

The coeliac vaccine to enter clinical trials

Dr Robert Anderson* updates us on the progress into the development of the coeliac vaccine.

Towards the middle of 2008, the coeliac “vaccine” developed in Melbourne will be ready for testing in volunteers with biopsy-proven coeliac disease and following a strict gluten free diet.

It has been ten years since the research programme supporting the coeliac vaccine began (modestly) in England, and continued in Melbourne since 2002. If ultimately successful, the vaccine will have global consequences for the medical treatment of coeliac disease. The coeliac vaccine will also provide a model for treatment of other immune diseases such as type-1 diabetes and be one of several “peptide based therapeutic vaccines” for immune and allergic disease such as asthma (1).

Very few new technologies have a single home. The coeliac vaccine was conceived in Oxford, England with the discovery of the one critical part of wheat gluten toxic in the common genetic version (HLA DQ2) of coeliac disease (2). As much as the identity of the toxic component of gluten was important, it was the way in which it was found that has proven to be even more important. By eating gluten in wheat, rye, or barley for three days (even a single meal will suffice in some people), immune cells (T cells) that damage the small intestine are mobilised into blood for a few short days (3). The T cells in blood can be monitored and analysed to define what part of gluten they recognise. The parts of gluten recognised by the vast majority of T cells involved in coeliac disease can be condensed to a few “short” fragments of gluten that remain after its digestion in the gut. These gluten fragments can be synthesised using fairly standard chemistry and are the basis for the coeliac vaccine.

The first challenge for the vaccine was to convince experts in coeliac disease that the new “gluten challenge” method to study the immune response was reliable. In 2007, seven years after the original report from Oxford, the key findings were fully replicated by highly respected European researchers (4). During the intervening seven years, more and more data was accumulating in Melbourne using the “gluten challenge” method to test all the various components of wheat, rye, barley and oats using T cells from coeliac volunteers (5).

The second major challenge for the vaccine has been to determine the number of gluten components needed to be included; too many would make the vaccine impractical because of the intricacies of manufacturing and testing a complex mixture. That challenge is now resolved and the vaccine has been successfully manufactured. Progress is on track for the anticipated testing in coeliac volunteers this year.

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For a new drug to be accepted for use in people in Australia, Europe, or North America it must have progressed successfully from Phase 1 (safety) studies usually involving up to about 30 volunteers, to Phase 2 (efficacy) studies to show that “it works” in people with the medical condition of interest (typically about 200 volunteers in several locations around the world), and to Phase 3 (similar to Phase 2 but involving several thousand volunteers in many sites around the world).

The third challenge for the coeliac vaccine, and other drug supplements to improve the effectiveness of the gluten free diet, has been commercial.



If the medical condition to be treated is fairly common, funding for drug development is relatively straightforward after Phase 2 when a drug has been shown to be safe and reasonably effective. But funding for drug development is a major issue if the disease targeted is uncommon or not traditionally treated by drugs, like coeliac disease. Investors are often anxious that the “market” is not sufficiently defined to be able to calculate the returns on their investment. For coeliac disease, this has been important, as most investors in drug development are American, and the low level of awareness (and diagnosis) of coeliac disease in North America has, until recently, limited development of treatments for coeliac disease apart from increasingly sophisticated recipes for gluten free food.

Currently, the gluten free diet is the only treatment for coeliac disease. But to develop a drug for coeliac disease and show it is both at least as safe and as effective as the gluten free diet will require millions of dollars, involve thousands of volunteers in several countries and the resources of a large pharmaceutical company.

Since the gluten free diet only involves dietary change, and foods need only be shown to be safe and to comply with labelling regulations, there has been surprisingly little impetus to show how effective the gluten free diet is in treating coeliac disease. For the estimated 600,000 people diagnosed with coeliac disease (out of the 5 million with coeliac disease in North America and Europe) who require the gluten free diet to remain in good health, there is little comfort in knowing that there have been only three “randomised, controlled”

studies of the gluten free diet – one in children and two in adults – the largest with 57 participants (6-8). Little wonder then that there continues to be debate over the safe limit to gluten contamination in food.

The effectiveness of the gluten free diet and any new treatment needs to be assessed by biopsy of the small intestine, as well as symptoms and control of long term complications like osteoporosis. However, repeated endoscopy and collection of biopsies is expensive and unpleasant for volunteers, so studies to establish the effectiveness of “cheap” treatments like the gluten free diet have been limited in size and complexity (in reality, the gluten free diet is not cheap – the cost is similar to ongoing medications for blood pressure combined with a drug for high cholesterol, around A\$1000 annually).

Testing of drugs for coeliac disease must be much more rigorous than those for dietary treatment. But how effective does a drug need to be for the treatment of coeliac disease? In a recent study from Italy, it was found that two years after adopting a gluten free diet, about half those people diagnosed with coeliac disease continued to have villous atrophy as severe as when they were first diagnosed (9). Only about one in five of those with severe intestinal damage (villous atrophy) on a gluten free diet had raised (abnormal) blood levels of transglutaminase antibody, meaning that standard blood tests to monitor disease activity were relatively ineffective. Probably this study means that the amount of gluten needed to raise blood levels of transglutaminase antibody is much lower than that needed to allow healing of the small intestine, and that many Italian coeliacs are in fact following a gluten reduced rather than gluten free diet.

There is great interest in finding a new treatment for coeliac disease more convenient and consequently more effective than the gluten free diet. The coeliac vaccine is a promising new approach to treat coeliac disease and will begin its passage through clinical trials in 2008. Nexpep Pty Ltd is the company undertaking the development of the coeliac vaccine, and Nucleus Network, Centre for Clinical Studies (CCS), Alfred Hospital in Melbourne, will be conducting the Phase 1 clinical trial. Phase 1 study of the coeliac vaccine will proceed once approved by the hospital ethics

committee. Since drug trials for coeliac disease will become more common, in early 2008 a pilot study will be run by Nucleus Network to confirm the best way to use a gluten challenge to assess the effectiveness of drugs for coeliac disease. Volunteers for clinical trials will be invited once ethics approvals have been granted. Prospective volunteers interested in these studies can contact Nucleus Network and be updated as information comes to hand.

Oddly enough, the development of drugs for coeliac disease will cause attention to shift back to the gluten free diet. The short-comings of the gluten free diet need to be addressed with a clear understanding that it is a medical treatment.

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