Microscopic Colitis Foundation

MICROSCOPIC COLITIS NEWSLETTER

Volume 8, Issue 9
July, 2022

Faulty Perceptions About Celiac Disease That Continue to Persist

Even though celiac disease has existed for about 10,000 years, misconceptions, and misguided opinions about treatments continue to persist. And sadly, if they have persisted this long, they will probably continue far into the future; possibly indefinitely. About 2000 years ago, a Greek physician known as Aretaeus of Cappadocia identified the disease and named it koiliakos, based on the word “koelia” which means abdomen (Imaware, 2020, February 20)[1].

Seventeen centuries later, Doctor Mathew Baillie suggested that the disease appears to be related to diet, since people who eat a diet consisting almost entirely of rice seemed to generally avoid the problem. But despite the fact that he published his opinion on the disease, as is typical for treatments that are not based on the use of a “prescription drug”, his work was generally ignored. Finally, Doctor Samuel Gee, an English doctor who was well-known for his work in pediatric diseases, proved that a gluten-free diet brought significant health improvements for celiac patients. So, a diet connection was finally definitely established.

More recent research has established more details, and slightly better understanding, of course, but nothing has really changed significantly about the basic treatment — patients simply need to stop ingesting gluten, in order to completely resolve the symptoms. And yet, huge sums of money continued to be spent on research, searching fruitlessly for a “cure”.

But the word “cure” implies a complete resolution of issues.
That means not only a resolution of clinical symptoms displayed by patients, but also the prevention of any physical digestive system damage that can be detected by a pathology examination. In this case, logic tells us that an actual “cure” is only possible if certain genetic changes are made to the human DNA. The necessary changes would either allow our digestive system to completely digest the gluten molecule, or alternatively, genetic changes could be made to our immune system, so that it would no longer react to certain antigenic sequences in the gluten molecule.

Are any researchers working on either of these possibilities?
If they are, they don't seem to be publicizing that fact. Instead, they continue to research the development of various chemical compounds designed to assist in the digestion of the gluten molecule. Like everyone else, researchers like to eat, so when choosing a research project, they tend to go with the money. Everyone (every gluten sensitive individual, at least), wants a pill that they can simply swallow, so that they can once again eat foods that contain gluten. Why is this the case?

Gluten is as addictive as opium.
In addition to the production of many antigenic sequences, the digestion of the gluten molecule results in the production of gluteomorphins, also known as gliadorphins. In the human brain, these opioid peptides tend to be just as addictive as many controlled substances. So, it's no wonder, that everyone craves gluten.

Is celiac disease even a disease?
The Oxford dictionary defines “disease” as, “a disorder of structure or function in a human, animal, or plant, especially one that produces specific signs or symptoms or that affects a specific location and is not simply a direct result of physical injury.” It could certainly be argued that “celiac disease” is a result of a physical injury. No human can properly digest gluten, because the human digestive system evolved without any exposure to gluten.

When we attempt to digest gluten, the resulting undigested fractions (peptides) cause physical injury to our intestines. They do this by provoking increased intestinal porosity, which results in inflammation of the cells in the mucosal layer of the intestines. While it might appear that this is an indirect injury, it's direct in the sense that there is a direct cause/effect relationship. In other words, for celiacs, eating gluten definitely results in clinical symptoms caused by physical injury of the intestines. And of course, this is also true for the type of non-celiac gluten sensitivity that many of us have developed, as the result of the development of MC.

Let's look at the basic facts:

1. The “disease” is caused by the ingestion of gluten.
2. Avoiding the ingestion of gluten completely resolves/prevents the symptoms.

Obviously, even if a pill could be perfected that totally resolved celiac issues, unless the pill were taken before every meal that contained

gluten, for the rest of a patient's life, celiac symptoms word return, following the ingestion of gluten. So, could a treatment based on this type of technology be realistically labeled a "cure"? In fact, it would simply be a lifetime treatment, if the symptoms of the disease were to be avoided for life. Yet the search for such a "cure" continues.

No one wants to change their diet.
Consequently, gluten sensitive patients appear to be dictating the direction of research. With this encouragement, researchers continue to pursue the development of enzymes to assist in the digestion of the gluten molecule. And despite the fact that this can only result in a lifetime treatment program that will cost patients many thousands of dollars, over their lifetimes, everyone seems to refer to this approach as a "cure".

Even the New York Times makes this mistake.
A prime example of this lack of logic is a recent title of a New York Times article published on June 1, 2022, titled "Are We Close to a Cure for Celiac Disease?", (as if a cure is even possible with this type of research). On June 7, the newspaper published an "updated" version of the article in which the title had been changed to, "Are We Close to a Treatment for Celiac Disease?" (Callahan, 2022, June 1)[2]. Apparently, they caught a lot of flak with that original version, possibly from Doctor Fasano, himself.

The article describes the current state of research regarding treatments for celiac disease, and Dr. Alessio Fasano, arguably the world's leading authority on celiac disease, freely admits in the article that none of these treatments could be construed as a "cure". Yet the original title of that article proves that the illusion of a cure for celiac disease continues to dominate everyone's thinking regarding the treatment of celiac disease. Hopefully, that major correction in the title suggests that mainstream thinking about this disease may finally be becoming more realistic.

The Celiac Disease Foundation lists 24 treatments currently in medical trials.
These research trials, which focus on the use of medications to prevent, or minimize typical celiac symptoms following an exposure to gluten, fall into three general categories (Celiac Disease Foundation, n.d.)[3].

1. Enzymes designed to assist in the digestion of the gluten molecule.
2. Products that assist keeping the tight junctions of the intestinal mucosal lining closed.
3. Products that attempt to prevent, or minimize the immune system response to gluten.

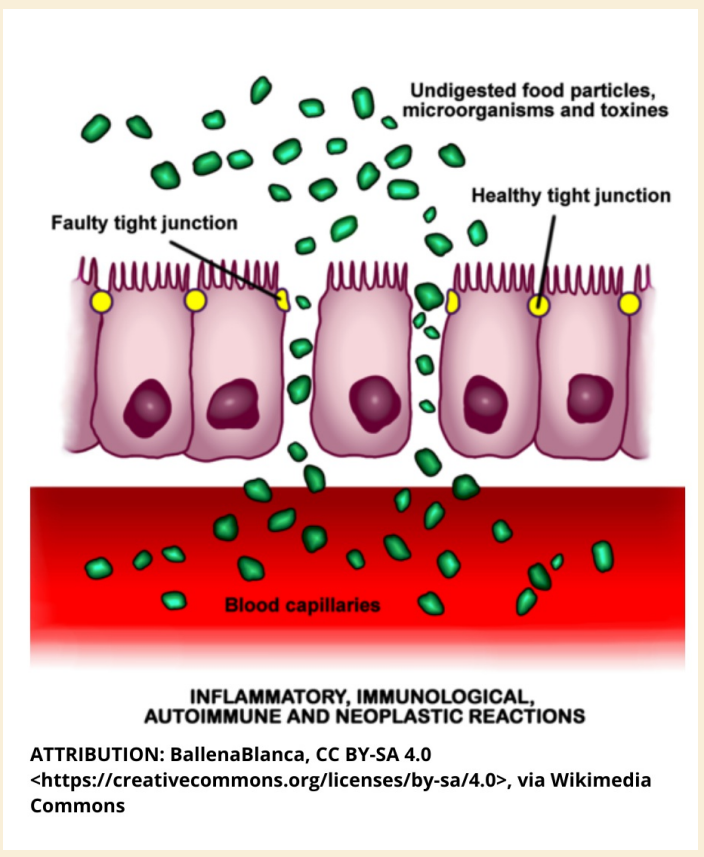
Note that three basic types of clinical trials are needed when seeking FDA label approval for a new drug.
1. Phase 1 clinical trials prove safety of the treatment.
2. Phase II clinical trials prove the efficacy of the treatment.
3. Phase 3 clinical trials determine whether the treatment is better than what's already available, and proves that the treatment is at least better than a placebo.

Examples of proposed treatments in the first category (enzymes)
AMY02, currently in preclinical studies, TAK-062, which has

successfully completed a phase 1 trial, and latiglutenase, (a mixture of two enzymes claimed to digest gluten), which is in a phase 2 trial.

Note that most over-the-counter products sold for this purpose typically have not been shown to actually provide benefits in official medical trials. Most of them have a common problem, according to published medical articles based on either actual test trials, or database searches for proof of efficacy — although they might help to break down gluten in a test tube demonstration, when exposed to the typically low pH levels found in the stomach, they lose efficacy. The previous newsletter, volume 8, issue eight, published June, 2022, discussed this problem in more detail.

Examples of proposed treatments in the second category (intestinal mucosal barrier enhancers)
IMU–856, currently in a phase 1 trial, and larazotide acetate, currently in a phase 3 trial.



ATTRIBUTION: BallenaBlanca, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons

Note that Doctor Fasano and his associates first discovered that zonulin regulated the tight junctions, over 20 years ago (Fasano, et al., 2000)[4]. After it was resold a time or two, this technology has evolved into a series of medical trials of a product known as larazotide, which is now in a phase 3 trial. If the trial results are favorable, this product might be available on the market within two or three more years. But this clearly demonstrates how products resulting from medical discoveries typically require decades, rather than years, of development and testing, before they are able to receive FDA approval.

Examples of proposed treatments in the third category (items that inhibit the immune system's response to gluten)
TAK – 101 (which aims to induce gluten tolerance), teriflunomide (an oral immunomodulatory agent), and ZED1227 and GSK3915393 (Transglutaminase 2 [TG2] inhibitors). The first three are in phase 2 trials, while the last one (GSK3915393) is still in a phase 1 trial. KAN-101, which successfully completed a phase 1 trial, supposedly targets T cells, and re-trains them to tolerate gluten. Note that methotrexate, for example, is an immunomodulator, so clearly, drugs in this class (presumably including teriflunomide) tend to suppress the immune system.

What can we conclude from all this?
Probably, in two or three years, FDA approved treatments for gluten sensitivity may begin to appear on the market, if all goes according to plan. However, please note that as pointed out in the New York Times article, “If proven safe and effective, these potential therapies probably would not be cures for celiac disease or “a free ticket for high-gluten consumption,” but they could mitigate the effects of accidentally eating small amounts, Dr. Verdú said.”

References

1. Imaware. (2020, February 20). Retrieved from https://www.imaware.health/blog/quick-history-and-evolution-of-celiac-disease

2. Callahan, A. (2022, June 1). Are We Close to a Treatment for Celiac Disease? Retrieved from https://www.nytimes.com/2022/06/01/well/celiac-disease-treatment.html

3. Celiac Disease Foundation. (n.d.). Future Therapies for Celiac Disease. Retrieved from https://celiac.org/about-celiac-disease/future-therapies-for-celiac-disease/

4. Fasano, A., Not, T., Wang, W., Uzzau, S., Berti, I., Tommasini, A., & Goldblum, S. E. (2000). Zonulin, a newly discovered modulator of intestinal permeability, and its expression in coeliac disease. The Lancet, 355(9214), 1518–1519. Retrieved from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(00)02169-3/fulltext#%20