NEWS IN BRIEF

FDA approves first drug for primary progressive multiple sclerosis

The FDA approved Roche's ocrelizumab for the treatment of relapsing and primary progressive multiple sclerosis (PPMS), wrapping up a 40-year development history for the anti-CD20 monoclonal antibody (mAb). This is the first drug approval for PPMS, a form of the neurodegenerative disease that affects around 15% of multiple sclerosis patients and is characterized by steadily worsening neurological function without any early relapses or remissions.

Over decades of research, scientists have laboriously overturned the view that T cells are the only driver of autoimmune damage in multiple sclerosis. They have shown that B cells can contribute to disease pathogenesis through antigen presentation, autoantibody production and cytokine secretion. Clinical studies with the B cell-depleting anti-CD20 mAb rituximab also showed signs of early promise in PPMS. Although the community was dismayed when the development of rituximab for PPMS was suspended in 2010, ocrelizumab is a next-generation fully humanized anti-CD20 mAb that finally fills the gap.

In a phase III study in 732 patients with PPMS, 33% of ocrelizumab-treated patients had disability progression confirmed at 12 weeks, compared with 39% of placebo participants. Neurologists welcomed these results, even if some cautioned that the treatment benefit is modest. Adverse events that were more frequent with ocrelizumab than with placebo included infusion-related reactions, upper respiratory tract infections and oral herpes infections. The treatment may also increase the risk of neoplasms.

Companies are developing other candidates that modulate a range of targets — including Novartis's sphingosine 1-phosphate receptor modulator siponimod and AB Science's tyrosine kinase inhibitor masitinib — for primary and secondary progressive forms of multiple sclerosis (*Nature* **540**, S7–S9; 2016).

Asher Mullard

FDA approves first deuterated drug

The FDA approved Teva Pharmaceuticals' deutetrabenazine for chorea associated with Huntington disease, providing the first approval of a drug that contains the heavy hydrogen isotope deuterium.

Early adopters first started tinkering with the use of deuterium in drug candidates more than 50 years ago. Because deuterium–carbon bonds are stronger than hydrogen–carbon bonds, a few researchers hoped that the isotope would help drugs better withstand drug-metabolizing enzymes such as the cytochrome P450s. Renewed interest in this approach in recent years led to a few deuterated candidates entering the clinic (*Nat. Rev. Drug Discov.* 15, 219–221; 2016).

Deutetrabenazine, like other candidates in the first wave of deuterated drugs, uses heavy hydrogen to improve the dosing and safety profiles of an already approved agent. Deutetrabenazine is a deuterated version of tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor that the FDA approved for the treatment of chorea associated with Huntington disease in 2008. The new contender seems to offer a lower risk of depression, somnolence and akathisia than the established competition. It still carries a black box warning, however, citing the risk of depression and suicidality.

Teva, which gained the drug through the 2015 acquisition of Auspex, initially submitted deutetrabenazine for FDA approval in 2015. In 2016 it received a complete response letter citing the need for deeper analysis of the drug's metabolites.

Concert Pharmaceuticals, whose discovery focus is wholly on deuterated drugs, has also developed candidates to compete with nearly identical approved agents. Concert's phase II candidate CTP-656, for example, is a deuterated version of Vertex Pharmaceuticals' cystic fibrosis transmembrane conductance regulator (CFTR) potentiator ivacaftor for cystic fibrosis. CTP-656 seems to offer a longer half-life and a slower clearance profile than the approved small molecule. In March, Vertex acquired CTP-656 for US$160 million upfront and $90 million in potential milestones.

Companies have started using deuterium in novel drugs as well. Vertex incorporated the isotope into its DNA-dependent protein kinase (DNA-PK) inhibitor VX-984, one of three DNA-PK inhibitors in phase I trials. In January, Merck KGaA licensed the drug from Vertex.

Teva's deutetrabenazine is also currently under FDA review for tardive dyskinesia, with a PDUFA decision due by the end of August. In April, the agency approved the first ever tardive dyskinesia drug, giving the green light to Neurocrine Biosciences' VMAT2 inhibitor valbenazine.

Asher Mullard

FDA approves dupilumab for severe eczema

The FDA approved Regeneron and Sanofi's first-in-class candidate dupilumab for the treatment of moderate-to-severe eczema.

T helper 2 type responses have emerged as a unifying feature of various inflammatory and allergic diseases, such as eczema and asthma. As a result, type 2 cytokines — including interleukin 4 (IL-4) and IL-13 — have come under the spotlight as promising targets for selective treatment of these indications. Dupilumab is a first-in-class monoclonal antibody (mAb) that modulates both IL-4 and IL-13 signalling; the mAb binds to the IL-4 receptor subunit alpha (IL-4Rα), which can also dimerize with a subunit of the IL-13 receptor to control IL-13 signalling (*Nat. Rev. Drug Discov.* **15**, 35–50; 2016).

In three randomized, double-blind placebo-controlled trials of the mAb in 2,119 patients, 36–39% of patients achieved 'clear or almost clear' skin at 16 weeks of treatment, compared with 10–12% of patients in the control arm. Common side effects included injection site reactions, cold sores in the mouth or on the lips, and eye and eyelid inflammation.

The mAb is also in phase III trials for asthma and for nasal polyposis, and in phase II trials for oesophagitis.

Companies are also developing candidates that take out IL-4 and IL-13 signalling by binding to the cytokines directly. Sanofi's first-in-class bispecific antibody SAR156597 binds to both cytokines. It is in phase II trials for idiopathic pulmonary fibrosis. AstraZeneca's IL-13-targeting mAb tralokinumab is in phase III trial for asthma and phase II development for eczema. Other anti-IL13 mAbs that are in phase II trials include Roche's lebrikizumab and Celgene's RPC4046.

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