Clin. Invest. (2012) 2(7), 667–669

CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in clinical investigation

Drug to treat form of Gaucher disease gains US FDA approval

Elelyso™ (taliglucerase alfa) has been approved by the US FDA for long-term enzyme-replacement therapy for a form of Gaucher disease, a rare genetic disorder.

Elelyso is administered as an injection to patients with a confirmed diagnosis of Type 1 Gaucher disease, in order to replace the missing enzyme that typifies the disorder. The injection should be administered every two weeks by a healthcare professional.

It is estimated that there are approximately 6000 sufferers of Type 1 Gaucher disease in the USA. The disease occurs in people who produce a reduced amount of the enzyme glucocerebrosidase. This deficiency causes lipids to accumulate in organs including the spleen, kidneys and liver. Symptoms of the disease include low platelet counts, anemia, liver or spleen damage and bone problems.

> "It is estimated that there are approximately 6000 sufferers of Type 1 Gaucher disease in the USA."

Julie Beitz, Director of the Office of Drug Evaluation III (the US FDA's Center for Drug Evaluation and Research, MD, USA) stated that "today's approval provides for a new enzyme replacement therapy for the select number of patients with Type 1 Gaucher disease." She added that "it also demonstrates the FDA's commitment to developing treatments for rare diseases."

A total of 56 patients with Type 1 Gaucher disease, due to the small number of sufferers, were enrolled in two clinical trials to evaluate the efficacy of Elelyso.

In a multicenter, double-blinded, parallel-dose trial, 31 adult patients who had not previously received enzyme-replacement therapy were selected at random to receive the drug at a dose of 30 or 60 units/kg. This trial evaluated the efficacy of Elelyso for use as an initial therapy.

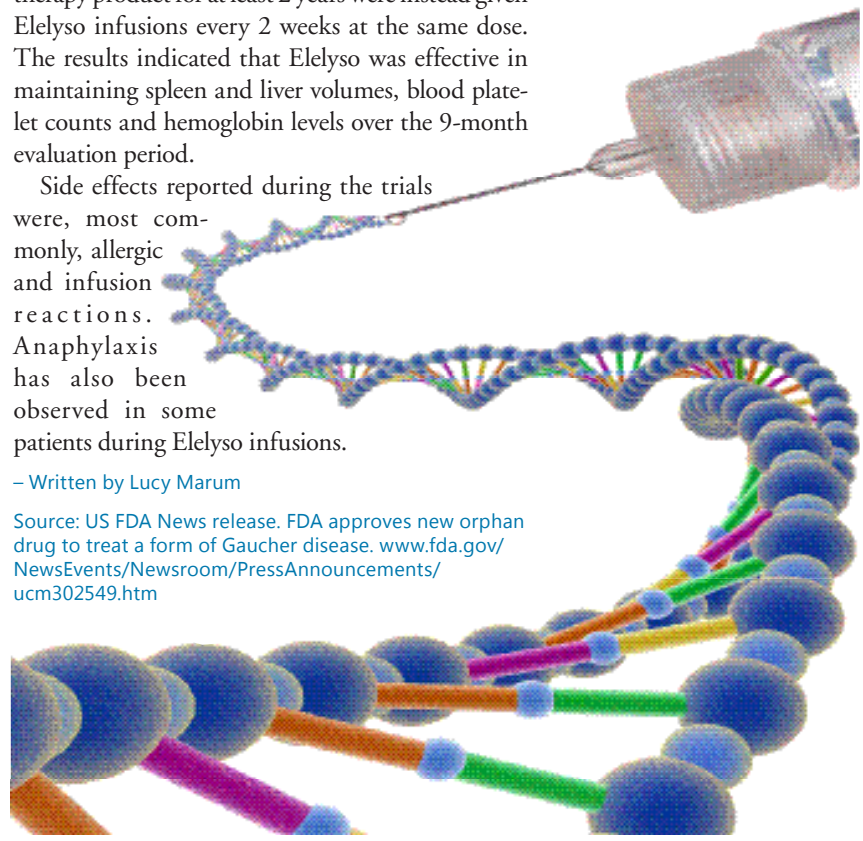
The study results showed that Eleyso satisfied the study's primary end point – a reduction in spleen volume – at both doses. After 9 months of treatment, spleen volume was reduced from baseline by an average of 29% in patients receiving a dose of 30 units/kg and by an average of 40% in those receiving 60 units/kg. Liver volume, blood platelet counts and haemoglobin levels also improved.

In the second study, a multicenter, open-label, single-arm trial, the efficacy of Elelyso was assessed in 25 patients with Type 1 Gaucher disease whose treatment was switched from imiglucerase. Patients who had been receiving the enzyme replacement therapy product for at least 2 years were instead given Elelyso infusions every 2 weeks at the same dose. The results indicated that Elelyso was effective in maintaining spleen and liver volumes, blood platelet counts and hemoglobin levels over the 9-month evaluation period.

Side effects reported during the trials were, most commonly, allergic and infusion reactions. Anaphylaxis has also been observed in some patients during Elelyso infusions.

– Written by Lucy Marum

Source: US FDA News release. FDA approves new orphan drug to treat a form of Gaucher disease. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm302549.htm



ISSN 2041-6792 10.4155/CLI.12.71

Phase I trial results reported for external trigeminal nerve stimulation treatment of post-traumatic stress disorder and major depressive disorder

Results from the first Phase I open-label clinical trial studying the effects of external trigeminal nerve stimulation (eTNS™) as a supplement to pharmacotherapy in patients with post-traumatic stress disorder (PTSD) and major depressive disorder (MDD).

The findings from the first six-subject cohort were presented at the 52nd annual New Clinical Drug Evaluation Unit Conference (AZ, USA) by Ian Cook, of the University of California (UCLA; LA, USA) and a Senior Medical Advisor to NeuroSigma, Inc.

The study follows similarly designed eTNS trials at UCLA, where promising results were generated for the treatment of both epilepsy and major depression. In the present trial, subjects had a mean age of 54, a median of 28 years since traumatic exposure, and suffered from both PTSD and MDD. Participants' current episodes were required to be at least 4 months in duration, with non-response to one or more antidepressant drug.

Subjects placed stimulating eTNS electrodes on their foreheads for approximately 8 hours while sleeping each night for the 8-week period. The severity of symptoms of PTSD and depression was measured using standard rating scales every 2 weeks. Mean decreases in PTSD measures of 36% and depression measures of >50% were reported.

Ian Cook, presenting the study results, said: "These findings are very encouraging. The combination of depression and an anxiety disorder, like PTSD, is usually difficult to treat effectively." He added that, "the participants in the study told us that eTNS was easy to use at home and led, in some instances, to the best mental health they had experienced in years."

"We expect these results, along with results from the remaining subjects in this Phase I trial, to form the basis for an upcoming Phase II clinical trial that will examine efficacy, tolerability and safety in a larger sample with a double-blind, controlled trial design."

Lodwrick Cook, Chairman of NeuroSigma (CA, USA) said, "PTSD is a serious global disorder drastically in need of promising new therapies. As Americans, we have an obligation to do our utmost to help the thousands of fellow citizens who are stricken by PTSD as a result of both military- and non-military-related traumatic events. We are very pleased by the preliminary results and applaud the efforts of the clinical team at UCLA."

– Written by Lucy Marum

Source: Neurosigma press release. Interim results reported for Phase I open-label clinical trial for the treatment of PTSD and MDD using external trigeminal nerve stimulation (eTNS™) – The USB Port to the Brain. www.neurosigma.com/press%20releases.html

US FDA-approved drug boosts cancer vaccine's efficacy

Researchers have demonstrated that the US FDA-approved drug daclizumab improves the survival of breast cancer patients taking a cancer vaccine by 30% in a proof-of-concept study.

While cancer vaccines can be successful over a short period, eventually the immune system stops responding and the tumor begins to grow once more. Regulatory T cells (Tregs) are integral to this reduced response, as they regulate the immune system to reduce its response once infection has been cleared. Tumors exploit Treg cells and the cells even surround the tumor, preventing tumor-fighting cells from reaching the cancerous cells within.

Daclizumab is a therapeutic, humanized monoclonal antibody currently approved to prevent rejection in kidney transplantation. The drug targets the CD25 receptor on the surface of T cells. Tregs require IL-2 for most of their functions and it is with the CD25 receptor that IL-2 binds; therefore depleting Tregs of IL-2 in the presence of daclizumab.

A team of researchers from the Perelman School of Medicine and the Abramson Family Cancer Research Institute at the University of Pennsylvania (PA, USA), hypothesized that daclizumab would be effective in depleting Tregs and thus enabling restoration of the immune system when needed.

During the proof-of-concept study, published in *Science Translational Medicine*, ten patients with metastatic breast cancer were administered daclizumab prior to receiving an experimental breast cancer vaccine developed at the University of Pennsylvania. By depleting the Tregs of IL-2, the authors found the cells converted to normal T cells, thus no longer surrounding the tumor and increasing immune response.

Robert Vonderheide, a senior author on the study, discussed the study's promising results, "Daclizumab worked incredibly well, there were no detectible side effects and the T-cell conversion in the patients on daclizumab lasted 2 months. Their tumors didn't shrink, but in six out of the ten patients the tumors did stop growing, and the daclizumab patients had an increased survival of approximately 7 months compared with patients on the cancer vaccine alone."

The authors feel this proof-of-concept study has a wide-range scope of therapeutic implications in the cancer field. It is widely known that Tregs can block the immune system response to many types of cancer and thus the application of antibodies, such as daclizumab, may also be successful in increasing immune response against other cancer types.

– Written by Caroline Purslow

Sources: University of Pennsylvania press release. www.uphs.upenn.edu/news/News_Releases/2012/05/fda/
Rech AJ, Mick R, Martin S *et al.* CD25 blockade depletes and selectively reprograms regulatory T cells in concert with immunotherapy in cancer patients. *Sci. Transl. Med.* 16(4), 134 (2012).

Research suggests presentation bias in industry-funded psychiatric clinical trials

A study recently published in the *Journal of Clinical Psychopharmacology* indicates that industry-funded research presentations, at psychiatry's largest annual conference, report overwhelmingly positive results.

The study, carried out by two psychiatrists from the University of Michigan (MI, USA) and Yale University (CT, USA), analyzes presentations given at the 2009 and 2010 American Psychiatric Association's annual meetings.

There were 278 studies across both meetings that compared two or more therapeutics for the treatment of a variety of psychiatric illnesses. The authors discovered that 195 of these studies have been supported by industry with the remainder funded by other means. This information was then hidden to enable the authors to analyze the studies without being aware of the funding source.

When evaluating the studies, the researchers discovered that 97.4% of the industry-sponsored studies relayed positive data on the medication being tested. A meager 2.6% reported mixed results and no industry-sponsored trials were presented at the conference that had negative results. In contrast, where industry was not the source of the funding, 68.7% of the presentation data were positive, 24.1% mixed and 7.5% contained negative results.

Srijan Sen, lead author and assistant professor of psychiatry at the University of Michigan Medical School, commented on the bias reported in his study, "presentation bias echoes the publication bias that has been seen in research published in major journals." Publication bias arises when published data contain an overly large proportion of positive results not representative of study outcomes as a whole, thus mirroring the bias seen at the American Psychiatric Association meetings.

There have been attempts to reduce publication bias by both research journals and funding agencies. Both parties now require pharmaceutical companies to register the clinical trials they are conducting and to include the registration number when publishing the data, thus giving members of the scientific community the information required to trace which trials are being published and which remain unpublished; potentially owing to negative results.

– Written by Caroline Purslow

Source: Sen S, Prabhu M. Reporting bias in industry-supported medication trials presented at the American Psychiatric Association meeting. *J. Clin. Psychopharmacol.* 32(3), 435 (2012).

The mechanism of action of tafamidis in treating amyloid disease is disclosed

Tafamidis was recently approved in Europe and is currently under review by the US FDA for the treatment of amyloid disease. In recent Phase II/III clinical trial, the drug has been shown to delay the progression of nerve destruction in polyneuropathy patients. Tafamidis has also demonstrated efficacy in the treatment of transthyretin (TTR) amyloid fibrils, a classic symptom of Alzheimers disease.

A recently published paper in *Proceedings of the National Academy of Sciences* by Christine E Bulawaa (Pfizer, MA, USA) and colleagues have described the molecular and structural role that tafamidis plays in the treatment of TTR aggregation and, along with recent clinicl trials, show for the first time that amyloid disease can be treated by reducing amyloid formation. The TTR protein can aggregate in older people, leading to cardiomyopathy and forms of polyneuropathy, and can be fatal if left untreated.

Research by the group looking for TTR amyloidogenesis inhibitors has been progressing for many years and led to the discovery of benzoxazoes and the formation of tafamidis. Tafamidis was designed to bind to the natural functional TTR structure and prevent it from deviating from its natural functional form into the amyloid state.

It is known that TTR naturally comprises a tetramer of four copies of the protein. When these tetramers separate, the proteins undergo shape changes and misassemble into dysfunctional amyloid aggregates. TTR amyloidoses are caused by mutations in the TTR protein, which cause the tetramers to weaken, this reduces the tetramers ability to stick together and causes early onset TTR amyloid formation.

The study detailed the mechanism by which tafamidis stops this disruption of the tetramers. As TTR is the secondary carrier of throxine in the blood, the TTR tetramer has two unoccupied thyroxie binding sites that can be found on the longest and weakest seam of the tetramer. Tafamidis is able to bind to this binding site and keep the tetramer together.

Tafamidis was able to kinetically stabilize the tetramer in both mutated and wild-type TTR proteins by increasing the energy barrier for tetramer dissociation and stabilizing the protein, thus decreasing the rate of amyloid formation. Although there are hundreds of mutations in the TTR protein, the vast majority are able to find tafamidis.

– Written by Claire Attwood

Source: Bulawaa CE, Connelly S, DeVitc M *et al.* Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1121005109 (Epub ahead of print) (2012).

The editorial team welcomes suggestions for timely, relevant items for inclusion in the news. If you have newsworthy information, please contact:

Cara Sutton,
Managing Commissioning Editor, *Clinical Investigation*
Tel.: +44 (0)20 8371 6090;
E-mail: c.sutton@future-science.com