

Survival times were doubled in brain tumor patients receiving a vaccine that primes the immune system to attack cancer cells, compared with patients receiving standard care

Promising brain tumor vaccine could prolong patients' lives

Promising results of a vaccine against glioblastoma multiforme (GBM) tumors in prolonging patients' lives have been presented at the American Society of Clinical Oncology Annual Meeting in Chicago (IL, USA) in June 2008.

Vaccination with CDX-110, together with standard of care temozolomide, in patients with glioblastoma multiforme increased time to progression and overall survival compared with a matched historical control group in these Phase II studies," stated lead investigator John Sampson, of the Duke University Medical Center, NC, USA.

The vaccine induces immune responses against epithelial growth factor receptor variant III (EGFRvIII), a protein present in approximately half of GBM tumors, but absent in normal tissues. This leads to the killing of these tumor cells and prevention of their regrowth. The study was carried out at Duke University's Preston Robert Tisch Brain Tumor Center (NC, USA) and funded by the US NIH and Celldex Therapeutics (NJ, USA), a subsidiary of Avant Immunotherapeutics.

The study involved 23 GBM patients receiving standard therapy. The patients received the vaccine monthly in conjunction with temozolomide, a chemotherapeutic agent. Temozolomide appeared to enhance the immune response to EGFRvIII.

"This reflected something of a surprising conclusion, because it stands to reason that chemotherapy, which suppresses the body's immune system, would make the vaccine less effective," said the lead investigator John Sampson of Duke University. "What we found was that the opposite is true. While the body is recovering from chemotherapy, immune response is actually stronger, as the immune system overcompensates in order to right itself. It's the perfect time to introduce a vaccine."

Vaccinated patients survived for 33.1 months from diagnosis, whereas

GMB patients receiving only standard therapy only lived for 14.3 months on average. Vaccinated patients also showed longer survival time without tumor regrowth and progression (16.6 vs 6.4 months in nonvaccinated patients).

"We're more than doubling survival time in this (vaccinated) group, and we have some patients who are 4, 5 or 6 years out from diagnosis, which is virtually unheard of in these people," said Sampson. "This vaccine represents a very promising therapy for a cancer that comes out of the blue and robs people of something most of us take for granted – time. The possibility of doubling expected survival – with few if any side effects – would represent a big step and a lot of hope for this group of patients."

Only minor side effects (swelling at the infection site) were observed. The vaccine will enter a Phase III clinical trial at more than 20 sites across the USA.

Dr James Perry, head of neurology at Sunnybrook Health Sciences in Toronto, Canada, sounded a note of caution, however, pointing out that the patients selected for this trial were younger than average and had specific tumor features found in only one in 10 glioblastoma multiforme patients. "So it isn't the answer to the disease, but our hope in the field is that it is the answer to ... this 10% of the patients," he explained. If the planned clinical trials are successful, "we can start to find out what are the unique attributes of those other nine out of ten patients. But this is the first one, it's the one out of the gate, and hopefully if it proves to work, it would be a breakthrough therapy."

Sources: Sampson JH, Archer GE, Bigner DD *et al.*: Effect of EGFRvIII-targeted vaccine (CDX-110) on immune response and TTP when given with simultaneous standard and continuous temozolomide in patients with GBM. Presented at: *American Society of Clinical Oncology Annual Meeting*, Chicago, IL, USA 30 May–3 June (2008).

Immune-modulating drugs may carry risks of serious infections

Drugs commonly prescribed to treat immunological conditions, such as rheumatoid arthritis and inflammatory bowel disease, may carry risks of serious infections other than the known risk of TB, according to the results of a new survey. These findings suggest that physicians should be vigilant not just for TB, but for a range of different infections in patients taking these drugs.

This study specifically focused on drugs that curb the immune response through inhibiting the action of the proinflammatory cytokine TNF- α . It has already been established that these anti-TNF- α agents are associated with an increased risk of TB infection and, to date, much attention has been focused specifically on TB cases associated with the drugs.

A recently published article presented the results of a nationwide survey and identified a range of serious infections in patients receiving anti-TNF compounds. In this survey, 426 infectious disease physicians, members of the Emerging Infections Network of the Infectious Diseases Society of America, reported on the infections they had observed within the previous 6 months. In this context, cases of *Staphylococcus aureus*, histoplasmosis and nontuberculosis mycobacterial infections were all reported more commonly than was TB.

The results of this study suggest that patients using anti-TNF therapy might be at an increased risk of a number of serious infections, and that physicians should be cautious of infections other than TB in individuals who are either currently using or initiating anti-TNF therapy.

Source: Winthrop KL, Yamashita S, Beekmann SE, Polgreen PM; Infectious Diseases Society of America Emerging Infections Network: Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. *Clin. Infect. Dis.* 46(11), 1738–1740 (2008).

In brief...

Neonatal chimerization with human glial progenitor cells can both remyelinate and rescue the otherwise lethally hypomyelinated shiverer mouse.

Windrem MS, Schanz SJ, Guo M *et al.*: *Cell Stem Cell*. 2(6), 553–565 (2008).

In a study thought to be the first of its kind, researchers demonstrated complete rescue in a mouse model of congenital hypomyelinating disorder using human stem cells. Investigators used 'shiverer' mice, that lack normal myelination of nerve fibers and die within 20 weeks of birth. The cell therapy promoted re-myelination of nerve fibers, and in some of the mice led to dramatic functional improvements and even complete cure, extending their lifespan considerably. The researchers hope that these findings might lead to a stem cell therapy for children with rare congenital hypomyelination disorders, who are deficient in myelin, just like the mice used in these studies, causing severe disability and limiting their life expectancy.

Cellular and behavioral interactions of gabapentin with alcohol dependence

Roberto M, Gilpin NW, O'Dell LE *et al.*: *J. Neurosci.* 28(22), 5762–5771 (2008).

This study suggests that gabapentin, traditionally used to control seizures, could be used to treat alcohol-dependence. Previous studies have shown that gabapentin can significantly reduce alcohol intake and cravings following detoxification in alcoholics. This new study provides some insight into the neural signaling mechanism of gabapentin in combating alcohol dependence. The effects of gabapentin on the behavior of alcohol-dependent and nondependent rats were analyzed. It was found that alcohol-dependent rats, which received gabapentin, drank significantly less alcohol and exhibited less anxiety when faced with alcohol abstinence, in comparison with rats that did not receive gabapentin. No change in behavior was seen in nondependent rats receiving the drug. The effects of gabapentin were blocked in the presence of a GABA(B) receptor antagonist, indicating that gabapentin's cellular mechanisms are likely due to changes in the release of the transmitter GABA at inhibitory synapses. The researchers hope to eventually launch clinical trials to assess the efficacy of gabapentin as a potential treatment for alcohol dependence.

TAPAS good for your heart

Follow-up analysis at 1 year indicates that thrombus aspiration improves cardiac outcome.

According to results published recently in *The Lancet*, the initial benefits observed in treating patients with acute myocardial infarction with thrombus aspiration (TA), rather than conventional percutaneous coronary intervention (PCI), translate into clinical benefit 1 year on.

The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) was initiated to determine whether thrombus aspiration could improve reperfusion following interventions for acute myocardial infarction. PCI is the current standard treatment for heart attack patients. However, spontaneous or angioplasty-induced embolization of atherothrombotic material during the procedure is common, leading to vascular obstruction, larger infarct size and increased mortality.

Initial results from the single-center, randomized trial indicated that TA led to improved myocardial reperfusion compared with conventional PCI; however, investigators were keen to assess whether these promising initial results also produced improved longer-term outcomes. Patients enrolled on the trial between January 2005 and December 2006 at the University Medical Center, Groningen, the Netherlands, were randomly assigned to either TA (n = 535) or conventional PCI (n = 536). Of these, data were

available on 1060 (99%) at 1 year follow-up. The primary end points of the study were cardiac death or nonfatal reinfarction.

At 1 year, cardiac death had occurred in 3.6% (19 of 535) of patients in the TA group and 6.7% (36 of 536) in the PCI group (hazard ratio [HR]: 1.93; 95% confidence interval [CI]: 1.11–3.37; p = 0.020). When considering 1-year cardiac death or nonfatal reinfarction, this occurred in 5.6% (30 of 535) of the TA, and 9.9% (53 of 536) of the PCI group (HR: 1.81; 95% CI: 1.16–2.84; p = 0.009).

The authors concluded that: "Compared with conventional PCI, TA before stenting of the infarcted artery seems to improve the 1-year clinical outcome after PCI for ST-elevation myocardial infarction."

If, as implied by these initial results, TA significantly improves myocardial perfusion, the technique may influence clinical guidelines and enter the standard approach to patients with acute MI. "We are the first to demonstrate the efficacy of thrombus aspiration in terms of improved clinical outcome. Based on these results, thrombus aspiration will be increasingly utilized in routine clinical practice ..." the authors commented.

Source: Vlaar PJ, Svilaas T, van der Horst IC *et al.*: Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 371, 1915–1920 (2008).

About the Bulletin Board

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Raptiva® appears safe for long-term use in psoriasis patients

A review of data based on 10 years of experience using Raptiva® (efalizumab) in patients with moderate-to-severe chronic plaque psoriasis has confirmed that the drug has a favorable long-term safety profile. The data are encouraging, providing support for the use of Raptiva as an appropriate long-term treatment option for sufferers of this life-long condition.

‘The data are encouraging, providing support for the use of Raptiva as an appropriate long-term treatment option.’

Psoriasis is a common chronic inflammatory skin condition, affecting approximately 2% of the UK population. The condition causes skin cells to grow abnormally, resulting in thick, red, inflamed, scaly patches of skin, most commonly on the knees, elbows, trunk and scalp.

The etiology of psoriasis is unknown and, although there are a number of medications available to help control the

symptoms, there is, as yet, no cure. Patients with moderate-to-severe psoriasis require life-long treatment, and there is currently a significant unmet clinical need for durable psoriasis therapies – drugs that can be safely used in the long-term to effectively manage the disease.

Raptiva is a humanized anti-CD11a monoclonal antibody that binds to and blocks the activity of CD11a on the surface of T cells, thereby inhibiting the T-cell mediated processes involved in the pathogenesis of psoriasis.

In this recent review, data was gathered from over a decade of clinical experience and post-marketing surveillance of Raptiva, and a safety review was carried out. The results demonstrated that Raptiva has a favorable safety profile, with no reported increase in adverse events.

Notably, recent research has shown that the chronic inflammation that causes the visible symptoms of psoriasis on the skin also significantly affects the organs beneath the skin. Psoriasis sufferers are at a significantly increased risk of

comorbidities, such as obesity and diabetes, and the disease reduces life expectancy by up to 10 years.

‘In order to manage psoriasis more effectively and to control the associated systemic inflammation, the focus should be on treating patients earlier and more aggressively.’

In order to manage psoriasis more effectively and to control the associated systemic inflammation, the focus should be on treating patients earlier and more aggressively. There is consequently a real need for drugs that are well tolerated and associated with favorable long-term safety profiles. The findings of this recent safety data analysis are therefore encouraging for those afflicted with moderate-to-severe psoriasis, providing support for the long-term use of Raptiva in many of these patients.

Source: *5th European Association of Dermatology and Venereology Spring Symposium*. Istanbul, Turkey, 22–25 May (2008). www.eadv.org

New drug candidate for the treatment of Alzheimer’s disease

A novel drug candidate has been shown to offer nerve cell protection in patients suffering from Alzheimer’s disease.

AL-108 was seen to protect patients with mild cognitive damage against memory loss. The discovery of AL-108 came about from the hypothesis that proteins produced by glial cells may be able to repair cell damage brought on by neurodegenerative disorders, since glial cells provide support and protection for neurons and are involved in neuronal repair.

Professor Illana Gozes, Tel Aviv University, Israel, and her team of researchers identified ADNP, a protein involved in brain repair.

‘Results show that AL-108 is able to protect against the formation of amyloid plaques, a feature associated with Alzheimer’s disease.’

One fragment of the protein (NAP) was seen to display significant neuroprotection, and was able to protect nerve cells against severe oxidative stress. ‘What happens in the nerve cells of Alzheimer’s brains can be likened to a derailed train, says Professor Gozes. The nerve cell skeleton – the microtubules – are like the rails, and a protein called tau functions like the ties between the rails. In Alzheimer’s, the ties

fall off, the tracks fall apart and nerve cells die. AL-108, however, seems to prevent this process from accelerating’.

Results show that AL-108 is able to protect against the formation of amyloid plaques, a feature associated with Alzheimer’s disease. In addition, AL-108 appears to protect against a decline in cognitive function.

AL-108 has recently passed a Phase II study in a US FDA-approved clinical trial. It is currently being developed by Allon Therapeutics, Vancouver, BC, Canada, and is expected to reach the market in approximately 5 years.

Source: Tel Aviv University press release. Available at: www.tau.ac.il