.[7] These observations provided a convincing rationale for exploring immune checkpoint-blocking antibodies for the treatment of PML.

The case series from the National Institute of Health included eight patients who were treated with one to three infusions of pembrolizumab.[1] The patients had different underlying conditions, including chronic lymphatic leukemia, non-Hodgkin lymphoma, idiopathic lymphopenia, and HIV infection. Of these eight patients, five (63%) improved or stabilised, two (25%) deteriorated, and one (13%) did not show any clinical, radiological, or virological response. The two (25%) patients with HIV-associated PML had been on effective anti-retroviral therapy and had undetectable HIV viral load (blood and CSF), yet they were progressing without clinical or radiological evidence of immune reconstitution syndrome before pembrolizumab was started. They both stabilised or improved after pembrolizumab treatment.

The accompanying case reports describe one patient with idiopathic primary immunodeficiency whose PML improved after treatment with nivolumab,[2] and one patient with common variable immunodeficiency complicated by diffuse large cell B-cell lymphoma and chemotherapy whose PML responded to pembrolizumab.[3]

Together, these observations indicate that immune checkpoint-blocking antibodies can be a useful therapeutic option for some patients with PML. Checkpoint-blocking antibodies have a substantial risk of adverse effects, notably drug-induced autoimmune reactions.[8,9] In the National Institute of Health case series, recurrent skin rashes, which occurred in two (25%) patients, were recorded as the only notable therapy-associated adverse reactions. As stated in the accompanying editorial,[10] the reports are encouraging but more data and experience are needed to further define the efficacy and risk profile of immune checkpoint blockade in PML with different underlying conditions.

Reinhard Hohlfeld
Institute of Clinical Neuroimmunology, Ludwig Maximilians University, D-81377 Munich, Germany; and Munich Cluster for Systems Neurology, Munich, Germany
reinhard.hohlfeld@med.uni-muenchen.de

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β-secretase inhibitors for Alzheimer's disease: heading in the wrong direction?

The global effort to decipher the molecular basis of Alzheimer's disease and develop disease-modifying treatments, which began in the mid-1980s, has accelerated in the last several years. Genetic, neuropathological, biochemical, and human biomarker analyses all suggest an early role for accumulation of the amyloid β protein

(Aβ) in limbic and neocortical brain regions serving cognition; thus, attempts to neutralise or lower Aβ have received the most attention. Two articles[1,2] report the seemingly paradoxical worsening of cognition during clinical trials of inhibitors of BACE (β-site amyloid precursor protein [APP] cleaving enzyme). This protease initiates the generation of Aβ by cleaving the full-length APP. BACE is enriched in neurons and can cleave dozens of other protein substrates, many of which are important for neuronal function.

Egan and colleagues[1] report adverse neurological effects, including cognitive worsening, in patients with prodromal Alzheimer's disease in a trial of the BACE inhibitor verubecestat. This agent had previously been tested in patients with mild-to-moderate Alzheimer's disease, and no beneficial slowing of cognitive decline or any cognitive worsening was reported, despite lower Aβ in CSF and decreased amyloid plaque burden by PET scanning.[3] Egan and colleagues' trial in approximately 1450 patients with prodromal Alzheimer's disease and elevated brain amyloid was stopped in February, 2018, when a futility analysis revealed no clinical superiority of either verubecestat dose (12 mg/day or 40 mg/day) over placebo. At that point, approximately 235 participants in each of the three groups had completed their scheduled 104 weeks of treatment. The primary outcome was the mean change from baseline in the Clinical Dementia Rating Scale Sum-of-Boxes (CDR-SB; higher scores represent worsening). At week 104, this mean change was 1·58 in the placebo group versus 1·65 in the 12 mg/day group (p=0·67), and versus 2·02 in the 40 mg/day group (p=0·01). In an exploratory analysis across all time points, higher CDR-SB scores in the 40 mg/day group were reported at weeks 13, 26, and 52, suggesting that the worsened cognitive performance began relatively early after treatment initiation. Hippocampal volume measured by MRI declined by a mean of –6·1% in the placebo group and –6·7% in the 40 mg/day group over the 104 weeks. In the small number of CSF samples collected, the levels of Aβ42, Aβ40, and sAPPβ were each reduced by more than 60% from baseline on verubecestat, as expected from previous trials. Common adverse events reported more frequently at 40 mg/day of verubecestat than placebo included anxiety (9·1% *vs* 4·3% of participants), sleep disturbance (9·1% *vs* 4·5%), and depression (10·3% *vs* 5·2%).

Henley and colleagues[2] reported similar cognitive worsening in an analysis of a trial of another BACE inhibitor, atabecestat, in 557 participants with pre-symptomatic Alzheimer's disease and positive amyloid PET scans (the EARLY trial). In this secondary prevention trial, participants were randomly assigned to placebo or 5 mg/day or 25 mg/day of atabecestat. Administration of the inhibitor was discontinued in May, 2018, because of hepatic-related adverse events, but a safety follow-up is ongoing. The primary endpoint was change from baseline on the Preclinical Alzheimer's Cognitive Composite (lower scores represent worsening), which is sensitive to the memory and cognitive declines that mark the development of symptomatic Alzheimer's disease. In light of the worse outcome with verubecestat,[1] an expedited interim analysis of the EARLY trial was done. This analysis revealed that, after 6 months of treatment, the mean difference in the change from baseline on 5 mg atabecestat versus placebo was –0·26 points (p=0·34) but, on 25 mg versus placebo, it was –1·12 points (p<0·001), suggesting significant cognitive worsening at the higher dose. The differences in cognitive performance were also significant at 12 months, with the caveat that participant numbers had declined substantially by then. Adverse events related to cognition, anxiety, sleep and dreams, and depression were all more frequent with atabecestat than placebo.

What might explain these very disappointing results? Although target engagement (ie, Aβ decrease) by the inhibitor was shown for verubecestat[1] and can be assumed for atabecestat, the cognitive worsening is unlikely to be due to excessive lowering of Aβ, which would be expected to show little decline from its extremely elevated pathological levels in just 3 months. Rather, it is highly probable that the cognitive and behavioural problems represent interference with the normal BACE processing of its numerous substrates implicated in ion channel formation, synaptic maintenance, axon guidance, and other vital neuronal functions. Support for this hypothesis comes from a study of conditional BACE1 knock-out mice in which the enzyme was lowered markedly in adulthood, and shorter and disorganised infrapyramidal bundles in the mossy fiber region of the hippocampus were reported.[4] Interestingly, a separate knock-out mouse of the BACE1 neuronal substrate CHL1, important for correct axon guidance, produced a phenocopy of this effect.[5]

To elucidate the adverse neural effects of BACE inhibitors, we have done electrophysiological analyses of verubecestat and two other clinical BACE inhibitors (lanabecestat and LY2886721).[6] All three compounds significantly inhibited long-term potentiation in mouse hippocampal slices and altered other features of presynaptic and postsynaptic plasticity. These neurobiological data are consistent with the impaired memory and cognition reported in the human trials.[1,2] The effects are likely to represent interference by structurally distinct, but functionally similar, BACE inhibitors in the physiological processing of neuronal substrates of BACE (eg, CHL1; β2 subunit of the voltage-gated sodium channel; neuregulin, SEZ2), which are required for correct neurotransmission and other essential functions. The rapid (<3 months) decline in cognitive function and then apparent stability raise the question of whether recovery of cognition might occur once an agent is stopped; there are preliminary oral reports of this being the case. To achieve safe, chronic inhibition of this Aβ-generating protease in patients with presymptomatic or mildly symptomatic Alzheimer's disease, compounds that selectively reduce the processing of APP more potently than that of other substrates will need to be identified. The two BACE inhibitors that remain in clinical trials (elenbecestat and umibecestat) have not yet led to significant cognitive problems, so these adverse phenomena might not affect all members of the class.

Finally, the recent cessation of a phase 3 trial of aducanumab (an anti-Aβ antibody) occurred for a different reason: insufficient efficacy in an interim futility analysis, but without adverse events. The reason for this failure, despite its promising initial report in a small phase 1 trial,[7] will require publication of detailed analyses, including so-called spaghetti plots, to learn whether a subset of the approximately 3250 patients with mild Alzheimer's disease experienced some blunting of cognitive decline. Another antibody (BAN2401) targeting Aβ oligomers has now entered phase 3 after encouraging phase 2 data in approximately 850 patients with mild Alzheimer's disease: robust plaque clearing and less cognitive decline compared with placebo. Moreover, the complexity of mechanisms and targets in Alzheimer's disease is leading to several other approaches to treatment, including vaccines and antibodies against the tau protein that comprises the neurofibrillary tangles. We should do all we can in our ongoing quest to identify safe and efficacious disease-modifying agents for the individuals and families affected by this scourge, today and in the years ahead.

Dennis Selkoe
Department of Neurology, Harvard Medical School, and Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA
dselkoe@bwh.harvard.edu

I declare no competing interests.

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