dada2
FOUNDATION

Question & Answers from Global Patient Gathering
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Q: Is the gene therapy research measuring how effective the treatment could be for DADA2 patients with bone marrow failure too? Or is it a subset of those symptoms?

A: When you start a clinical trial, you have to be very specific about what you are going to measure. In many disease scenarios, that is not really an issue. In DADA2, it is a bit of an issue, because we could be looking at inflammation/vasculitis as one group of patients, bone marrow failure as a second group, or immunodeficiency as a third group. For the very first set of trials, we have to pick the group most likely to yield measurable success—meaning we need markers we can observe in the patient after they receive the drug to confirm that it is working. That is the "why." As for the "how"—yes, I think bone marrow failure is one of the areas where gene therapy is likely to be applied early. Part of the reason is that you can actually collect stem cells from the patient, treat them in the laboratory, keep them there, and observe how they respond. If they respond positively—that is, if they appear to be improving—that would lead us to believe the patient would more than likely respond and recover. So bone marrow failure is high on the list.

We can test a patient's likelihood of responding to gene therapy in the laboratory before they ever receive the drug, because the last thing you want is to put someone through the entire clinical trial process if they are unlikely to respond.

Q: It sounds like the first gene therapy approvals may happen through the European agency, since both gene therapy research teams are based there. If their regulatory agency approves a therapy, would that automatically apply to the U.S. FDA? Or would U.S. patients need to go through an entirely separate process?

A: If the U.S. approves something, it is not automatically approved in Europe, and vice versa. However, the approval process for the second country is significantly abbreviated, because we already know from the first clinical trial—in the region where it was approved—what we need to measure, including the appropriate dose.

In the first approval process, one of the key requirements is to give different groups of patients escalating doses across a range, because you never want to start by giving too much and risk harm. You begin at a very low dose—safe, but not effective. You move to the next dose—still safe, with hints of benefit. Then perhaps a third dose where the drug proves both safe and effective.

When seeking approval in a second country, you do not have to repeat all of that. You simply enroll a small number of patients, administer the dose established by the first regulatory agency, and observe them under protocols closely modeled on the original. As is often the case, you get the same result, and the approval process is greatly abbreviated.

Q: You mentioned that TNF blockers do not target immunodeficiency, but if I understood correctly, gene therapy does, because it addresses the root cause of DADA2?

A: This is one of the great conundrums of DADA2. When we look across patients with the same gene and the same mutation, we see that they fall into one of three broad categories: the first is inflammation/vasculitis, the second is bone marrow failure, and the third is immunodeficiency.

We do not yet know why that happens. In theory, you would expect that a person with the same gene and the same mutation would have the exact same set of symptoms. That is simply not the case with DADA2.

TNF is a molecule that sits at the intersection of many different inflammatory pathways, and if we can inhibit its activity, we can inhibit inflammation very specifically. A buzzword in the rare disease field today is “repurposing,” which refers to taking a drug approved for one indication and applying it to an entirely different one. TNF blockers were first developed for inflammatory diseases like rheumatoid arthritis—designed, tested, and approved for that purpose. But when researchers began studying DADA2, they came to understand that TNF may play a key regulatory role in the inflammatory aspects of the disease. They made an educated bet, gave these patients TNF inhibitors, and it worked.

However, we also know that inflammation does not play a role in bone marrow failure in DADA2, and that TNF is not involved in the immunodeficiency phenotype. So, not surprisingly, TNF inhibitors do not benefit patients who fall into those categories—and understanding why is something the entire scientific and medical community is actively working to address.

So why would gene therapy work? In all three of these disease presentations, the underlying root cause is a deficiency of the enzyme ADA2. In theory, if we bypass the approach of blocking downstream problems and instead correct it at the root level—simply replacing ADA2 through gene therapy—that should provide benefit across all three aspects of DADA2.

Q: Given that TNF inhibitors do not work for the immunodeficiency and bone marrow failure phenotypes, does that mean the precise mechanisms driving those presentations in DADA2 are not yet well understood?

A: That is probably a fair characterization. The precise molecular mechanisms involved are not yet fully defined. We know a great deal about the regulation of adenosine, and we understand that having ADA2 present and functioning normally is important for bone marrow function and maintenance, as well as for the development of the antibody-producing component of the immune system that is affected by DADA2. We also know that inflammation—the primary

pathway targeted by TNF inhibitors—is not playing a central role in bone marrow failure or immunodeficiency. So it makes sense that TNF inhibitors do not work for those phenotypes. That said, it does not mean that patients with bone marrow failure or immunodeficiency should never receive TNF inhibitors, because the three categories are not mutually exclusive—there is substantial overlap.

It is quite possible, for example, that someone whose primary presentation is bone marrow failure still has symptoms of inflammation or vasculitis. In that case, TNF inhibitors would be appropriate to manage the inflammatory component of their condition—even though they would not benefit from those medications with respect to the bone marrow failure itself.

Q: What stage of clinical trials are the two gene therapy research groups currently in?

A: The most important thing to understand is that neither of the two groups- in Italy or in the UK- has yet reached the clinical trial stage. However, both are very close. The primary hurdle remaining is not scientific but financial: they need funding to execute the trial. I believe Despina has already applied for funding to initiate her clinical trial.

As of today, there is no open clinical trial to enroll in- and that is important to understand. But one may be available in the near future.

Q: How would one volunteer or ask to be on a clinical trial?
A: The first step is simply being aware that a trial exists and that is genuinely the hard part. Now that you know which two groups are furthest along, you can follow their progress. Each institution will issue a press release on the day a clinical trial opens. You can also count on the DADA2 Foundation to make a major announcement at that time. It will appear on our website, in our newsletter, and for something this significant and exciting, it may even arrive in your email inbox—if we have your contact information. That is why it is important that we know how to reach DADA2 patients.

If you are not yet registered with us, please make sure we have your email address. We will learn about a trial opening at nearly the same moment as the researchers, they will call us directly and we will immediately spread the word. When a trial does open, your next step would be to go to your doctor, who will likely not yet know about it, and say, “There is a clinical trial for DADA2 in Milan, Italy, please help me get into it.” Your doctor will then be able to refer you to that clinic.

Most clinical trials have significant enrollment criteria, and we do not yet know exactly what those will be. They will likely include things such as: confirmation of a DADA2 diagnosis, results of genetic testing, results of enzyme testing, a description of your symptoms, and how long you have been symptomatic.

There will be additional criteria we cannot anticipate yet. If you meet the enrollment requirements, your only remaining challenge will be geography.

Q: Given that there's such a low number of diagnosed patients worldwide, will there be enough to adequately conclude all three phases of the trial?

A: Yes. You may recall that one of the slides mentioned shortcuts that have been built into the approval requirements specifically for rare diseases—precisely because patient populations are often very small.

In December 2025, the FDA announced a new expedited approval pathway specifically for rare diseases called “Plausible Mechanism.” Under this pathway, you can skip much of the traditional testing and seek approval with a smaller patient cohort, provided that—after demonstrating safety—you can provide a sound scientific rationale for why the therapy should work. For a disease like DADA2, that rationale is straightforward: DADA2 is caused by a deficiency of the enzyme ADA2 in the blood, and the therapy replaces that enzyme in the blood.

I am confident that under this FDA approval pathway, approval could be achieved with a very small patient cohort—though I would rather not cite a specific number. To put it in context: many standard clinical trials involve hundreds of patients. For a rare disease like DADA2, approval might be achievable with as few as 10 patients, provided the majority—say, 8 out of 10—achieve a positive outcome.

Q: Would gene therapy ever become available to symptomatic carriers in the U.S.? And should those of us who are carriers pursue VUS testing as well, to better position ourselves for potential clinical trials?

A: Broadly speaking, for autosomal recessive diseases like DADA2, it has long been taught that carriers would not be symptomatic. More recently, however, we have seen important examples of autosomal recessive diseases in which carriers experience symptoms ranging from mild to very severe. What we know today, primarily from the work of Dr. Isabel Meyts in Belgium, is that symptomatic DADA2 carriers clearly exist, and some of them are very severely affected. If we were to stratify patients from mildly to severely impacted, some carriers fall in that upper range.

Do symptomatic carriers exist? The evidence tells us the answer is absolutely yes. There is still a great deal of work to do to build a stronger scientific foundation for that conclusion and make a more compelling case to those who remain skeptical.

As for whether carriers would be eligible for gene therapy, the direct answer is that they would probably not be among the first patients enrolled. I think two things need to happen to change that. First, we need to build an airtight scientific argument that certain carriers can be very severely impacted. Second, gene therapy needs to demonstrate

effectiveness in patients with more traditional DADA2 presentations. Once both of those are established, it would become clear to everyone that gene therapy should be extended to certain carriers as well.