Coeliac UK report – Dr Jason Tye-Din
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The role of avenin-specific T cells in oats toxicity in coeliac disease

The clinical question: Optimal treatment of coeliac disease requires strict removal of dietary gluten. While wheat, rye and barley are the major sources of gluten harmful to people with coeliac disease, there is some concern that oats, which contain gluten-like proteins called avenins, could also cause adverse affects in some. The current medical approach to identifying people who are sensitive to oats necessitates a prolonged oats challenge, typically in the order of many months, and small bowel biopsies to assess for intestinal damage. Coeliac antibody testing is not sensitive enough to detect potential adverse effects. Thus, there is a need to better identify people with coeliac disease who can safely consume oats, or conversely, identify those who may be at risk of issues (such as intestinal damage, symptoms or medical complications) from oats causing coeliac-related inflammation.

Our prior research: We have shown that key peptides in oats avenin trigger a potentially damaging immune (T cell) response in almost 10% of people with coeliac disease (Hardy et al. J Autoimmunity 2015). These key peptides look very similar to barley peptides that drive barley toxicity in coeliac disease. The oats avenin response can be readily detected by a 3-day oats challenge followed by blood tests on day 6. In those who mount an adverse oats response the blood will contain avenin-specific T cells circulating from the small intestine.

This approach, first developed by Dr Bob Anderson, is now widely employed. It has been used by our group to establish the design of the coeliac therapeutic vaccine, Nexvax2 (Tye-Din et al, Science Translational Medicine 2010). We have also used it to assist in the successful breeding selection of barley strains by CSIRO that have ultra-low gluten content, Kebari (Tanner et al, Aliment Pharmacol Ther 2010), and test the efficacy of enzyme therapies such as ALV-003 for coeliac disease (Tye-Din et al, Clin Immunol 2010). We have also shown a simple blood based diagnostic test for coeliac disease (interferon-□ cytokine release assay; CRA) can be used in place of more complicated laboratory assays such as the interferon-□ ELISpot (Ontiveros et al. Clin Exp Immunol 2014). Separately, the CRA is being validated as a simple diagnostic for coeliac disease.

This project's goal: To determine if the CRA test can simply and accurately assess for oats sensitivity in people with coeliac disease. This study will assess this immune test against the "gold-standard" of 3-month oats challenge and small bowel biopsies. Specifically, we wish to assess whether detection of avenin-specific responses after 3-day oats challenge identifies people with coeliac disease at risk of damage from prolonged oats ingestion.

Current Progress: In the first 6 months of our project, we have been able to achieve the following:

1. Employ Dr Emma Halmos as a post-doctoral researcher in our team. She is a coeliac-specialising dietitian with clinical feeding trial experience. She is playing a major role in the recruitment of participants for this study, participant dietary assessment and monitoring, and is working closely with our lead human immunology scientist (Dr Melinda Hardy), research nurse (Ms Cathy Pizzey) and research officer (Ms Amy Russell).

2. Update our current ethics approval to enable gastroscopies to be performed before and after a 3-month oats challenge in both adults and teenagers (aged 13-17). This has now been approved by the relevant ethics committees.

3. Recruited 33 people with HLA-DQ2.5+ coeliac disease from our coeliac database who are willing to undertake oats challenge for 3-days. 20 of these people are also willing to undertake the follow-up 3 months oats challenge with pre- and post- gastroscopy to assess intestinal biopsies. Ongoing recruitment is underway with a new advertisement placed in the Coeliac Victoria e-newsletter. This received a good response of 25 people (so far) interested in hearing more about the oats study.

4. To date, 3-days oats challenges have now been completed in five volunteers. We have used Tilquihillie puddings oats imported from Scotland that are certified wheat gluten free (<3ppm) – these oats have been used by us in our previous work. In Australia, no brand of contamination-free oats is marketed.

Interestingly, two have shown oats avenin-specific responses using the ELISpot approach. Blood was also collected for the CRA test but this will be batch tested at a later date. All five participants are moving forward into the 3-month oats challenge after a washout period has been completed. We will then be able to determine if the oats T cell response predicts for oats induced intestinal inflammation.

In summary, the project is progressing well. All relevant ethics are in place and recruitment from our database has been strong. The oats challenge assays have commenced and, importantly, we have identified some oat T cell responders. This will enable us to compare to outcomes after the 3-month challenge to determine the role of the CRA test.

We are extremely appreciative of the support from Coeliac UK and its members that has enabled this research to proceed. We look forward to providing an update in the next 6 months.

Addendum: We have recently received funding from Coeliac Australia to support our oats research platform, and the goals dovetail nicely with this Coeliac UK supported project. Specifically, this funding is aimed at determining specific guidelines for the feeding of oats to people with coeliac disease in Australia (compared to the UK, oats are currently excluded from the gluten free diet). As such, it is geared towards establishing the safety of oats following 3-month oral challenge, and supports greater numbers of people to undertake this with gastroscopy and biopsies. The funding from Coeliac Australia will allow us to strengthen the Coeliac UK study by increasing sample size and allowing additional readouts to be assessed.

Specifically, it will provide funding to:

1. Increase sample size, to move the findings from a pilot study of this diagnostic test to one that is more definitive.
2. Allow us to perform gastroscopies and small bowel biopsies in more volunteers. This will underpin the development of clinical practice guidelines.
3. Allow us to do more detailed immune testing of biopsies. In addition to traditional histology, we can now perform cytokine mRNA assessment in the biopsy, which may be a more sensitive marker to detect early damage from oats prior to the development of villous atrophy or raised intra-epithelial lymphocytes.

4. Allow us to employ the “gold-standard” ELISpot immune readout after 3-day oats challenge to compare with the CRA assay.
5. Allow us to test T cell “non-responders”. We can now assess this group to determine if they can be “made” to respond to oats simply by repeating an oats challenge or giving the person a 3-day barley challenge. We hypothesise that prior oats or barley exposure will “prime” the immune system to have a greater response the second (or subsequent) time around. This has potential relevance for why oats may be toxic in only a subset of people with coeliac disease. It would also provide in vivo evidence, for the first time, of grain cross-reactivity i.e. one grain (i.e. barley) driving the toxicity of another (i.e. oats) due to similarities in their sequences.