BIOBUSINESS BRIEFS

TRIAL WATCH

Apixaban beats warfarin in stroke trial

Results from a clinical trial of the novel oral anticoagulant apixaban in patients with atrial fibrillation showed that this factor Xa inhibitor was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding and resulted in a lower mortality rate (*N. Engl. J. Med.* **365**, 981–992; 2011). Until recently, vitamin K antagonists such as warfarin were the standard treatment for preventing thrombosis. However, the use of vitamin K antagonists is associated with several problems. "These drugs have a delayed onset of action, they interact with food and other drugs, and have variable pharmacokinetics and pharmacodynamics such that regular laboratory monitoring and dose adjustments are required to ensure a therapeutic level of anticoagulation is maintained," notes Kenneth Bauer, director of thrombosis clinical research at the Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA.

The trial — named ARISTOTLE — studied 18,201 patients with atrial fibrillation (a risk factor for stroke), and compared warfarin (administered at a dose to achieve a target international normalized ratio of 2.0–3.0) to apixaban (administered at a dose of 5 mg twice daily). Unlike warfarin, apixaban selectively inhibits just one coagulation factor. "Factor Xa is an attractive target for anticoagulants because it is positioned at the start of the common pathway of coagulation, and so it acts at a point in the cascade where there is less amplification of thrombin generation. Furthermore, by not inhibiting thrombin activity directly, at appropriate doses apixaban might better facilitate haemostasis without causing excessive bleeding compared with other agents," explains Bauer.

The primary outcome of the trial was the rate of ischaemic or haemorrhagic stroke or systemic embolism. In the apixaban group this was 1.27% per year, compared with 1.60% per year in the warfarin group ($P < 0.001$ for non-inferiority, $P = 0.01$ for superiority). Secondary end points included the rate of major bleeding, which was reduced (2.13% per year in the apixaban group, compared with 3.09% per year in the warfarin group; $P < 0.001$), and the rate of death from any cause, which was also decreased (3.52% in the apixaban group, compared with 3.94% in the warfarin group; $P = 0.047$).

As well as apixaban, other oral anticoagulants might soon replace warfarin. Dabigatran, a direct thrombin inhibitor, was approved as an alternative to warfarin in 2010. In addition, rivaroxaban — another factor Xa inhibitor — received a positive opinion from the US Food and Drug Administration (FDA) advisory panel in September, and it is anticipated that the FDA will decide in early November whether to approve rivaroxaban for use as an alternative to warfarin.

Kurt Huber, Director of the Department of Cardiology and Emergency Medicine at the Wilhelminen Hospital, Vienna, Austria, highlights that these new oral anticoagulants could eventually lead to more frequent use of anticoagulation therapy: "For example, about 30%

REGULATORY WATCH

Leading Hedgehog inhibitor submitted for approval as skin cancer drug

Genentech has filed a new drug application with the US Food and Drug Administration for vismodegib, a Hedgehog (HH) pathway inhibitor that has shown promising results in a Phase II trial in patients with advanced basal cell carcinoma (BCC).

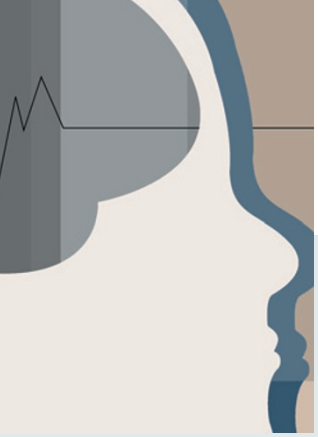
The results of the trial, which enrolled 104 patients, were presented at the seventh European Association of Dermato-Oncology meeting earlier this year. Vismodegib was found to substantially shrink tumours or heal visible lesions in 43% of patients with locally advanced BCC and in 30% of patients with metastatic BCC.

Some cancers — such as BCC, the most common cancer in the western world, and medulloblastoma, a childhood cancer with a poor prognosis — are associated with mutational activation of HH signalling in the absence of the ligand, which directly drives tumour cell proliferation (*Nature Rev. Drug Discov.* **5**, 1026–1033; 2006). In other cancers, such as pancreatic adenocarcinoma and small-cell lung cancer, overexpression of HH ligands by tumour cells drives cancer progression by increasing the production of growth and angiogenic factors from neighbouring cells.

"HH pathway inhibitors could provide new hope to patients with these cancers," says James K. Chen, Department of Chemical and Systems Biology, Stanford University School of Medicine, California, USA. "As HH signalling is not generally required for cell growth and function, vismodegib and other drugs that target this pathway may also avoid the side effects associated with conventional chemotherapies," he adds.

Vismodegib inhibits HH signalling by targeting the G protein-coupled receptor-like protein Smoothened (SMO). The only known function of SMO is to mediate HH signalling, so SMO-targeting drugs can be highly specific for this oncogenic pathway. "SMO is attractive because it was the first target in the HH pathway shown to be amenable to pharmacological intervention [*Science* **280**, 1603–1607; 1998; *Nature* **406**, 1005–1009; 2000; *Genes Dev.* **16**, 2743–2748; 2002], and is a commonly encountered target in small-molecule screening [*Proc. Natl Acad. Sci. USA* **99**, 14071–14076; 2002]. Several cyclopamine mimics (SMO-binding HH pathway antagonists), including a derivative of cyclopamine itself, are currently in clinical trials," explains Philip Beachy, Institute for Stem Cell Biology and Regenerative Medicine, Stanford, California, USA.

However, the development of resistance to drugs that target SMO might be a problem, as "there are likely to be mutations in SMO or other types of acquired drug resistance that diminish the effectiveness of some SMO antagonists", cautions Lee Rubin, Director of Translational Medicine at the Harvard Stem Cell Institute, Cambridge, Massachusetts, USA. "It may be preferable to find a drug that inhibits a downstream component of the HH signalling pathway, such as [the transcriptional activator] GLI, but whether



of patients with non-valvular atrial fibrillation who require therapy currently do not receive it. In theory, all patients with this condition should receive one of the new agents because there is — independently of whether the efficacy is equal to or better than warfarin — a significant reduction in fatal intracerebral bleedings for all new agents versus warfarin." However, Huber notes that in practice this could be problematic because the new agents are likely to have a much higher cost than warfarin, "so it may be that, for example, new drugs are given initially to patients in whom warfarin levels cannot be easily controlled within the given therapeutic range".

It is probably too early to say which of the new oral anticoagulants will be superior. "Comparisons across different trials can be challenging because the pivotal trials of dabigatran [*N. Engl. J. Med.* **361**, 1139–1151; 2009], rivaroxaban [*N. Engl. J. Med.* **365**, 883–891; 2011] and apixaban have somewhat different designs and study populations. Direct assessment of the oral anticoagulants will require head-to-head studies, which are not currently available," cautions Jessica Mega, at the Department of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA. "However, the results with the direct thrombin and factor Xa inhibitors have been very encouraging."

> "at appropriate doses apixaban might better facilitate haemostasis without causing excessive bleeding"

such compounds will be able to achieve the same degree of pathway specificity as SMO antagonists remains to be seen."

In addition, SMO inhibitors might not be effective in all types of cancer that involve aberrant HH signalling. In some cancers HH may not be the sole driver of tumour growth. "In these cancers, HH antagonists may need to be combined with other inhibitors," adds Rubin. "Nevertheless, these findings are very exciting and it will be interesting to see how effective vismodegib is against other tumours linked to HH pathway activation."

After a long series of basic science investigations, beginning with the genetic characterization and isolation of the *hh* gene in *Drosophila melanogaster* in the 1980s and 1990s, these findings with vismodegib highlight the clinical potential of targeting HH signalling for the treatment of cancer in humans. The trials that are currently underway with vismodegib and other HH inhibitors should reveal which tumours these drugs might be useful for. "Finding ways to prevent or overcome resistance mechanisms will also be integral to the implementation of HH pathway-targeting chemotherapies," concludes Chen.