

Clinical trials of ALVoo3 – what it means for Australian coeliacs?

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Despite best efforts at maintaining strict compliance to a gluten free diet (GFD), persisting small bowel damage (villous atrophy) occurs in a sizable proportion, in some studies in 50% or more, of coeliac disease sufferers. This persistent damage is presumably due to unintentional ingestion of small amounts of gluten. Persistent villous atrophy is concerning as it is associated with a three to four-fold increased risk of long term complications such as osteoporosis and cancer. Thus therapies to improve the efficiency of the GFD and improve small bowel healing are very attractive.

The accompanying press release by Alvine Pharmaceuticals reports on two recent trials showing a potential benefit for the use of ALVoo3, an enzyme preparation that degrades gluten. What is the significance of these clinical trials of ALVoo3, and how might these findings impact on the lives of Australians with coeliac disease?

Alvine Pharmaceuticals, based in the USA, has developed a preparation, ALVoo3, consisting of a mixture of two enzymes. These enzymes, called proteases, are highly targeted to particular regions within gluten that cause toxicity, and result in very effective degradation of toxic gluten fragments in the test tube. It is proposed that such a preparation, ingested at the same time as a meal contaminated by gluten, may potentially degrade the toxic gluten fragments and overcome the problems of unintentional gluten contamination.

Moving on from test tubes, Alvine Pharmaceuticals sought to determine the efficacy of ALVoo3 in a clinical trial including volunteers with coeliac disease. They engaged the expertise of a coeliac research team, based at the Walter and Eliza Hall Institute in Melbourne, renowned internationally for their pioneering research into understanding the immune response

to gluten. The resulting collaboration brought together investigators from The Alfred Hospital, Burnet Institute, Nucleus Network (an early phase clinical trials company), and Nexpep P/L (a Melbourne based coeliac therapeutics company). The involvement and assistance of The Coeliac Society of Victoria was pivotal to the success of the study, and the response to recruitment was overwhelming and extremely positive.

The study, conducted in mid 2008, involved 20 coeliac disease volunteers from The Coeliac Society of Victoria. Each volunteer participated in a three-day “gluten challenge”, with 10 consuming gluten pre-treated with ALVoo3, and 10 consuming gluten pre-treated with an inactive agent (placebo). The study measured immune responses in blood six days after commencing the challenge. The majority of those who consumed placebo-treated gluten developed coeliac immune responses in their blood as expected, but none of the 10 participants that consumed ALVoo3-treated gluten developed any immune response. This result shows that ALVoo3 can efficiently abolish the immune response to gluten ingestion in people with coeliac disease when used as a food processing aid (ie. to pre-digest gluten).

The next study performed by Alvine Pharmaceuticals was to determine whether ALVoo3 can work as a supplement to the diet, and not just as a food processing aid. It showed that ingestion of an ALVoo3 preparation can very efficiently degrade a gluten containing meal in the stomach of healthy (non coeliac) volunteers. This study provides “proof of concept”, supporting the notion that ALVoo3 can degrade gluten when used as a dietary supplement.

While these results are encouraging, they are early findings in a small number of people. Known as Phase 1 studies, they are conducted to primarily demonstrate safety of the product. Further studies are needed before clear recommendations on the role of ALVoo3 can be made. This will include larger studies involving participants with coeliac disease, and

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importantly, assessment of small bowel biopsies. Planning for Phase 2 studies of ALVoo3 are currently underway, and we shall be hearing more about these studies over the next year.

GFD supplements like ALVoo3 are unlikely to allow a normal gluten containing meal to be consumed, but may “decontaminate” meals containing trace amounts of gluten. If shown to be effective, ALVoo3 may be useful in those people with coeliac disease who fail to achieve small bowel healing despite best attempts at a strict GFD, where small amounts of gluten contamination are suspected to be the cause.

The successful clinical trial in Melbourne underscores the importance of collaboration and an effective network encompassing clinicians, researchers, patients, and the Coeliac Society. Many exciting new research opportunities await, with several possibilities for new therapeutics in coeliac disease. Regardless of the project, the goodwill of society members promises many more successful collaborations in the future.

Both authors would like to thank all those who participated in the recent Alvine Study based in Melbourne.

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MEDIA RELEASE

Alvine Pharmaceuticals reports positive results with ALV003 in phase 1 trial of therapy in development of celiac disease.

Results Underscore Meaningful Advancements Being Made Towards Finding An Effective Pharmaceutical Therapy for Individuals Suffering From Celiac Disease.

SAN CARLOS, Calif., October 29, 2008 – Alvine Pharmaceuticals, Inc., today announced proof of concept in a Phase 1 Trial of ALV003, an oral protease therapy in development to detoxify gluten, intended for use by patients with celiac disease. The trial results confirmed that single doses of up to 1,800 mg of ALV003 were safe and tolerable in healthy volunteers. Doses at the 300 mg level achieved up to a 96% reduction of gluten in a meal in the stomach at 30 minutes, and were well tolerated by patients with celiac disease. In addition, doses as low as 100 mg were shown to be biologically active in degrading gluten in the stomach. Based on these

results, Alvine plans to initiate Phase 1/2a multidose trials in early 2009.

“The outcome of the Phase 1 Trial of ALV003 is a major step toward providing people with celiac disease a better quality of life, as there are currently no approved pharmaceutical therapies available,” said Dr. Ciarán P. Kelly, Medical Director of the Celiac Center at Beth Israel Deaconess Medical Center and Harvard Medical School. “Given the difficulty of following a strict gluten free diet, and the potentially serious health consequences of gluten exposure, there is a great medical need for ALV003 and other new therapies targeting celiac disease.”

In addition to reporting Phase 1 results today, Alvine presented data in October, 2008 at the United European Gastroenterology Week conference in Vienna, Austria from a study in patients with celiac disease. The study demonstrated that patients with celiac disease who ingested gluten pre-treated with ALV003

showed elimination of peripheral gluten specific reactive T cells as measured by ELISpot responses. The study, conducted at the Alfred Hospital and Burnet Institute in Melbourne, Australia, suggests that a gluten specific ELISpot response may be a useful test for assessing the effectiveness of therapeutics in subjects with celiac disease.

“Results from these studies support the use of ALV003 as a drug to be taken with meals to address unintentional gluten exposure. In addition, the ELISpot study provides evidence that treatment of gluten with ALV003 may result in a reduction in the immune response to gluten in patients with celiac disease,” said Dr. Peter H. R. Green, Professor of Clinical Medicine and Director of the Celiac Disease Center at Columbia University. “These results provide a strong rationale to advance the clinical development of this compound as a treatment for celiac disease.”

Media release