



Potential Pharmaceutical Treatments for Celiac Disease: An Interview with Joseph Murray, MD

The celiac disease patient community actively follows the news regarding non-dietary treatments for the autoimmune disease. Of note, over the past year many patients have seen the various advertisements and news announcements regarding three pharmaceutical therapies in clinical trials. These include ALV-003, a protease therapy that breaks down gluten; larazotide acetate, a tight junction regulator; and NexVax2, a desensitizing vaccine.

As part of the National Foundation for Celiac Awareness' (NFCA) programming for our June Webinar "*Celiac Disease: Immunology 101 and the Drug Development Process*," we wanted to learn more about these three non-dietary treatments through the perspective of a leading celiac disease clinician. NFCA is excited to share with you an interview with Joseph Murray, MD*, Consultant, Division of Gastroenterology & Hepatology, Professor of Medicine, Mayo Clinic College of Medicine and NFCA Scientific/Medical Advisory Council Member.

Question 1

Q. Can you briefly summarize how these three drugs are hypothesized to work?

A. These three experimental approaches to treat celiac disease work in quite different ways. First, ALV-003 is a protease therapy that breaks down the particular protein sequences that seem to trigger celiac disease. Proteins, including gluten, are made up of building blocks called amino acids. The characteristics of each protein are really determined by the sequence of amino acids or building blocks of which they are made. There are specific codes or sequences of amino acids, especially glutamine and proline that are present in the gluten molecules that seem to trigger celiac response. These sequences are contained in the middle of those protein segments, called peptides. In order to detoxify these, those segments need to be broken up. To do this requires an enzyme that will particularly target those sequences. ALV-003 is a combination of two different enzymes that specifically target these damaging sequences present in the gluten molecules. The combination is particularly designed to be highly efficient and effective, even in the context of the stomach. In order to function, this combination of enzymes must rapidly and effectively break down these gluten proteins, cutting them at locations that will prevent or destroy any peptides that could trigger a response. The work published so far suggests that this can be effective at greatly reducing the number of immunogenic or immune-stimulating proteins remaining during digestion.

Larazotide acetate is a regulator of tight junctions. What this means is our intestine functions both as a barrier and as a sieve. It needs to allow nutrients to pass into the body as well as exclude bugs that could be bad for us or do us harm. It also allows for the careful sampling of what is going through our intestine by our immune system so it can test out to see if it is good or bad for us. The lining of the intestine is a single cell layer thick. Crucial to the barrier function are the tight junctions. These are the connections between the cells; some would liken them to rivets or spot welds that keep the cells together. But, really this concept of a spot weld or a rivet doesn't acknowledge the dynamic nature of these tight junctions—they can open and close in response to needs that may occur because of our need to let more in or exclude certain damaging bugs or molecules. An original observation by Alessio Fasano showed that in the intestine when exposed to gluten there is a release of a substance known as zonulin, now known to be pre-haptoglobin 2, and this

seems to cause the tight junctions between cells to open, increasing intestinal permeability. Larazotide acetate is a particular peptide molecule that prevents the zonulin effect, effectively tightening up the tight junctions between the cells and reducing the permeability, what also might be known as a leaky gut. This is administered at or shortly before exposure to gluten and would mitigate the effect that gluten produces on the intestine. Hence, it would likely need to be taken shortly prior to any potential exposure to gluten.

NexVax 2 takes advantage of the concept of tolerance and/or anergy in the immune system. Basically the concept is this—when the immune system is exposed to a foreign antigen, one to which it has already learned to react badly or be sensitive to, that if the system is exposed to this on a continuous basis especially in the absence of danger signals, then the immune system may learn to tolerate or at least suppress its usual response to the foreign antigen or entity. NexVax 2 is based on work performed by Dr. Robert Anderson to identify what appear to be some of the most important peptides or small protein sequences that trigger a celiac response and, if this works, it should not only suppress a response to those particular sequences, but also provide broader suppression even to other related sequences that are present within gluten and could trigger a response in celiac disease. The broad concept has been previously tried with other allergens, such as cat allergen, and has shown promise in those areas.

Question 2

Q. Can you explain whether these drugs are expected to allow a person with celiac disease to return to a normal gluten-containing diet or to act as a supplement to the gluten-free diet?

A. It is not likely that any of these three approaches will be “a passport to eating gluten with impunity.” Rather, it will likely reduce the impact that inadvertent or low to moderate level gluten ingestion may have on the patient. That said, it doesn’t completely preclude the possibility that, for example using an immunotherapy approach, a very robust level of tolerance could be achieved.

Question 3

Q. Are the drugs currently in development similar to any other drugs currently on the market for other autoimmune diseases?

A. There are many drugs that have been in development or actually being used for autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and psoriasis. Some of these may have applicability to celiac disease, though in general, because of their potential for immune suppression, celiac disease might not be a logical target for such types of treatment. Because we know so much about how celiac disease comes about, there are many other targets specific to the treatment of celiac disease that are in pre-clinical development.

Question 4

Q. Are you able to share what stages in the development or clinical trial process are these drugs currently in?

A. Virtually all the other potential treatments for celiac disease (outside of the three outlined above) are still in what is called pre-clinical development, meaning that they have not yet entered human use. One exception is a drug by a company, Chemocentryx, and this was the subject of a trial in humans in Finland, which was completed 3 years ago. The results have never been released or published and one can only assume that this was at best a negative study. Other entities are involved in the various stages of testing—some before and some already in commercialization pathways. These are inherently very slow development processes.

Question 5

Q. Do you think it would be possible to treat celiac disease with a combination of two or more of these drugs? How?

A. Combining different approaches may be possible; however, just like a long approval process is needed for individual therapies, an almost very similar proven process will be necessary when looking at combinations of therapies, not only for increasing the effectiveness, but also maintaining a low level of risk.

Question 6

Q. We know that very little is understood about non-celiac gluten sensitivity, but based on our understanding that these patients cannot tolerate gluten in a mechanism that is different from celiac disease, do you anticipate that any of the pharmaceutical therapies currently under investigation might be able to treat patients with non-celiac gluten sensitivity?

A. The issue of non-celiac gluten sensitivity is difficult probably because of several reasons. It may not represent a single entity, but rather may be multiple different entities that could produce a similar symptom. Until we know the mechanism(s) that underlie non-celiac gluten sensitivity, we really cannot come up with a rationale therapy directed at this. More likely, we will continue to treat these patients on a symptomatic basis, perhaps borrowing from medication used for conditions such as irritable bowel syndrome. Hence, it is unlikely that there are any pharmacological therapies under investigation to treat patients with non-celiac gluten sensitivity.

Question 7

Q. We know that it is important that a pharmaceutical treatment for celiac disease be as safe and effective as a gluten-free diet in order to be FDA approved. As a clinician, what are your major concerns about the current treatment for celiac disease (gluten-free diet), and how do you envision that a pharmaceutical treatment could fill that void?

A. The gluten-free diet is the current foundation of treatment for celiac disease; however, it is neither user-friendly nor is it totally effective for every patient because of ongoing gluten contamination that can occur inadvertently, cross-contact with foods that may contain gluten in processing or in the kitchens, especially commercial kitchens, may be an issue, or

indeed patients succumbing to temptation may also be a source of gluten contamination of the diet. Hence, the therapy is less than ideal. Patient's perception of the diet often is that of a very socially-restrictive, as well as substantial cost. This is a gluten-filled world—while we would hope that patients with celiac disease who need to avoid gluten will be able to avoid it, we also must recognize on a practical levels that some contact will occur, and this may occur to a level sufficient to cause ongoing or recurrent injury in the intestine. Hence, alternative or additional therapies are highly desirable for the management of celiac disease. Of course, these therapies need to be safe—that means not in themselves producing side effects nor should they mask symptoms while allowing ongoing damage to occur. This itself could produce a hazard for later or delayed complications in a patient who may think, based on a lack of symptoms, that they are doing well. In addition, there is the potential moral hazard of perhaps permitting people to become much more casual with their dietary restriction in such a way or to such an extent that actual damage occurs despite the active treatment. I fully expect that there will be at least adjunctive therapies available for our patients within 5-10 years; hopefully, these will enable patients to live a freer lifestyle and whilst they may not consist of a passport to eat gluten with impunity, it may at least allow for a higher level of safety, particularly when the patient has less than complete control over gluten contamination of their diet.

Additional Resources

To learn more about this topic, visit the NFCA Webinar archive to view the archived version of the June 2013 webinar, “*Celiac Disease: Immunology 101 and the Drug Development Process.*”

www.CeliacCentral.org/Webinars/Archive

****Disclosure Statement from Joseph Murray, MD: “I have advised Alvine Pharmaceuticals and ImmusanT and have undertaken several trials for Alba Therapeutics.”***