NEWS IN BRIEF

GSK launches mega trial of p38 MAPK inhibitor in acute coronary syndrome

Mixed results from Phase II trial of the anti-inflammatory drug candidate losmapimod prompt pivotal study in heart attack patients.

The lowdown: GlaxoSmithKline (GSK) is moving a small-molecule inhibitor of the p38 mitogen-activated protein kinase (MAPK) α- and β-isoforms forward for the short-term treatment of acute coronary syndrome on the basis of mixed results from a Phase II trial (*Lancet*; 13 Jun 2014). In the trial in 526 patients with non-ST-segment elevation myocardial infarction, losmapimod missed the primary end points of inflammation (assessed by concentrations of C-reactive protein (CRP) at 12 weeks) and infarct size. "In retrospect … we might have expected that serum concentrations of [CRP] ... would normalise by week 12 and that this timepoint would provide an insensitive signal of biological activity," the authors write. Efficacy signals on CRP at 72 hours, B-type natriuretic peptide (BNP) at 12 weeks, and imaging measures of left ventricular function and end-diastolic and end-systolic volumes led the authors to conclude that treatment "might improve outcomes after acute coronary syndromes". They add that losmapimod and related compounds have also been associated with reduced circulating markers of inflammation and vascular inflammation in trials in other cardiovascular indications.

Many other drug developers have been stumped on the p38 MAPK front because of intolerable liver, skin and neurological adverse events (*Nature Rev. Drug Discov.* **8**, 480–499; 2009). GSK's latest results do not show any major liver or other safety signals, although there were numerical yet statistically insignificant increases in alanine aminotransferase (ALT) concentrations that were three or more times the upper limit of normal (ULN), serum creatinine concentrations at 12 weeks and adverse events leading to study drug termination with losmapimod treatment.

A Phase III trial will now randomize 25,500 patients who have presented with acute coronary syndrome (specifically, a heart attack) to twice-daily oral treatment with losmapimod or placebo for 3 months. The primary end point is the composite measure of time to first occurrence of cardiovascular death, myocardial infarction or severe recurrent ischaemia requiring urgent coronary artery revascularization. The study should be completed in December 2018.

Losmapimod is the only p38 MAPK inhibitor in development for acute coronary syndrome. Array's ARRY-797 is in Phase II development for congestive heart failure.

The news came less than a month after GSK reported that its anti-inflammatory candidate darapladib — an inhibitor of lipoprotein-associated phospholipase A2 — had failed in a Phase III acute coronary syndrome trial (see page 481).

Biogen Idec storms haemophilia markets

The FDA approved Biogen Idec's long-acting haemophilia A drug, months after approving its long-acting haemophilia B drug.

The lowdown: In June, the US Food and Drug Administration (FDA) approved Biogen Idec's Eloctate for adults and children with haemophilia A. The recombinant drug is made up of factor VIII fused to the Fc domain of human immunoglobulin G1. The Fc domain binds to the neonatal Fc receptor, which delays lysosomal degradation of immunoglobulins by cycling them back into circulation, extending the therapeutic's half-life beyond that of previous factor VIII therapies. Eloctate can be injected once every 3–5 days, compared with every 2–3 days for older options. Thomson Reuters Cortellis predicts US$1.5 billion in annual sales by 2019, on the basis of forecasts from four analysts.

Would-be competitors are working on several other potentially long-acting factor VIII therapies. Phase III candidates include: Bayer's BAY81-8973, a recombinant factor VIII with an improved glycosylation pattern; Bayer's BAY94-9027, a pegylated factor VIII; CSL Behring's CSL627, a single-chain factor VIII; Novo Nordisk's NN7088, a glyco-pegylated factor VIII; and Baxter's OBI-1, a porcine factor VIII for patients who have neutralizing antibodies to replacement human factor VIII.

In March, the FDA also approved Biogen Idec's Alprolix, a factor IX molecule fused to the Fc domain of human immunoglobulin G1, for haemophilia B. Alprolix can be injected up to once every 10 days, compared to every 2–4 days for older options. Cortellis predicts annual sales of $379 million in 2019, on the basis of forecasts from two analysts.

Alprolix too could soon see competition from long-acting factor IX therapies that are in the clinic, including Novo Nordisk's Phase III pegylated factor IX N9-GP and CSL Behring's Phase III factor IX–albumin fusion protein CSL654.

Takeda's integrin inhibitor scores inflammatory bowel disease approvals

US and European regulators approved Takeda's vedolizumab for ulcerative colitis and Crohn's disease.

The lowdown: For the millions of patients around the world with Crohn's disease and ulcerative colitis, flare-ups are treated with diarrhoeal drugs and corticosteroids, whereas more severe symptoms are treated with immunosuppressants and tumour necrosis factor (TNF)-specific monoclonal antibodies (mAbs). But the TNF-specific mAbs are only effective in around two-thirds of patients and often lose their efficacy over time. Vedolizumab, an integrin receptor antagonist, is the newest addition to the arsenal for these patients in need.

Integrin receptors mediate cell–cell interactions, and by inhibiting these interactions the drug blocks a set of circulating inflammatory cells from migrating into inflamed areas of the gastrointestinal tract. Biogen Idec's integrin inhibitor natalizumab, first approved for multiple sclerosis, was also approved for Crohn's disease in the United States in 2008, but its link with the fatal viral brain infection progressive multifocal leukoencephalopathy (PML) has restricted uptake. However, whereas natalizumab binds to both α4β1 and α4β7 integrins, vedolizumab preferentially binds α4β7 integrin and so is thought to have a cleaner safety profile (*Nature Rev. Drug Discov.* **12**, 411–412; 2013). No cases of PML have been seen to date with vedolizumab.

BioMedTracker forecasts annual sales of over US$1 billion by 2019.

Several other α4β7 integrin-specific antibodies are also in development for inflammatory bowel disease indications. Roche's etrolizumab is in Phase III trials for Crohn's and for ulcerative colitis, and AstraZeneca and Amgen's AMG181 is due to enter Phase III trials for ulcerative colitis by the end of the year.

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