Novel animal study suggests potential treatment for tumor-associated epilepsy

Gliomas remain one of the most common and difficult-to-treat brain tumors, despite the advancements in the understanding of their origin and biology. Originating from glial cells, these tumors often exhibit the ability to cause seizures in individuals, presenting a major debilitating symptom to the sufferers. However, novel research by investigators from the University of Alabama at Birmingham (AL, USA), published in *Nature Medicine*, has furthered our understanding of this process by implanting gliomas of human origin into mice in order to study the effects in greater detail. The researchers discovered that these newly implanted gliomas released glutamate, an excitatory neurotransmitter, causing excessive and uncontrolled depolarization in the brain resulting in the presence of seizures in these animal models.

Observational statistics suggest that 80% of individuals affected by gliomas will experience at least one seizure event in their lifetime, and of these patients a third will develop tumor-associated epilepsy as diagnosed by recurring seizures due to the presence of the tumor. "Understanding why the seizures occur and how to counteract them could help us substantially improve the quality of life for people with glioma," explained Jane Fountain, Program Director at the NIH's National Institute of Neurological Disorders and Stroke (Bethesda, MD, USA).

Speaking about the misunderstandings of the origin of these seizures, Harald Sontheimer, senior author of the paper, conveyed the following to *Therapy*: "The finding that gliomas are deliberately leasing a neurotransmitter that causes seizures provides us with a drugable target to treat patients where before we had no handle on the source of the problem. The fact that an already US FDA approved drug can be used for this purpose is an added advantage as it allows immediate clinical use."

After the initial transplantation of human gliomas into the brains of the mice models, the researchers documented that a third of the animals began to display behavioral and physical signs that were consistent with a definition of a seizure. These tumors demonstrated an elevated level of glutamate, in addition to prolonged and excessive activity (in comparison to normal brain tissue) when stimulated by an electrical source. Advancing these findings, the researchers investigated the potential use of sulfasalazine in reducing these pathological effects. This drug acts by inhibiting the system Xc (-) transporter, which is responsible for a system that results in the exporting of glutamate. The results showed a reduction in both the glutamate levels in the gliomas and the frequency of seizures in the mouse models.

Although the research shows a benefit in these models, the authors are wary about translating the results to human patients. Previous work with sulfasalazine proved ineffective and potentially dangerous, resulting in the early termination of a trial. Nevertheless the authors are hopeful that the creation of a novel compound based on the existing drug could be of some benefit and may even act to reduce the growth of the tumor.

Furthermore, Sontheimer explains that an alternative approach to the treatment may be more positive than the previous trial, "The previous trial enrolled a very small number of patients who were in a dire state of health, which few physicians would enroll in a clinical study. It is unclear whether the administration of sulfasalazine worsened their disease. It certainly did not have much of a chance to improve it. An appropriately powered study, enrolling a much larger number of patents that are still in reasonably good health with a Karnofsky scale of at least 70 should be pursued with specific emphasize on evaluating benefits on seizure status."

Source: Buckingham SC, Campbell SL, Haas BR et al. *Glutamate release by primary brain tumors induces epileptic activity.* Nat. Med. *17(10), 1269–1274 (2011).*

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Pivotal Phase III study demonstrates substantial symptom relief in patients with systemic juvenile idiopathic arthritis treated with canakinumab

Novartis(Basel, Switzerland) have announced positive results from the first pivotal Phase III trial of canakinumab for the treatment of systemic juvenile idiopathic arthritis (SJIA) at the 2011 European Pediatric Rheumatology Congress in Bruges, Belgium. The results demonstrated that all primary and secondary end points have been met.

Systemic juvenile idiopathic arthritis is the most severe form of juvenile arthritis affecting less that one child per 100,000 worldwide. Unlike more common forms of arthritis, SJIA is a systemic condition with inflammation affecting the whole body as well as the majority of joints. Patients present with recurrent arthritis flares that are potentially lifelong.

The study, involving 84 patients between the ages of 2 and 19 years with active SJIA, was a Phase III, 4-week, randomized, double-blind, placebo-controlled study. Patients were given a single subcutaneous dose of canakinumab (4 mg/kg, up to 300 mg) or placebo. A total of 83.7% of patients experienced at least a 30% improvement in symptoms achieving the primary end point. The primary end point was the proportion of patients demonstrating a 30% improvement from baseline at day 15 in at least three of the six variables included in the adapted American College of Rheumatology (ACR) Pediatric 30 criteria. The criteria are regularly used to assess the success of treatments in SJIA. The six variables were as follows; functional ability, number of joints with active arthritis, number of joints with limited motion, physician's assessment of disease activity, guardian or patient assessment of overall condition, and laboratory-measured levels of C-reactive protein.

Canakinumab is a human monoclonal antibody targeted at IL-1β developed by Novartis. Excessive production of IL-1β contributes to many inflammatory diseases, including SJIA. Canakinumab neutralizes IL-1β for a sustained period of time, thus inhibiting inflammation. The compound was approved for the treatment of cryopyrin-associated periodic syndromes by the US FDA in June 2009. Recent trials in gout patients showed promise; however, the drug was rejected by the US FDA for this indication in June 2011.

David Epstein (Head of Pharmaceuticals Division, Novartis) commentated on canakinumab and its use in SJIA and other inflammatory conditions, "These results are a positive development for patients suffering from this very severe autoinflammatory condition. We are committed to investigate ACZ885 in a range of inflammatory diseases where IL-1β plays a key role and high unmet medical needs exist."

A second Phase III study is looking to determine whether canakinumab can extend the period between arthritic flares and either reduce or eliminate corticosteroid use. Results from the second Phase III study will be presented later this year with Norvartis looking to apply to worldwide regulatory bodies for regulatory approval of canakinumab for the treatment of SJIA in 2012.

Source: Press release: www.novartis.com/newsroom/media-releases/en/2011/1547308.shtml

Glucagon-like peptide-1-based therapy for diabetes may be linked to an increased risk of pancreatic cancer

Two specific glucagon-like peptide-1-based therapies, sitagliptin and exenatide, may be associated with pancreatitis, pancreatic and thyroid cancer, a study recently published in the journal *Gastroenterology* indicates.

Researchers from the Larry L. Hillblom Islet Research Center (David Geffen School of Medicine, Los Angeles, CA, USA) investigated the use of sitagliptin and exenatide in diabetic patients by examining the US FDA's database for adverse events reported between 2004 and 2009. The adverse events they measured included increased rates of reported pancreatitis, pancreatic and thyroid cancer, and all cancers associated with sitagliptin or exenatide, compared with other therapies. The results were compared with adverse events from four other medications, which were used as controls.

The researchers found a sixfold increase in the odds ratio for reported cases of pancreatitis with these drugs, compared with the control therapies. Pancreatic cancer was more commonly reported among patients who took the two drugs than those who

were treated with the other therapies. All other cancers occurred similarly among patients who took sitagliptin compared with other therapies. The findings are consistent with case reports and animal studies that had previously indicated an increased risk for pancreatitis with glucagon-like peptide-1-based therapy.

Peter Butler of the Larry L. Hillbloom Islet Research Center told *Therapy*, "Type 2 diabetes is a major health problem worldwide with increasing numbers of people developing the condition. Therefore the safety of the drugs prescribed for diabetes is obviously very important."

Although Butler states that, "The approach we took to examining the US FDA adverse event reporting system was carefully undertaken in order to minimize false-positive findings." In the study the authors caution that, "For now this analysis of the US FDA database does not establish that pancreatitis, pancreatic and thyroid cancer are caused by GLP-1-based therapy, it simply raises the level of concern that they may be, and that the appropriate prospective studies are required to rule them out."

Since the first recommendation for treating patients with Type 2 diabetes is lifestyle modification, and if this is not sufficient metformin use is recommended. Butler makes it clear that, "The GLP-1 drugs under discussion here are only to be used by these guidelines if additional therapy is still required."

Butler explains that "as the GLP-1 class of drugs are the most recently available we know the least about their safety at this stage and so as with all new classes of drugs, caution in monitoring potential unexpected side effects is required. Our analysis does not warrant changing practice guidelines at present but rather increasing the level of scrutiny of these drugs to establish one way or the other if the potential problems that have been raised are real."

Source: Elashoff M, Matveyernko AV, Gier B, Elashoff R, Butler P. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterology *141(1), 150–156 (2011).*

Study demonstrates upfront combination chemotherapy is not more effective than sequential use of chemotherapy in patients with advanced, nonresectable colorectal cancer

A Phase III open-label, randomized study recently published in *The Lancet Oncology* has determined that treatment of patients with advanced, nonresectable colorectal cancer with upfront combination chemotherapy is not more effective and is more toxic than sequential treatment with the same combination of cytotoxic drugs.

Prior to this study, the optimum use of cytotoxic drugs for advanced colorectal cancer had not been defined. The aim of the study was to determine whether sequential or upfront combination therapy is optimum. Patients diagnosed with advanced, measurable, nonresectable colorectal cancer were randomly assigned (1:1 ratio) resulting in 205 patients per group. Patients received either first-line treatment with bolus (400 mg/m^2) and infusional (2400 mg/m^2) fluorouracil plus leucovorin (400 mg/m^2; simplified LV5FU2 regimen), second-line LV5FU2 plus oxaliplatin (100 mg/m^2; FOLFOX6), and third-line LV5FU2 plus irinotecan (180 mg/m^2; FOLFIRI) or first-line FOLFOX6 and second-line FOLFIRI. The primary end point of the study was progression-free survival following two lines of treatment.

Following the two lines of treatment median progression-free survival was measured at 10.5 months in the sequential group and 10.3 months in the combination group. Six deaths resulted from toxic effects of treatment, all of which were in the combination group. During first-line chemotherapy significantly fewer hematological and nonhematological adverse events were recorded in the sequential group.

Conclusions from the study demonstrate that upfront combination chemotherapy for the treatment of advanced colorectal cancer is not more effective than sequential chemotherapy and increases the risk of toxicity and adverse effects.

Source: Ducreux M, Malka D, Mendiboure J et al. *Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial.* Lancet Oncol. 12(11), 1032–1044 (2011).

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Future Medicine Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK; Tel.: +44 (0)20 8371 6090;
Fax: +44 (0)20 8343 2313; l.mcguinness@futuremedicine.com