Clin. Invest. (2011) 1(9), 1211–1215

CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

First drug in over 50 years gains EU approval for stroke prevention in atrial fibrillation

Boehringer Ingelheim's breakthrough oral anticoagulant Pradaxa® (dabigatran etexilate) has received approval from the European Commission for the prevention of stroke in patients with atrial fibrillation (AF). This means that, for the first time in over 50 years, a new, effective and convenient treatment for the prevention of AF-related strokes will be available to millions of AF patients across Europe.

The most common sustained heart rhythm condition, AF, affects around 1% of the total population. Up to three million people globally suffer strokes related to AF each year, since the condition raises the risk of stroke by five-times. Strokes related to AF are particularly severe, causing a 60% increase in the likelihood of disability, and a half of those affected by AF dying within 1 year.

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The use of the thrombin inhibitor dabigatran etexilate has been approved for use in the prevention of stroke and systemic embolism in adult patients with nonvalvular AF with one or more risk factors. For the majority of patients, a dose of 150 mg is recommended, while the 110 mg dose is available for patients with an increased risk of bleeding, elderly patients aged 80 years or over and those who are co-administered with dabigatran etexilate and the calcium-channel blocker verapamil. Lars Wallentin of Uppsala University Hospital (Sweden) speaking to *Clinical Investigation*, highlights an additional benefit of the drug. "As [the drug] can be given as a fixed dose it is an important step forward concerning patient acceptability and convenience of care."

The approval is based on the results from RE-LY®, which, with over 18,000 patients included, is one of the largest ever studies conducted in the AF field. The study was a prospective, randomized, open-label with blinked end point evaluation trial, which compared two fixed doses of dabigatran etexilate (100 and 150 mg twice daily) with open-label warfarin. Compared with warfarin, dabigatran etexilate 150 mg reduced the risk of stroke and systemic embolism by 35%, while significantly lowering the risk of intercranial bleeding. Dabigatran etexilate 110 mg twice a day was shown to significantly lower the rate of major bleeding in comparison with warfarin, while being non-inferior to the alternative drug in reducing the risk of stroke and systemic embolism.

Dabigatran etexilate 150 mg is the only novel oral anticoagulant proven to be superior to well-controlled warfarin that is approved for stroke prevention in AF in Europe. "Future clinical investigations in this area now need to be with dabigatran as the new standard of care, rather than warfarin," Wallentin tells *Clinical Investigation*.

The therapy has been approved for the same use in the USA, Canada, Japan, Australia and other countries across four continents. Dabigatran etexilate was also granted EU approval for the primary prevention of blood clots in adults who have undergone elective total hip or knee replacement surgery.

Sources: Breakthrough therapy Pradaxa® (dabigatran etexilate) first drug in 50 years to gain approval for stroke prevention in atrial fibrillation in EU: www.boehringer-ingelheim.com/news/news_releases/press_releases/2011/04_aug_2011_dabigatranetexilate.html

ISSN 2041-6792

10.4155/CLI.11.123

Results of a clinical trial gives hope for molecular therapy in the treatment of muscular dystrophy

A clinical trial involving a molecular technique for the treatment of the lethal genetic disease Duchenne muscular dystrophy (DMD) has produced significant positive results. The technique, originally developed at the University of North Carolina (NC, USA), aims to restore the function of the defective dystrophin gene using strips of genetic code called antisense oligonucletides.

The study, by researchers from the UK, USA and Australia, demonstrated that a Phase Ib/IIa trial of the treatment restored expression of dystrophin, the critical muscle protein missing in patients with the progressive neuromuscular condition. It was also shown that the treatment, which involved the systemic delivery of the phosphorodiamidate morpholino oligomer AVI-4658 (eteplirsen), produced no serious adverse events related to its administration.

"DMD is a lethal disease caused by defects, mostly deletions, in a gene that codes for dystrophin, an essential muscle protein," co-author Ryszard Kole, of the Lineberger Comprehensive Cancer Centre (NC, USA), tells *Clinical Investigation*. The disease affects one in 3500 newborn boys, who eventually lose their ability to walk and breathe. "Patients become non-ambulant at the age of 10–12 and usually do not survive past [their] early twenties," says Kole. In a milder form of the disease, called Becker muscular dystrophy, the muscle protein is largely functional as the genetic defect leads to only one missed component. Patients of this disease can have a normal lifespan.

The treatment was administered intravenously to 19 DMD patients over the course of 12 weeks. The current study investigates a method of using antisense oligonucleotides to mask sections of code, in order to change the lethal form of the illness to the survivable. Co-author of the report, Dominic Wells of the Royal Veterinary College (London, UK), talking exclusively to *Clinical Investigation*, explains that "there was clear evidence of a reduction in inflammation in the muscles of patients treated with the two higher doses, suggesting that increased dystrophin expression was beneficial and did not evoke an immune response." Following treatment, the patients demonstrated an increase of protein levels of up to 16% of normal muscle.

> "...there was clear evidence of a reduction in inflammation in the muscles of patients treated..."

Although the trial was not sufficient in duration to demonstrate a clinical benefit, Wells highlighted the future potential of the findings of this project. "This encourages further trials to determine the best dosing regime to deliver real clinical benefit to patients with DMD. It also encourages the development of additional antisense sequences to target other exons as, due to differences in mutations, only a subset of DMD patients will benefit from skipping exon 51 using AVI-4658." Kole adds "it gives me tremendous satisfaction that the approach I invented some 20 years ago is now tested in, and gives hope to, patients."

The research team plan to expand their studies, increasing both the dose and duration of treatment. Wells informs *Clinical Investigation* that AVI BioPharma is currently enrolling DMD patients by invitation to a trial of weekly intravenous injections of the same drug at two higher dose rates (30 and 50 mg/kg of AVI-4658 [eteplirsen]), plus a placebo group for a 24-week study based at Nationwide Children's hospital (OH, USA). "If the trial is successful it will bring us one step closer to providing much needed treatment for DMD patients," concludes Kole.

Sources: Clinical trial of molecular therapy for muscular dystrophy yields significant positive results: www.medicalnewstoday.com/releases/231710.php; Cirak S, Arechavala-Gomez, Guglieri M *et al.* Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphoridiamate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *The Lancet* DOI: 10.1016/SO140-6736(11)60756-3 (2011) (Epub ahead of print).

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Daclizumab meets main goal of mid-stage MS trial

Abbott and Biogen Idec have recently announced that the experimental once-monthly multiple sclerosis (MS) drug daclizumab has met the main goal of a mid-stage Phase IIb trial. In the latest study, daclizumab caused a significant reduction of annualized relapse rates in MS patients compared with placebo.

The results of this trial, along with previous clinical data, support the drug as a new approach to the treatment of relapsing-remitting MS (RRMS), the most common form of the condition. Daclizumab was shown to be more effective than many commonly used MS treatments.

"The results of this trial, along with previous clinical data, support the drug as a new approach to the treatment of relapsing-remitting MS ... Daclizumab was shown to be more effective than many commonly used MS treatments."

The year-long SELECT study randomized 600 patients with RRMS to receive one of two doses of daclizumab or placebo every 4 weeks. Top-line results indicated that the annualized relapse rate was reduced by 54% in the group receiving low doses of the agent and by 50% in the high-dose group,in comparison with those given a placebo.

New study questions reliance on animal models for clinical research

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Abbott and Biogen Idec claim that daclizumab use also led to a significant reduction in the number of new brain lesions between weeks 8 and 24 and that patients treated with the compound had reductions in the risk of sustained disability progression at 1 year. The high- and low-dose groups exhibited a 54 and 43% decrease in risk of sustained disabilty in 1 year, respectively.

In addition, a reduction in the proportion of patients who relapsed was reported. While these results are favorable, the trial reported some adverse events, including increases in serious infections and skin problems in patients on the drug. Additionally, liver enzyme tests, which measure the organ's function and help detect damage, were abnormal in 4% of patients, compared with less than 1% of those on placebo. A full analysis is being conducted into whether these liver abnormalities are reversible once the drug is discontinued.

> "While these results are favorable, the trial reported some adverse events, including increases in serious infections and skin problems in patients on the drug."

The companies hope to confirm the results of the SELECT study in a latter Phase III trial. The second registrational study, DECIDE, began in 2010 and is evaluating daclizumab compared with Avonex® (INFβ-1a) in patients with RRMS.

Sources: Abbott, Biogen Idec's daclimuzab meets main goal of mid-stage MS trial: www.firstwordpharma.com/node/896865; Biogen, Abbott MS drug shows positive data in major study: www.biogenidec.com/press_release_details.aspx?ID=5981&ReqId=1594585

Results of research conducted at Washington University (St. Louis, MO, USA) show that human and mouse hearts differ in their response to two cardiovascular drugs. The report demonstrates the importance of working with human hearts, showing that a drug target that may appear promising in a mouse model may not necessarily work in humans.

The study focused on the KATP ion channel in the heart, a potassium channel sensitive to the presence of ATP. In terms of drug therapy, this channel is both a favorable and dangerous target. It plays a major role in cardiac protection during ischemia, but can also contribute to life-threatening arrhythmia during a heart attack.

Igor Efimov, co-author and distinguished Professor at the Department of Biomedical Engineering, Washington University, explains the study focus to *Clinical Investigation*, "Change in the ATP:ADP ratio during metabolic inhibition caused by ischemia opens KATP channels, which causes dramatic shortening of the action potentials in the heart cells. Such shortening is particularly proarrhythmic, as we demonstrate in our experiments in live human heart tissue from both the atria and ventricles." This can potentially kill the patient.

The KATP channel can have either of two subunits sensitive to the presence of ATP, SUR1 and SUR2. Efimov and Nichols have previously found, now published in the January 2010 issue of the *Journal of Molecular and Cellular Cardiology*, that the SUR1 gene is expressed only in the atria of mice. Conversely, SUR2 was reported to be expressed only in the ventricles of mice.

"Previous findings held promise for a very attractive drug therapy that could be cardiac-chamber specific", Efimov tells *Clinical Investigation*. "A drug could be designed to control either subunit and thus control KATP channels in the atria without affecting the ventricles and *vice versa*." The recent study explored whether this was applicable in the tissue of the human heart, by reporting on two drugs that have already been tested in the mouse heart and yielded positive results.

"Experiments in the human heart did not confirm mouse findings", says Efimov. The study finds that healthy humans express SUR2 in both the atria and ventricles and SUR1 in only the ventricles. Patients with ischemic heart disease and/or heart failure express both SUR1 and SUR2 in the atria and ventricles, therefore a chamber-specific treatment based on KATP channels is unlikely.

Efimov suggests that the failure of promising drugs to pass clinical trials is due to the large difference in gene expression between mice and humans: "The major implication [of this study] is that mouse models of cardiac arrhythmias should be taken with a great deal of caution. Significant differences in mouse and human cardiac electrophysiology make translation of findings made in the mouse to clinical practice a daunting task."

Looking to the future, Efimov advises that hypothetical therapy needs to be assessed prior to going to clinical trials: "The current translational paradigm accepted in cardiovascular medicine needs to change by incorporating a new step between animal models and clinical trials."

Sources: Fedorov VV, Glukhov AV, Ambrosi CM *et al.* Effects of KATP channel openers diazoxide and pinacidil in coronary-perfused atria and ventricles from failing and non-failing human hearts. *J. Mol. Cell. Card.* 51 (2), 215–225 (2011); New study calls into question reliance on animal models in cardiovascular research: www.eurekalert.org/pub_releases/2011-08/wuis-nsc080311.php

Push renewed for minorities in clinical trials

The number of minority participants in clinical trials has shown no increase in the past 30 years according to findings presented at the National Medical Association (NMA) 2011 Annual Convention and Scientific Assembly (Washington, DC, USA). Although members of the medical community argue that wider participation is essential to identify differences in reactions and healthcare, the number of minority participants and researchers continues to remain lower than in the general population.

> "...minorities only account for 10% of participants in multicenter clinical trials ... numbers have seen no improvement since the 1980s."

Nine experts spoke on 'Increasing Diversity in Clinical Research', the work of the NMA's Project IMPACT. The project is an initiative that aims to increase the awareness, knowledge and participation of African–American physicians and patients in all aspects of biomedical research and clinical trials.

One expert from the team, Kwame Osei, from Ohio State University College of Medicine (OH, USA) states that minorities only account for 10% of participants in multicenter clinical trials. He added that, despite being told that participation would increase as more trials focused on areas of interest for minority groups, numbers have seen no improvement since the 1980s.

James H Powell, President at Strategic Medical Associates (OH, USA) and principal investigator for Project IMPACT, stated that only part of the issue of participant shortage can be attributed to mistrust of the medical system, despite widely held belief in the medical community. Speaking to *Clinical Investigation*, he highlighted the importance of diversity in research, "the lack of minority involvement in clinical trials contributes to circumstances that lead to health disparities. The medical care of minority patients is not fully informed by clinical trial data that fail to include them."

The concern over minority representation among clinical investigators is shared by the NIH. The NIH Taskforce for the Inclusion of Women and Minorities in Clinical Research are soon to release a report reiterating and elaborating on the institutes commitment to increasing diversity among participants and investigators in clinical trials. The goal of the NIH will be to ensure women and minorities are included in all trials, to ensure valid analysis of potential differences in safety or efficacy between and within different populations.

> "The medical care of minority patients is not fully informed by clinical trial data that fail to include them"

Looking to the future, Powell and Michael Lenoir, co-principal investigator for Project IMPACT, tell *Clinical Investigation* that the project "will increase our efforts to raise awareness and educate minority patients/consumers about clinical trials, the need to be involved and their protections in the process."

Sources: NIH, NMA renew push for minorities in clinical trials: www.medscape.com/viewarticle/746988; Project I.M.P.A.C.T: About us http://impact.nmanet.org/about-i-m-p-a-c-t

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