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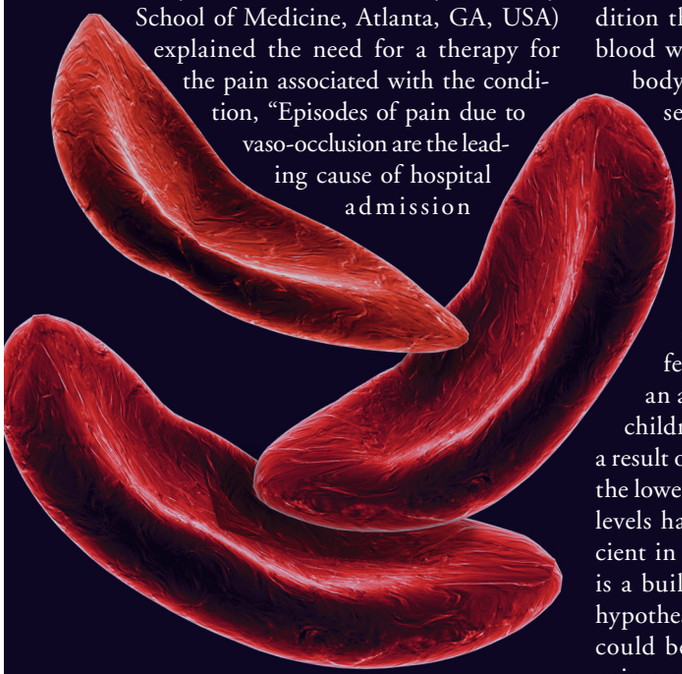
CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Arginine therapy: a potential treatment for sickle cell pain

The first randomized, placebo-controlled study was innitiated in order to reveal the benefits of using arginine therapy in children diagnosed with sickle cell disease who have been hospitalized due to severe pain. The results seem to suggest that arginine therapy could be a potential inexpensive and safe therapy for the episodes of acute pain that are suffered by patients with sickle cell disease. The first author on the study, Claudia Morris (Emory University School of Medicine, Atlanta, GA, USA) explained the need for a therapy for the pain associated with the condition, "Episodes of pain due to vaso-occlusion are the leading cause of hospital admission and emergency room visits and are associated with increased mortality, yet there is no effective therapy targeting the underlying cause." She went on to say, "Treatment consists only of symptom relief with pain medicines and hydration. There is an urgent need for new therapies for acute sickle cell pain, and a greater than 50% reduction in use of opioid pain medication was a remarkable finding."



Sickle cell disease is an inherited condition that can lead to the blockage of blood within the smaller vessels of the body and in turn can lead to both severe pain and organ damage. Arginine can be obtained as part of a child's diet or can be administered as a nutritional supplement. The authors of the current study had previously demonstrated that during a pain episode, children suffering from sickle cell disease had an acute arginine deficiency. Those children who had to be hospitalized as a result of the pain were shown to possess the lowest arginine levels. As nitric oxide levels have also been shown to be deficient in sickle cell disease and arginine is a building block of nitric oxide, the hypothesis by researchers is that arginine could be a potential treatment for the pain associated with the disease.

> "...during a pain episode, children suffering from sickle cell disease had an acute arginine deficiency."

Prior research by the researchers also demonstrated that one single dose of arginine administered to patients diagnosed with sickle cell disease as well as the acute pain episodes associated, showed an apparent significant dose-dependant increase in levels of plasma nitric oxide concentration. Using this previous study-related knowledge, the current study enrolled 38 children diagnosed with sickle cell disease who had been hospitalized for a total of 56 episodes of pain related to the condition. With the aide of arginine the results demonstrated that there was a 54% decrease in the use of opioid-based pain medications, as well as lower pain scores when the children were discharged from the hospital in comparison with those who had received placebo.

The study also highlighted the apparent lack of safety concerns when using arginine. Use of arginine did not significantly reduce the length of stay in the hospital but there was a decrease of approximately 17 h in the arginine-treated group. However, researchers believe that if the drug was delivered earlier, this may impact the length of stay more significantly. The researchers also note that a larger multicenter trial is required to both confirm the observations seen as well as test what effects are achieved by delivering the arginine therapy earlier.

– Written by Priti Nagda

Sources: Morris CR, Kuypers FA, Lavrisha L *et al.* A randomized, placebo-controlled trial of arginine therapy for the treatment of children with sickle cell disease hospitalized with vaso-occlusive pain episodes. *Haematologica* 98(9), 1375–1382; Emory Health Sciences, Emory new center: http://news.emory.edu/stories/2013/09/arginine_therapy_for_sickle_cell_pain/

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Primary safety end point achieved for saxagliptin

AstraZeneca and Bristol-Myers Squibb recently announced results from the SAVOR trial that showed that patients with Type 2 diabetes who are at high risk of cardiovascular events had no increased risk of cardiovascular death, non-fatal myocardial infarction (MI) or non-fatal ischemic stroke when saxagliptin (Onglyza®) was added to their current treatment regimen.

> "The results from SAVOR add important evidence to the overall body of data to further define the clinical profile of saxagliptin..."

There have been serious concerns raised in the past about the link between Type 2 diabetic treatments and cardiovascular events, such as stroke and heart attack. It is estimated that cardiovascular events could be the cause of death in as many as 80% of individuals with Type 2 diabetes. In this randomized, double-blind, placebo-controlled study, 16,492 patients with Type 2 diabetes and at high risk of cardiovascular events were randomized to received either saxagliptin or placebo (n = 8280 and n = 8212, respectively). It was observed that cardiovascular death, non-fatal MI or non-fatal ischemic stroke (i.e., the primary composite end point) occurred in 7.3% (n = 613) of individuals in the saxagliptin group compared with 7.2% (n = 609) of individuals in the placebo group (hazard ratio: 1.00; 95% CI: 0.89–1.12; non-inferiority p-value < 0.001; superiority p-value = 0.99). However, saxagliptin did not meet the primary efficacy end point of superiority to placebo for the same composite end point. In addition, it was observed that there were greater reductions in blood sugar levels from baseline in the saxagliptin group when compared with the placebo group. More individuals from the former group also achieved or maintained the goal HbA1c level of <7% compared with the latter group at 2 years (40.0 vs 30.3%; p < 0.001).

Deepak Bhatt, of Brigham and Women's Hospital (MA, USA) and a principal investigator for the study explained the importance of the trial, "Given the correlation between diabetes and cardiovascular complications, there is a need for thorough assessments of the cardiovascular risks among therapies that improve glycemic control. The results from SAVOR add important evidence to the overall body of data to further define the clinical profile of saxagliptin for the treatment of Type 2 diabetes."

Saxagliptin is currently approved in 86 countries worldwide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. However, saxagliptin has not yet been studied in patients with a history of pancreatitis.

– Written by Natasha Leeson

Source: AstraZeneca press release: www.astrazeneca.com/Media/Press-releases/Article/20130902---onglyza-saxagliptin-achieves-primary-safety

New hope for pain relief in osteoarthritis using bisphosphonates

Research carried out at St George's, University of London (London, UK), has given new hope to the possibility that a drug usually taken by osteoporosis sufferers may have the potential to provide pain relief in patients suffering with knee and hip osteoarthritis.

Osteoporosis is a rheumatic disease characterized by fragile bones that is also often very painful. The joint condition results in bony growths, cartilage damage and sore tissue. Nidhi Sofat, senior researcher of the recent study, commented that, "Osteoarthritis is the most common form of arthritis worldwide. It causes damage to bone and cartilage in the joints of affected people. Most treatment is focused around pain relief, as no robust treatments have been discovered that slow down the progression of the disease."

Bisphosphonates are commonly prescribed to patients with osteoporosis, as they have the ability to change the structure of bone. There has been speculation for some time that bisphosphonates could also be used to reduce joint pain and discomfort in patients with osteoarthritis. Researchers at St George's, led by Sofat, looked at past studies in patients being treated with a variety of bisphosphonates for hand, knee, spine or hip osteoarthritis.

Sofat expains, "Our study looked at whether there were any bisphosphonate drugs that have been shown to influence pain and/or disease progression that could be used in osteoarthritis treatment." The researchers found that, out of 3832 patients studied, most bisphosphonate drugs provided limited pain relief.

Despite this disappointing general finding, some specific forms of bisphosphonates did appear to have some effectiveness at managing pain associated with osteoarthritis. Specifically, the use of zoledronate and alendronate for 6 months appears to improve knee and hip osteoarthritis. In addition, alendronate may even be more effective than existing pain-relieving drugs for the relief of pain relating to hip osteoarthritis.

"More research needs to be carried out to determine which patients could benefit most from this type of intervention" Sofat concludes. "Osteoarthritis is a long-term chronic condition, so it's essential that we work to understand whether the use of these medicines in the long term could be tolerated."

– Written by Sophie Breeze

Sources: St George's, University of London news: www.sgul.ac.uk/media/latest-news/bisphosphonates-could-offer-effective-pain-relief-in-osteoarthritis-research-finds; Davis AJ, Smith TO, Hing CB, Sofat N. Are bisphosphonates effective in the treatment of osteoarthritis pain? A meta-analysis and systematic review. *PLoS ONE* 8(9), e72714 (2013)

Marketing authorization received from the European Commission for Tafinlar® (dabrafenib) for treatment of melanoma

Tafinlar® (dabrafenib; GlaxoSmithKline plc, NYSE: GSK) has been granted marketing authorization in the EU as an oral targeted monotherapy treatment for unresectable or metastatic melanoma in *BRAF* V600 mutation-positive adult patients, who constitute approximately 50% of cutaneous melanoma patients. It is also licensed in the USA, Canada and Australia but is not authorized for use in patients with wild-type *BRAF* melanoma.

"Dabrafenib represents an important advance in the treatment of advanced *BRAF*-mutation-positive melanoma..."

BRAF is part of the MAPK pathway. Mutated *BRAF*, the target of dabrafenib, has been shown to result in disruption of cellular regulation, promoting cell production. Subsequently, the drug results in inhibition of oncogenic signaling and inhibition of tumor cell proliferation.

Authorization follows results from several clinical trials, including the Phase III BREAK-3 study that compared dabrafenib with dacarbazine in 250 previously untreated *BRAF* V600 mutation-positive unresectable or metastatic melanoma patients. In the analysis following a data cut-off in June 2012, median progression-free survival for dabrafenib was reported to be 6.9 months, compared with 2.7 months for dacarbazine. Median overall survival was also higher, at 18.2 months compared with 15.6 months for dacarbazine. The safety profile of dabrafenib, based on data from five clinical monotherapy studies and including data from 578 patients, indicates that the most frequently occurring adverse drug reactions were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, skin papilloma, alopecia, rash and vomiting.

Paul Nathan (Mount Vernon Cancer Centre, Middlesex, UK) commented that, "Dabrafenib represents an important advance in the treatment of advanced *BRAF*-mutation-positive melanoma and for the first time gives patients and their clinicians a choice of treatment options."

– Written by Francesca Lake

GlaxoSmithKline press release: GSK receives marketing authorisation from the European Commission for Tafinlar™ (dabrafenib), an oral treatment for unresectable or metastatic melanoma in adult patients with a *BRAF* V600 mutation: www.gsk.com/media/press-releases/2013/gsk-receives-marketing-authorisation-from-the-european-commissio0.html

Pomalidomide in combination with dexamethasone approved for use in refractory multiple myeloma

Multiple myeloma is characterized by uncontrollable replication and accumulation of plasma cells in the bone marrow, which in turn disrupts the production of normal blood cells. Treatments for multiple myeloma include chemotherapy with agents such as bortezomib and lenalidomide. If such treatments are successful it is almost inevitable that most multiple myeloma patients will eventually experience relapse of the disease. Relapsed or refractory multiple myeloma (rrMM) requires further treatment with different therapies, for which there are few effective agents known.

IMNOVID® (Celgene; Uxbridge, UK), also known as pomalidomide, is an oral immunomodulatory drug with a multimodal mechanism of action. When administered as a single agent pomalidomide has demonstrated limited efficacy in rrMM patients. However, synergistic effects have been noted when it is used in combination with dexamethasone. A recent Phase III, multicenter, randomized, open-label study further investigated the efficacy and safety of administering pomalidomide in combination with dexamethasone in patients with rrMM. The results of this trial, termed MM-003, are currently reported in the September issue of *Lancet Oncology*.

"Unfortunately the prognosis for relapsed and refractory multiple myeloma is poor as there are few effective therapeutic options for people living with this disease," commented Steve Schey of Kings College London (London, UK), UK principal investigator of the MM-003 study. "While remission is generally achieved after initial treatment, in the majority of cases the cancer returns and these patients relapse, requiring further treatment. The results of this study have shown that there is a new and effective treatment available for patients who have failed all existing options."

The MM-003 study accrued 455 rrMM patients from Australia, Canada, Europe, Russia and the USA between March 2011 and September 2012. Patients were assigned in a 2:1 ratio to receive either low-dose dexamethasone and pomalidomide or high-dose dexamethasone alone until disease progression or unacceptable toxicity was encountered. All these patients had been previously treated with and were no longer responding to both bortezomib and lenalidomide. Three hundred and two patients were randomized to receive oral pomalidomide plus low-dose dexamethasone, while the remaining 153 received high-dose dexamethasone. The primary end point of the study was progression-free survival.

After median follow up of 10 months, there was significant improvement in median progression-free survival in the pomalidomide + low-dose dexamethasone arm compared with the high-dose dexamethasone arm (4 vs 1.9 months, respectively; $p < 0.0001$). Common adverse events in both of the treatment groups included grade 3–4 hematological symptoms such as neutropenia, anemia and thrombocytopenia.

Following this study, the oral regimen of pomalidomide combined with low-dose dexamethasone could be considered as a new treatment in rrMM patients. Indeed, the combination has been approved for the treatment of adult rrMM patients who have received at least two prior therapies, inclusive of bortezomib and lenalidomide, and have experienced disease progression on the last therapy administered. Pomalidomide has been approved for use in the UK and Ireland by the European Medicines Agency since August 2013.

– Written by Emily Brown

Source: Miguel JS, Weisel K, Moreau P *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomized, open-label, Phase 3 trial. *Lancet Oncology* doi:10.1016/S1470-2045(13)70380-2 (2013) (Epub ahead of print); Celgene Press Release: http://ir.celgene.com/phoenix.zhtml?c=111960&p=irol-newsArticle&ID=1852208&highlight=

Chronic pain susceptibility may be linked to the brain's white matter

Researchers at Northwestern University (Chicago, IL, USA) have discovered that structural differences in the white matter of a person's brain can affect their susceptibility for chronic low back pain.

Chronic pain is an enormous burden on healthcare systems worldwide, and with chronic low back pain accounting for a large percentage of reported pain conditions, further research into possible causes and treatments is highly desirable. Traditionally, the cause of chronic pain was believed to be at the site of injury; however, the team at Northwestern University, led by senior author Vania Apkarian, were interested in looking at the potentially critical role the brain plays in the development and maintenance chronic pain.

In the study, the brains of 46 participants who had low back pain for 3 months, but no pain previously for at least a year, were scanned using a technique called diffusion tensor imaging (DTI). DTI can measure the structure of white matter, including the axons connecting different parts of the brain. Over the course of the study, which lasted for a year, approximately half of the patients recovered, while the other half had pain throughout the study, which was categorized as persistent. Analysis of the DTI scans revealed that there were consistent differences in the structure of the white matter between patients that recovered and those with persistent pain.

> "Prediction is the name of the game for treating chronic pain. [These] results support the notion that certain brain networks are involved with chronic pain."

Apkarian commented, "Our results suggest that the structure of a person's brain may predispose one to chronic pain." In support of this theory, the researchers also noted that the white matter structure of patients with persistent pain resembled DTI scans of patients known to suffer from chronic pain. In addition, the DTI scans of those that recovered from low back pain showed a similar white matter structure to healthy control subjects.

When using this information and studying the initial white matter DTI scans of the study participants, the researchers were able to predict to an accuracy of approximately 80% whether the participants would recover or experience persistent pain.

They were able to do this by further analysis of the DTI brain scans, specifically looking at the white matter structure connecting the nucleus accumbens and the medial prefrontal cortex. These two regions are believed to be involved with pain, and showed the greatest differences between the subjects who recovered and those who had persistent pain.

"We were surprised how robust the results were and amazed at how well the brain scans predicted persistence of low back pain," concludes Apkarian. "Prediction is the name of the game for treating chronic pain. Our results support the notion that certain brain networks are involved with chronic pain. Understanding these networks will help us diagnose chronic pain better and develop more precise treatments."

– Written by Sophie Breeze

Sources: National Institute of Neurological Disorders and Stroke press release: www.ninds.nih.gov/news_and_events/news_articles/pressrelease_brain_chronic_pain_09172013.htm; Mansour AR, Baliki MN, Huang L *et al.* Brain white matter structural properties predict transition to chronic pain. *Pain* 154(10), 2160–2168 (2013).

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New implantable vaccine heads to human clinical trials

An integrated group of engineers, scientists and clinicians have unveiled that they have started a Phase I trial of a novel implantable vaccine to combat melanoma.

Many cancer vaccines available currently require physicians to take immune cells out of the patient's body. These cells are then reprogrammed and returned into the patient. The new effort is the offspring of a novel model of translational research combining research led by David J Mooney (Wyss Institute at Harvard University, MA, USA) and Glenn Dranoff (Dana-Farber Cancer Institute Cancer Vaccine Center, MA, USA).

The novel approach, which was primarily reported in 2009 to eliminate tumors in mice, utilizes a disk-like sponge approximately the size of a fingernail and is composed of US FDA-approved polymers. The sponge is implanted underneath the skin, where it is designed to work 'on-site' to both recruit and reprogram the patient's own cells and instruct them to move through the body, target cancer cells and kill them.

> "The novel approach ... utilizes a disk-like sponge approximately the size of a fingernail and is composed of US FDA-approved polymers."

Although the technology was designed in the first instance to target and potentially treat cutaneous melanoma of the skin, it could have the potential to be applied to many forms of cancer. Mooney explains the importance of the collaborative effort of the individuals involved in the project, "Our vaccine was made possible by combining a wide range of biomedical expertise that thrives in Boston and Cambridge," adding that "It reflects the bioinspired engineering savvy and technology development focus of engineers and scientists at the Wyss Institute and Harvard SEAS, as well as the immunological and clinical expertise of the researchers and clinicians at Dana-Farber and Harvard Medical School."

The future of the novel technology appears positive, with recruitment of enrollments into the clinical trial already underway, the goal of which is to assess the safety of the vaccine within a human setting. The trial is expected to finish in 2015.

Dranoff explains the excitement surrounding the development, "It is rare to get a new technology tested in the laboratory and moved into human clinical trials so quickly," adding, "We're beyond thrilled with the momentum, and excited about its potential."

– Written by Priti Nagda

Sources: Wyss Institute at Harvard newsroom press release: http://wyss.harvard.edu/viewpressrelease/122

Study shows that alogliptin does not increase the rates of major adverse cardiovascular events in Type 2 diabetes

Takeda Pharmaceutical Company, ltd., (Osaka, Japan) recently announced that the primary end point of the EXAMINE trial has been reached. The primary end point of noninferiority of cardiovascular risk, when alogliptin (a dipeptidyl peptidase-4 inhibitor) was compared with placebo, was met with no increase in cardiovascular risk in Type 2 diabetes patients who are at high-risk for cardiovascular events. It is hoped that these data will be of benefit for clinicians treating individuals with Type 2 diabetes and high cardiovascular risk.

> "Given the EXAMINE study design and high-risk patient population evaluated, these results provide key insights to clinicians treating diabetes patients with coronary disease."

Previous studies have demonstrated the adverse link between glycemic control and macrovascular events in individuals with Type 2 diabetes, causing specific requirements regarding cardiovascular safety assessment before and after the approval of new antidiabetic therapies to be issued by the US FDA in December 2008. In this multicenter, randomized, double-blind trial, 5380 individuals with Type 2 diabetes and recent acute coronary syndrome, from 898 centers in 49 countries, were randomly assigned to receive either alogliptin or placebo and were followed for up to 40 months. A primary end point event occurred in 11.3% (n = 305) of individuals in the alogliptin group and in 11.8% (n = 316) of individuals in the placebo group (hazard ratio: 0.96; upper boundary of the one-sided repeated CI: 1.16; $p < 0.001$ for noninferiority). It was also observed that glycated hemoglobin levels were lower in the alogliptin group when compared with the placebo group (mean difference: -0.36%; $p < 0.001$).

William White (University of Connecticut School of Medicine, Farmington, CT, USA) principal investigator of the EXAMINE trial explained, "There is a need for safer glucose-lowering therapies in patients with diabetes who are at an elevated risk for cardiovascular disease. Given the EXAMINE study design and high-risk patient population evaluated, these results provide key insights to clinicians treating diabetes patients with coronary disease."

Alogliptin is not currently licensed or available in Europe.

– Written by Natasha Leeson

Sources: White WB, Cannon CP, Heller SR *et al.*; The EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with Type 2 diabetes. *N. Engl. J. Med.* doi:10.1056/NEJMoa1305889 (2013) (Epub ahead of print); Takeda press release: www.takeda.com/news/2013/20130902_5975.html