NEWS IN BRIEF

FDA rejects NASH drug

The US FDA has rejected Intercept's obeticholic acid for fibrosis due to nonalcoholic steatohepatitis (NASH), another setback for an indication beset with failures.

NASH is a form of liver disease that is marked by excessive fat accumulation, inflammation and cellular damage in the liver. It affects 3–12% of adults in the US and can lead to cirrhosis, liver cancer and liver failure, but there are as yet no approved drugs for the indication. Dozens of agents are in various stages of development for this disease, chasing disease-modifying activity and a projected US$15 billion market.

Intercept's obeticholic acid, a farnesoid X receptor (FXR) agonist, had been positioned for a first approval for this setting. In a 1,968-patient phase III trial of the drug, the primary end points were fibrosis improvement with no worsening of NASH, or NASH resolution with no worsening of fibrosis. It succeeded on the fibrosis front, with 18–23% of patients experiencing an improvement versus 12% on placebo, the company reported in *The Lancet* last year. But the trial missed on NASH resolution, with only 11–12% of treated patients experiencing improvement compared with 8% of placebo recipients.

The drug's side effects include pruritus and elevated LDL cholesterol levels. The FDA approved obeticholic acid for primary biliary cholangitis in 2016, but with a black box warning that incorrect dosing can lead to fatal liver failure.

According a press release from Intercept, the FDA did not approve the drug for NASH because "the predicted benefit of [obeticholic acid] based on a surrogate histopathologic end point remains uncertain and does not sufficiently outweigh the potential risks."

Intercept remains committed to the drug. "We strongly believe that the totality of data submitted to date both meet the requirements of the Agency's own guidance and clearly support the positive benefit–risk profile of [obeticholic acid]," said Intercept CEO Mark Pruzanski.

Asher Mullard

FDA rejects first DARPin

The FDA has rejected AbbVie, Allergan and Molecular Partners' VEGF-targeting abicipar pegol for wet age-related macular degeneration (AMD), owing to concerns over intraocular inflammation with the biologic candidate. While AbbVie is considering next steps for the programme, which it gained in its acquisition of Allergan, Molecular Partners is pivoting to other therapeutic opportunities.

DARPins (designed ankyrin repeat proteins) are low-molecular-weight biologics that bind targets with high affinity and specificity, promising advantages over monoclonal antibodies. Molecular Partners, founded in 2004 to advance this modality, prioritized abicipar pegol to validate the clinical potential of these agents. Whereas the VEGF-targeting antibody fragment ranibizumab is dosed monthly for wet AMD, phase III data shows that abicipar provides efficacy with quarterly dosing. But intraocular inflammation with abicipar was over 15% in this trial, compared with less than 1% with ranibizumab.

Molecular Partners' CEO Patrick Amstutz says the partners have since improved their ability to purify the biologic and that their internal data suggests that should reduce inflammation rates. "The question is how and if AbbVie will show that this new material is of the quality that you can give it on a global scale to many, many patients," he says.

Despite the disappointment for Molecular Partners, Amstutz still calls the abicipar data "highly validating". The company is now focusing on other programmes, with an emphasis on multi-specificity opportunities. Its immuno-oncology candidate MP0301, which is partnered with Amgen, binds fibroblast-activating protein (FAP) on cancer cells and 4-1BB on T cells to facilitate T cell clustering at tumour sites. "We're taking biology that has been shown in the clinic to be active — but too active — and seeing if we can find a molecular architecture via multi-specificity to create local activity," says Amstutz. A phase I dose-finding trial is underway, and combination trials could start next year.

Asher Mullard

COVID-19 platform trial delivers

Although more than 1,000 clinical trials are testing treatment options for COVID-19, few have provided clear-cut results as yet. An adaptive platform trial known as RECOVERY, looking at multiple different treatments in parallel in hospitalized COVID-19 patients in the UK, has now given a verdict on three potential therapies. In a first positive result, the anti-inflammatory drug dexamethasone improves outcomes in patients with severe disease.

As of the end of June, the trial had recruited more than 11,500 patients onto various treatments including usual care. In an analysis of dexamethasone, researchers looked at outcomes from more than 2,100 patients who were treated with the steroid, compared with more than 4,300 patients on usual care. Overall, 21.6% of patients on dexamethasone died within 28 days, compared with 24.6% of patients on usual care, the investigators reported in a press release in June and in a preprint *medRxiv* article. Efficacy was most pronounced in ventilated patients, in which treatment reduced deaths by one third, and in patients who required oxygen, in which treatment reduced deaths by one fifth. Treatment did not reduce mortality in patients with milder disease, who were not on respiratory support.

"It is likely that the beneficial effect of corticosteroids in severe viral respiratory infections is dependent on using the right dose, at the right time, in the right patient. High doses may be more harmful than helpful, as may corticosteroid treatment given at a time when control of viral replication is paramount and inflammation is minimal," the investigators wrote.

Increasing evidence suggests patient immune status may be important for COVID-19 therapeutics. Several immune-boosting agents are under clinical evaluation in patients whose immune systems may need help fending off infection.

Shortly after the disclosure of this landmark result, the RECOVERY trial reported that the HIV protease inhibitors lopinavir and ritonavir do not improve outcomes. Nearly 1,600 COVID-19 patients received lopinavir plus ritonavir, and their outcomes were compared with nearly 3,400 patients on usual care. On treatment, 28-day mortality was 22.1%, compared with 21.3% in the control arm, the investigators reported. These results were consistent across patient subgroups.

The RECOVERY trial has also found that hydroxychloroquine does not improve COVID-19 outcomes in hospitalized patients.

The WHO's Solidarity trial, an international platform trial, subsequently also discontinued its exploration of lopinavir plus ritonavir, and of hydroxychloroquine, on the basis of interim and other results showing little or no evidence of reduction in mortality with these agents.

The RECOVERY trial is ongoing, now testing the antibiotic azithromycin, the IL-6-targeted anti-inflammatory therapy tocilizumab and convalescent plasma.

Asher Mullard