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Recognizing & Treating Alpha-1 Antitrypsin Deficiency (AATD)

Announcer:
Welcome to CME on ReachMD. This activity entitled: *Recognizing and Treating Alpha-1 Antitrypsin Deficiency, or AATD*, is provided by the American Thoracic Society and AKH, and is supported by an educational grant from Takeda Pharmaceuticals USA Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Strange:
We're going to get started today on our webinar. Welcome all the attendees, both in present, in person, and remotely. We think we have a pretty good program for you today. And what we'll be doing, by way of moving through our agenda is really introducing the topic of alpha-1 antitrypsin deficiency, giving you a broad overview. We're going to be talking about screening and diagnosing this condition and talk about both the lung and the liver manifestations of disease, hopefully leading us into what's on the docket now as current therapy and also touching into many of the therapies that are in the pipelines for this relatively rare disease.

The most important piece of this for me, I think, though, is the ongoing questions that you can submit over the course of the next hour. So feel free to be typing in as we go with the questions that you might have, and we've on purpose, saved a lot of time at the end to answer everybody's questions and make this a webinar that works really for everyone.

Our overview is that alpha-1 antitrypsin deficiency is a genetic disease, and we've mentioned both the lung and deliver manifestations that often result. And with cystic fibrosis, these two genetic diseases are really our most common genetic diseases seen in pulmonary medicine. We have an awkward architecture of naming the different gene variants associated with alpha-1 with M alleles being present exclusively in almost 95% of all individuals that live in the United States and the world. But we do have these two different variants, one called the Z variant and one called the S variant, that are represented as point mutations in the SERPINA1 gene. And cumulatively, it's interesting that 5% of all individuals in the United States have at least one of these. And obviously, there are some demographic differences between different population groups. But with a prevalence this high, you'll recognize a lot of people are carriers of one or another of these alleles. And, and with that, as a background, we'll really be talking mostly about the severe deficiency state in which you inherit one abnormal allele from each of your two individual parents. But we'll touch on the MZ and the MF carriers throughout the webinar as well.

Like all good webinars, we are going to end up starting with a case. And so case one is Sarah Jones, she's 60 years old, about the age at which most individuals present with their alpha-1. She's only been seen by her primary care physician for her respiratory conditions, which as we all know, is not infrequent with 80% of our COPD population cared for in the primary care clinics. And when she has a cold or the flu over the past 10 years, she has this little bit of white sputum and has some wheezing intermittently. She's now presenting with noticing more dyspnea on activities of daily living. She was a smoker of a pack per day from age 18 to age 28, but quit 32 years ago, emphasizing the importance of taking a complete smoking history. And the primary care physicians gave her an as needed LABA/inhaled corticosteroid of formoterol/budesonide. That helped and she uses it intermittently when one of her spells of cough and wheezing is present. And I think we all recognize this is not an uncommon presentation as we move into this group of patients that are beginning to have symptoms of either asthma or COPD, or a new designation of overlap syndrome. And so I'm going to hand this bucket over to Cheryl, and she's going to talk about what studies we should do as both primary care and pulmonologists, and what diagnosis does she have and does it matter. Cheryl, take it away.

Dr. Pirozzi:
Thanks, Dr. Strange. Well, first, we should start by getting some more data to evaluate and better characterize her lung disease. So we start with PFTs; spirometry following her formoterol/budesonide shows moderate airflow obstruction with an FEV1 of 60% predicted. Her laboratory evaluation shows just 2% eosinophils. Her cardiac stress test is normal. And then we get an alpha-1 antitrypsin level, which is

very low at 27 milligrams per deciliter. And genotyping for alpha-1 shows ZZ genotype.

So what is alpha-1 antitrypsin deficiency? Alpha-1 antitrypsin is a serine protease inhibitor that is primarily made in the liver and then released into the bloodstream. Ninety-five percent is produced in the liver. It's also produced in small amounts by kidney, lung, and epithelial cells. As a protease inhibitor alpha-1 antitrypsin inhibits proteases, which are enzymes that break down proteins, and this includes most importantly, neutrophil elastase, which destroys connective tissue within the lung. So alpha-1 inhibits neutrophil elastase in the lung, interstitium, alveoli and airways. And in doing so, it protects the lung from damage to structural proteins, which can lead to emphysema. It also has other anti-inflammatory and immunomodulatory effects in the body. Alpha-1 antitrypsin deficiency is a genetic disorder leading to low levels of alpha-1 antitrypsin, which leads to organ injury. In the lungs, this is a loss of function effect that leads to destruction of lung parenchyma. In the liver, it's a different mechanism. It's a gain-of-toxic-function mechanism that leads to an abnormal protein folding leading to liver disease. Lower concentrations of alpha-1 antitrypsin lead to eventual breakdown or degradation of alveoli, reducing pulmonary elastic recoil and airflow, and leading to emphysema. The lung manifestations are predominantly emphysema-predominant COPD, less often bronchiectasis, sometimes a combination. Accumulation of alpha-1 antitrypsin in the liver leads to cirrhosis and an increased risk for hepatocellular carcinoma. And the liver manifestations vary by age. Infants may develop cholestatic hepatitis, children may develop chronic liver disease. In adults, we see chronic hepatitis or cirrhosis, and it can coexist with NASH and other liver disease.

How do we identify patients at risk for alpha-1 antitrypsin deficiency? First, take a good family history. This is a genetic disease that occurs from a single gene. But it has really a very heterogeneous or variable clinical presentation. It is autosomal codominant inheritance, which means that both copies of the gene, one from the mother and one from the father, get expressed. And this occurs from mutations and their SERPINA1 gene, which alter the structure of the alpha-1 antitrypsin protein, and often cause deficiency of alpha-1 antitrypsin. There are actually over 200 abnormal alleles that have been identified, but the most common abnormal ones, as mentioned before, are Z and S, and we'll talk more about those. The normal allele is called M. The lower alpha-1 level, the higher the risk for lung disease.

This figure here illustrates the probability of gene combinations from two parents who are MZ the various combinations of how they can pass on their genes to their children. So you can see that from two MZ parents, about 25% of the kids will be MM, which is normal. About 50%, statistically, would be MZ, which is associated with a mildly reduced level of alpha-1, and then 25% would be ZZ, which leads to severe deficiency.

I'm going to talk a little bit more about the most common alpha-1 antitrypsin alleles. M allele is the name for the normal allele. Most people are homozygous MM, and don't have any clinical disease.

The S allele is the most common abnormal allele. This leads to moderately low levels of alpha-1 antitrypsin. It's associated with a milder deficiency, and it doesn't accumulate as much within the liver cells as Z so it's less likely to cause liver disease.

Z allele leads to very low levels of alpha-1 antitrypsin, and the Z phenotype accounts for 95% of clinical illness at both lung and liver disease that we see. MZ patients heterozygous for Z will have just mildly low or near normal alpha-1 antitrypsin levels, but they are still at increased risk of lung and liver disease.

And then finally, the null allele leads to no alpha-1 antitrypsin protein production. So, homozygous null individual will have no detectable serum or plasma levels of alpha-1. This leads to earlier lung disease, but no liver disease.

When you identify a patient with alpha-1 antitrypsin deficiency, you are actually discovering an entire family at risk for lung disease. This figure shows a family tree from a real family affected by alpha-1 antitrypsin deficiency. So you may see one individual with ZZ genotype, but this may lead to the discovery of many people with severe and mild deficiency who are at risk for clinical disease. And this is why it's important to talk with your patients about the genetics and also offer genetic testing the family members.

Alpha-1 antitrypsin deficiency is common, but it's very under-recognized. It is one of the most common potentially fatal congenital disorders in adults in the U.S. It's estimated that up to 25 million people in the U.S. carry mutant alleles. Between 3 and 8% of people in the U.S. carry the S allele, and between 2 and 4% carry the Z allele. So pretty common if you test for it. The prevalence for deficiency in the U.S. is between 1 in 2,800, and 1 in 5,000 people. This means that over 100,000 patients should have severe deficiency, and less than 15% of these patients are diagnosed. Of the 15 million patients with COPD, about 1% have undiagnosed alpha-1 antitrypsin deficiency. It's definitely more likely to be found in COPD patients, so this was a population study of about 1,000 emphysema patients, and 1.9% were ZZ, and 8% were carriers MZ.

How does alpha-1 antitrypsin present? Well, the signs and symptoms are essentially the same as non alpha-1 antitrypsin COPD. Patients will present with cough, sputum, shortness of breath, wheezing just like our patients. Lung function is also really indistinguishable from other forms of COPD. So patients will have airflow obstruction and reduced DLCO. Imaging with chest x-ray and CT - classically alpha-1 antitrypsin deficiency leads to more lower lobe predominant panacinar emphysema and bronchiectasis. But this is about two-thirds of patients, and imaging can vary quite a bit and people may present with upper lobe predominance, central lobular emphysema that's indistinguishable from non alpha-1 COPD. So if you only test for it in this really classic presentation, you're going to miss a lot of patients.

Exposures play a huge role in who develops lung disease and how early. Most important risk factor is cigarette smoking. This increases the onset of respiratory symptoms and lung disease by as much as 19 years. Secondhand smoke and vaping, we have less data about this and alpha-1 patients, but we can infer from data and non-alpha-1 patients that secondhand smoke and vaping likely also increased

risk for lung disease. Occupational exposures like mineral dust exposure, agricultural work, the World Trade Center workers, these have all been associated with reduced lung function in alpha-1 patients. And air pollution exposure has been associated with more rapid lung function decline. The lower the alpha-1 level, the higher the risk for lung disease, particularly in the presence of these exposures.

So who should be screened or tested for alpha-1 antitrypsin deficiency? Asymptomatic people with a family history of alpha-1 antitrypsin deficiency should be screened. And it's important to know that this is not included in the U.S. newborn screening. Then there should be diagnostic targeted testing of symptomatic persons with these conditions. Everybody with COPD should be tested for alpha-1 antitrypsin deficiency. All symptomatic adults with persistent airflow obstruction. If you do an SPEP and there's an absent alpha-1 peak, patients with asthma who have fixed airflow obstruction, or don't respond well to therapy with normal lung function, early onset pulmonary emphysema, whether or not they're a smoker; dyspnea and cough occurring in multiple family members in the same or different generations, anyone with unexplained bronchiectasis, anyone with unexplained liver disease, and adults who have necrotizing panniculitis or granulomatosis with polyangiitis, the ANCA vasculitis, those latter two are associated with alpha-1 antitrypsin deficiency because of the increased proteolytic activity.

So there are diagnostic challenges. Many people, particularly older adults, have alpha-1 antitrypsin deficiency, and less than 15% of appropriate patients are actually screened for alpha-1 antitrypsin deficiency. Diagnostic delays are very common, on average five to seven years in case series to actually diagnose alpha-1 antitrypsin deficiency. The average age of diagnosis is increasing. And many patients initially are misdiagnosed with other lung disorders, most often asthma.

This image shows age on the X axis, and FEV1 percent predicted on the Y axis in ZZ individuals who are smokers in blue, and non-smokers in red. And you can see that kind of, in general, smokers are more likely to present at a younger age and with a lower FEV1, but many individuals, trying to circle with the arrow here, still present with normal FEV1 or at an older age. And non-smokers are really all over the board. So if you only test the classic smokers with early onset emphysema, you're going to miss a lot of alpha-1 antitrypsin deficiency patients.

Diagnosis is laboratory-based. You can kind of screen with an alpha-1 antitrypsin level, this is a serum blood test. It's good to know that it's an acute-phase reactant, so the level will go up if someone is sick or inflamed, so it's best to test when someone is well or at their baseline. There's a lot of overlap between normal than heterozygous individuals. So you can sometimes miss heterozygous, if you're only testing for the level. If you have high suspicion or family history, then you should be doing genetic testing or the genotyping. If someone has low serum alpha-1 level and you move on to genotyping.

Phenotyping is the term for identifying alpha-1 antitrypsin protein variants by electrophoresis. Genotyping is the name for DNA testing that will determine the genes from extracted DNA. And the number of genes or alleles tested for varies by lab, at least S and Z alleles, but many labs do a lot of alleles. And now you can send a cheek swab to screen for the 14 most prevalent genetic mutations associated with alpha-1 antitrypsin deficiency. Whole-gene sequencing is sometimes used.

Age at diagnosis also varies quite a bit. This is a series of about 300 patients with ZZ. And you can see, you know, people are getting diagnosed at all ages. The most common age at diagnosis is 40s and 50s. But over half of people are diagnosed after age 50. So it's still important to think of this disease in older patients.

I'm going to move on to case two. This is a 50-year-old man who has smoked a pack and a half per day for the past 33 years who presents for a checkup with his primary care physician at the assistance of his daughter. He says he feels fine, but his daughter has been noticing that he is much less active than he used to be and he's struggling to go on longer walks with the family. He has cough productive of a small amount of mucus each morning and his primary care physician recommends smoking cessation, of course, and a lung cancer screening CT based on his age and smoking history. His low-dose lung cancer screening CT demonstrates no concerning nodules, but shows emphysema. And remember, cigarette smoking increases the onset of respiratory symptoms and alpha-1 antitrypsin deficiency by as much as 19 years. So what further evaluation is needed for this gentleman? I'll turn this back to Dr. Strange now.

Dr. Strange:
Well thanks, Cheryl. We know we are not doing such a good job in our lung cancer screening agenda, either; similarly to our alpha-1 testing agenda in America. I think the last numbers I saw were about 10% of eligible individuals are getting lung cancer screens. We have a big lung cancer screening CT program here at the Medical University of South Carolina.

The observations that I've made are that when you don't see any nodules on your first lung cancer screening CT, they say, ‘Congratulations, Mr. Jones, you've done well, you haven't gotten any lung cancers here.’ And, and then the emphysema that you can see on these scans, even though they're low dose is just generally glossed over. And so, you know, our attempt has been to try and integrate some COPD care into our lung cancer screening program here. And as you all know, there's a huge smoking cessation effort that is mandated to be part of these programs. We've had some interest in trying to figure out if there isn't an also an alpha-1 diagnostic opportunity here.

And so that kind of leads us into, you know, what would that look like in a CT screening program. And it's really hard because the manifestations of alpha-1 in the lung can be chronic bronchitis, asthma, or bronchiectasis. And it's interesting when we watch the alpha-1 cohort that we now care for, as to how they were first diagnosed, and the most common missed diagnostic opportunity was actually a doctor that called the first disease asthma. And when we watch these younger individuals move through, there are a lot of people like our first case, as well, that have a little bit of cough and wheeze, who respond to bronchodilators and, therefore, leave the office of

primary care, in particular with asthma. And yet they have this more adult-onset asthma-like phenotype and transition into them having dyspnea that is not completely reversible, which is the diagnosis of COPD.

And so, the more mucus that you make, you'd think that we would think more about chronic bronchitis and bronchiectasis being non-emphysema related, but the unique thing about our alpha-1 cohort is they do have a lot of airways disease as well. And so at the end of the day, it really comes down to laboratory diagnosis rather than trying to think that you can pick the alpha-1 patient out of any clinical cohort. And yet, when you do CT scans on the alpha-1 population, they have disproportionate degrees of emphysema compared to the non-alpha-1 COPD patients.

So when we look at our some of our larger patient registries, both from the alpha-1 registry that was done at the NIH, and some of them that were done through AlphaNet later, the majority of people do have respiratory symptoms. Sometimes they come and go. But more than half of these individuals had emphysema with an average diagnostic age about 45. But as Cheryl mentioned, that is increasing as we walk through time, and an amazingly high number have chronic bronchitis. And so I do think that it's enormously difficult to not test someone with COPD even up into the 70s and 80s because we find alpha-1 patients there.

And this whole process of figuring out who to test is a little bit frustrating when only 1% of all your patients are destined to have severe deficiency of alpha-1. But in this group of patients with more emphysema, we'll find higher numbers of alpha-1 patients.

So we turn that question around – "once you've been diagnosed with alpha-1 what should you get" has been a topic that we have not really done quite as good a job honestly possibly could have. We believe everybody needs pulmonary function tests with bronchodilator testing at first evaluation. But we do recommend yearly testing to figure out who the rapid decliners in lung function are within our alpha-1 population. We have a fair amount of oxygen use. Our Gestalt has been that there is more oxygen needed because of the lower lobe emphysema in alpha-1 than comparable populations of usual COPD. And we also think because of the emphysema, that we're going to have lower diffusing capacities of lung for carbon monoxide, or DLCO values in an alpha-1 population than a similarly affected usual COPD population.

And that's led us to at least do comprehensive lung function tests in your first visit, and then pick and choose at least one test annually for the follow-up after that. Having recognized those that a lot of these people have a bronchodilator response and to compare yearly the spirometry results, some of which have bronchodilators added and some don't, just increases the variability. And so we try and do all of our yearly follow-up spirometries with post bronchodilator testing.

We have made the recommendation in the most recent alpha-1 guidelines that everybody should get a CT scan. This is different than usual COPD. And the reason that the authors felt that this non-evidence-based guideline, because there are no studies comparing CT versus no CT that are prospective and randomized, was that a CT scan is really the only way to determine who has bronchiectasis as part of their care. Because we have a very high frequency of symptomatic bronchiectasis in the alpha-1 population, that in the best study by Pauwels et al, actually averaged about 27% of individuals. That presence of bronchiectasis, we believe changes management. We're going to be using more antibiotics, more nebulized saline, more airway clearance techniques for what otherwise might be called chronic bronchitis, if you don't know that your patient has bronchiectasis.

And the last difference in our alpha-1 population, and a little bit unique for pulmonologists, is that we do need to monitor these individuals for liver disease. And our recommendations are at least a yearly test. It's easy to send in an AST and an ALT laboratory test once a year as part of a liver panel. But these go up and down with lots of frequency in the ZZ population. And instead, we're really much more interested in progression of liver disease to fibrosis. And fibrosis leading to portal hypertension is the reason that platelets tend to fall and INR tends to elevate and bilirubin elevations and albumin declines are really very important events. Of all of these, the most sensitive seems to be a low platelet count. And so if you're doing screening in your alpha-1 populations in your pulmonary clinics once a year, we do believe a CBC with platelets is a cost effective, very good screen. And the thrombocytopenia that happens as part of liver disease is often misinterpreted out in the community as a risk for idiopathic thrombocytopenic purpura or some other risks. And really, this is just the first sign of liver disease that often shows itself.

We've been searching for a test that is not a liver biopsy to grade the degree of fibrosis in the liver with some accuracy and we haven't found one yet, but we do believe that some of our MR techniques such as magnetic resonance elastography or vibration-controlled transient elastography, the brand name of which is FibroScan, will hold some value here. It's just these studies are only now being done in our alpha-1 population.

Commonly we are in the situation of knowing someone who has alpha-1 and then all the questions on lifestyle start moving into our practice. And so we do believe that everybody should be tested for hepatitis A and B, and C. Remember that our new hepatitis C testing recommendations are all individuals over the age of 18 should get a hepatitis C serology at least once, and more commonly with pregnancies and risk factors for other lifestyle abnormalities.

We don't know really what to say about alcohol intake, because we don't have very many clinical measures that the casual alcohol user has more risk of liver disease in our alpha-1 population. But if you do have cirrhosis or the stage of Metavir-4 fibrosis, everybody in the alpha-1 community and hepatology are aligned that alcohol intake should stop.

The most common that liver disease in America today associated with alpha-1 is actually a concomitant presentation with NASH, non-alcoholic steatohepatitis with alpha-1, and this is sometimes seen in our MZ carrier population. And so our recommendation to our alpha-1 population there is to maintain a lean body mass, stay skinny, treat your cholesterol, try not to get diabetes and metabolic syndrome.

And so this is our clinical evaluation of this group of individuals. And this wouldn't be done if you were just treating COPD. We think it's important to make the alpha-1 diagnosis.

The next set of topics in our clinic discussions really come around the issues of lifestyle and air quality. And as you all know, the ATS just put out their statement on wildfires and their effect on lung function. And so just recognize that the alpha-1 deficient population has less protection of the lungs for events that bring neutrophils into the lungs. And so this is the anti-neutrophil elastase protection is low, than anything cigarette smoking included, that brings neutrophils into the lungs, will likely cause more lung disruption and progression of emphysema compared to the normal situation. And so we show this diagrammatically here, but I think the point here, as we move from the deficiency state into therapy, which actually adds back alpha-1 and increases the protection of the lung, is that the other option is to decrease the events that bring neutrophils to lung and respiratory infections.

So we are a really aggressive community in alpha-1 trying to decrease infection risk. And we probably give a few more antibiotics than we should if you were just treating chronic bronchitis in an outpatient community practice due to usual COPD, just worried about the concomitant progression of emphysema that happens with excess neutrophils.

Well, this guy as you might imagine, showing up with his screening lung CT scan as emphysema obviously has alpha-1 antitrypsin deficiency, and his genotype also shows the ZZ deficiency. And so we're going to use his case to now transition into further evaluation and treatment, and what should be considered.

I think we've already touched upon this basis by which we're trying to figure out which individuals in the United States or in the world actually need therapy. And the therapies that we apply using intravenous augmentation therapies are designed to raise the alpha-1 level. And the ZZ and Z-null populations on the graph to the right have very low levels and the highest clinical rates of emphysema. So if you go screening your COPD population, you'll find a lot more of these carry MZ and SZ and MZ individuals, and the SZ, ZZ, and Z-null individuals are the individuals that we have more typically treated. A little bit of this depends onto the lab in which is tested. This theoretic protective threshold of 11 micromoles per liter, or equivalent to 57 milligrams per deciliter has been a threshold that was tested knowing that the majority of SZ individuals do not get emphysema and it crosses right through that 11 micromolar threshold. We wonder whether that threshold should be closer to 20, and the goal of all of our therapies are to get levels higher than 11. But you'll never find a ZZ individual, more than 11 micromoles per liter in their presentation. And so one of those questions where Cheryl presented that yes, you can have an acute-phase response. And in the inflamed state, these can send the MZ individual levels up into normal, this doesn't mean that I don't test my patients in the ICU with pneumonia that have COPD if they've not been tested for alpha-1 before, because if I find a ZZ in that venue, then they are going to never get a high alpha-1 level as well.

So I end up testing for alpha-1 whenever I see COPD has not had a previous alpha-1 test. I guess I have some biases there. But those are our guidelines in the ZZ, the Z-nulls, and SZs are usually not going to make it into the normal level with that strategy.

We are going to transition for the rest of our talk. And we have about half an hour into current treatments and to talk a little bit about some of the future treatments in the pipeline. And we've alluded to some of these already. And you know, it's really hard when you have a brand-new alpha-1 patient in your clinic, because the education about the disease state and the family testing and the liver disease and all the different immunizations and the environmental exposures to reduce risk, take about a two-hour time interval. And so we have lots of support in the alpha-1 community to help you with that. We'll talk more about the support of the patient organizations themselves later in the talk. But recognize this is also there are a group of physicians and other healthcare professionals in the United States to join together to really be a network to help the patients move along through this whole diagnostic and therapeutic journey.

As far as reducing symptoms, we believe most people are going to respond at least early on to bronchodilator therapy, even though they have emphysema. We use inhaled steroids similarly as we do to prevent exacerbations in the alpha-1 population. When I get people referred to me for alpha-1, the most frequent recommendation that I make that hasn't been done by referring physicians is actually the get-up-and-go-exercise agenda associated with pulmonary rehabilitation.

The treatment of acute exacerbations is supplemental oxygen, we don't think is any different. And I would only mention that these exacerbations are the times that bring excess neutrophils into the lungs. And so we really believe that you should allow, if someone on an alpha-1 augmentation therapy, that therapy to move into the hospital with the patient and get their infusion at the time in which they need it the most, which is the time to protect their lungs during a pneumonia or a severe neutrophil-rich acute exacerbation of COPD.

Our key that we're going to talk on for the next few minutes is to try and reduce lung destruction with augmentation therapy. This is once-a-week I.V. therapy that has been out there for more than 25 years now. We do have advanced therapies. Lung transplantation. We also have at least some treatment experience within the bronchial valves if fissures are intact on CT scan. What we do not believe should be done is lung volume reduction surgery and that this panacinar emphysema with decreasing the lower lung predominant emphysema by surgery, just leads to airspace enlargement as the rest of the lung goes and fills that space. And they experience out of the NETT, the National Emphysema Treatment Trial, was not a positive experience in the alpha-1 subpopulation that went into that study.

So we do believe that preventing exacerbations is just as important if not more so in the alpha-1 population than the usual COPD population, because they're associated with all-cause mortality and accelerate decline in lung function. And they're really common in the alpha-1 patient community.

One of our missed opportunities, we've really tried to see if augmentation therapy decreases exacerbations and have not found that signal yet. And so this may prompt a CT scan to look for bronchiectasis if you haven't already done it. And with that, we end up using a

fair number more antibiotics if bronchiectasis is found. We will use inhaled steroids. There is an experience with daily azithromycin and roflumilast, but it really hasn't been encapsulated in the alpha-1 population to the extent that there probably should have been.

So our unique therapy, unique to alpha-1, is I.V. alpha-1 augmentation therapy. This is called alpha-1 proteinase inhibitor based upon the FDA's label of these, but it's really just alpha-1 antitrypsin. As a pooled human alpha-1 preparation, so when you go to your plasma center and donate your plasma, it takes a bath of about 5,000 persons combined donations to make a batch of alpha-1. It then goes through quality testing over and above what each individual donor goes through to make sure that there are no infectious organisms moving through the production pipeline. So 25 years' experience has been really remarkable because even though we have theoretic risks of viral infections, there have been none transmitted, no HIV, no hepatitis A, B, C transmitted, and it's been an amazingly good safety profile that's been accumulated.

The obvious problem here is the high cost. It average is more than $100,000 per year. The average patient copay is somewhere between $1,000 and $2,000 in the United States, and different in different countries.

We will talk in a minute about when to start therapy, but we really don't have data on when to stop I.V. therapy because our recent data, Dr. 40:55 ___ had a paper that, just this past year, showing that there are mortality benefits even when FEV1 is really quite low, down to as low as 10%. The reason this therapy works is that it raises the alpha-1 levels, particularly in that first hour after infusion, and then there's a gradual decline over the course of the next week, allows for the next infusion to occur at the end of that period of time. Our four U.S. preparations are Prolastin-C liquid, and Glassia liquid, which is also FDA approved for home self-infusion, and then Aralast NP and Zemaira, which are lyophilized preparations that are mixed at the bedside before infusion.

The intravenous infusions send the blood levels up usually quite high. This has been tolerated amazingly well, even in liver-affected individuals. We very rarely have people with congestive heart failure that can't tolerate the extra protein load. We have a fair experience of giving that double-dose therapies every two weeks during times of travel for patients. We believe that is the safe thing to do. Our recommendation on who to start this therapy is really following the package inserts and our large treatment trials that have been done.

The conundrum here is that emphysema severity doesn't really track very well with FEV1. And we think FEV1 is not a very good measure of emphysema severity. And we'll occasionally see people with very advanced emphysema with near-normal FEV1's. For whatever reason, they have very minimal airways disease and therefore they can expel air and that first second really, really well.

The best evidence for effectiveness found in the NIH registry back in the early 1990s was between FEV1's of 30 and 65% predicted, but if you have emphysema and symptoms, that FEV1 is greater than 65%, we really believe that patients have benefit, after discussing the risks and the costs and the potential benefits in this rare disease population.

We have a unique opportunity in necrotizing panniculitis where the inflammatory, painful fatty disease that happens often on the buttocks and on other fatty areas of the body regresses. There are some very aggressive panniculitis patients in the United States that require higher-dose therapy occasionally.

We do believe that there are some dysfunctional alpha-1 alleles that are rare, like the F allele that have normal blood levels but deficiency genotypes. Cheryl mentioned the 14 variant tests buccal swabs that picks up the F or the I alleles, is another one similar to this. And when you combine that with the Z allele or have a homozygous state of FF or II, then those individuals we think should receive therapy even with levels greater than 11 micromolar.

We do have a fair amount of use in MZ genotypes the United States that we think is not recommended, and there have been no treatment trials in an MZ population that have been done, much less shown benefit. And we don't believe we should be giving this extensive therapy to those who don't participate in their own health improvement by smoking cessation.

Liver disease is not affected by the infusion, so we don't believe that's an indication for treatment. And after liver transplantation, this is actually the ultimate replacement of your dysfunctional genes in the organ that matters most because after a liver transplantation, your alpha-1 levels would return to normal because presumably you got your liver transplantation from an MM individual. Although there have been some transplants of alpha-1 livers into alpha-1 patients, unfortunately, in a family cohort, so think about that one if you run a liver transplant center. If you don't have airflow obstruction at all, and you have no symptoms, but you're ZZ, we believe you should be watched and not receive therapy.

We do have some data. And our first randomized placebo-controlled trial called RAPID, and is open label extension, were studies done in large numbers of alpha-1 with a special test called CT densitometry. And our argument here is that CT density really correlates with the severity of emphysema better than anything else that we do, and is better than FEV1 at actually measuring the abnormality associated with alpha-1. The open label extension trial also gave us some rates of decline in the CT emphysema, or rates of progression of emphysema on the CT scan.

And so RAPID was a two-year study looking at CT densitometry with five CT scans, and in the group receiving alpha-1 protease inhibitor in the teal color on the top, the decline over two years, and the mean was negative 1.51 grams per liter per year. And I think the point is that this is actually tissue being lost in the lungs of all of us. And these individuals were on placebo, on the total lung capacity scans that rate was almost one and a half times faster.

At the end of two years, patients were offered the extension in which everyone got alpha-1 protease inhibitor, in this case with Zemaira for the study group. And what happened here was that the rate of CT density declined parallel that of the population, and in the teal color

in the second year where alpha-1 therapy was followed by more alpha-1 therapy, there was no statistical difference between the rates of decline, suggesting that changing the slope of emphysema progression is a really important outcome measure for this group of the of these therapies. There are ongoing therapies looking at higher dose. We still have lots of questions around dosing, and those will be presented to the FDA when those are complete.

I think we're going to move on now to talk about some of the therapies in the pipeline for a minute or two before we take questions. So don't be afraid to start putting in some of your questions here as we move through our experimental therapies.

We've had experiments with inhaled alpha-1 therapies for many years. These inhaled therapies were very high concentrations in the airways. And yet we believe that emphysema occurring at the blood vessel and lung disease interface, and whether we can keep one tissue together and prevent emphysema progression with an inhaled therapy or not, will require additional trials. None of these trials have been powered sufficiently to look at emphysema progression. This time, what we know is that inhaled alpha-1 is safe. But it's not an FDA approved mechanism. We forever have been looking at recombinant alpha-1 trying to get the price down. And if we could get alpha recombinant and alpha-1 to a cheaper price point, then more patients would be able to receive this therapy around the world.

The current trials, when you just give the protein in its amino acid structure, it has a very short half-life, and you don't have the carbohydrate side chains associated with a native molecule, they give it a longer half-life as in a pooled plasma preparation. But the current trials going on by a company called Inhibrx have two alpha-1 recombinant molecules with an FC fragment of immunoglobulin in the middle of that too, that slows its release, slows its degradation inside the body and gives a very much longer half-life that might allow for as long as three-week interval of infusion.

Gene therapy trials are still in the works, and people are still trying to crack this nut. I think the hardest thing about alpha-1 is that it's a bulk protein, and these grams of alpha-1 have to be made every day to move through the bloodstream and into the lung, are very hard gene therapy targets to achieve. There are some small molecular weight correctors that look to improve the folding of alpha-1 inside the hepatocyte and allow this molecule to come through and out into the bloodstream. This would presumably correct both the lung and the liver disease if these correctors could be found to be strong enough and powerful enough.

There are moving through pathways for the large number of oral elastase inhibitors, specifically pills that would block neutrophil elastase within the lung. That might work for COPD in general without alpha-1 as well.

And lastly, on our list are the RNA-I therapies. These are inhibitors of transcription of alpha-1 within the hepatocyte that could cut off alpha-1 production in the liver, and therefore, presumably, cure liver disease. And so these are moving along nicely through Phase 2 studies at the FDA and look to prevent alpha-1 formation in the liver. And what we'll need for FDA approval there is probably similar to hepatitis C, once the offending agent is removed from the liver, then we'll have less reason to have to use other therapies and presumably prevent liver disease progression, if not make it better.

Cheryl, let's let move into what else to do for liver disease? I've run over on time a little bit, but we've still got some time here.

Dr. Pirozzi:
All right, well, I'll talk briefly about the alpha-1 antitrypsin related liver disease. Some of this we've touched on already.

Liver disease is most often associated with Z variants, although there are a few other rare alleles that can cause liver disease. The genetic mutation causes synthesis of a mutant protein, which abnormally folds in the endoplasmic reticulum of the hepatocytes. And so this prevents it from being secreted into the blood. Essentially, it gets stuck in the liver and polymerizes and this is what leads to liver injury, and cirrhosis and it increases risk for hepatocellular carcinoma. In ZZ individuals, fibrosis is not that uncommon; 35% will have liver fibrosis on biopsy. Although it's a lower percentage that have clinically significant disease. And MZ genotype is a strong risk factor for cirrhosis in the presence of other liver diseases like NASH.

So about 10% of ZZ patients get clinical liver disease. In infants, this can present with neonatal hepatitis as jaundice, sometimes death. It's often undiagnosed. It's not on the newborn screening panel. Some of these infants have been found to have a second defect in modifier genes in the autophagy pathways that leads to decreased degradation of the Z molecules and the liver cells, so kind of like a second hit. Seven percent of these infants will then develop liver cirrhosis.

In adults, liver disease is more occult until they develop portal hypertension and the associated signs and symptoms of that. The most sensitive test again is the low platelet count. Transaminase elevations are often mild, don't correlate well with the fibrosis score. And the biggest comorbidity is obesity. Alcohol use has effect as well. And we see liver disease in ZZ and MZ populations. Null alleles do not cause liver disease because there's no abnormal protein produced.

And the only effective therapy is liver transplant. The good news is that the new liver then makes normal alpha-1 protein after transplant, and the person no longer needs augmentation.

So we screen yearly for liver disease in adults after age 45 or 50. Because the traditional liver panel is often normal, we also will check platelets, which are the most common abnormality. The AST to platelet ratio is sometimes used for risk stratification.

And then for imaging, there are some newer options. You could do liver stiffness measurements with vibration-controlled transient elastography. That's what FibroScan is. And then there's an emerging role for MRI elastography as well. It's recommended that all alpha-1 individuals undergo liver ultrasound at the time of diagnosis, both for risk stratification and exclusion of cancer. But that's not as sensitive for liver fibrosis until cirrhosis is present.

Dr. Strange you want to finish us up and lead into questions?

Dr. Strange:
Well, sure. I guess our summary is that alpha-1 is underdiagnosed, and that's all of our jobs. And it's really a difficult topic. I think a lot of clinics lead by example. So if you and your clinic are testing every patient with COPD for alpha-1 and find one occasionally, then that's the best that we could ask for. And you're setting a good example for all the primary care doctors that are referring to you.

You know, the hard part here is that there are lots of different pulmonary presentations, emphysema, bronchiectasis, and asthma. It's not a very homogeneous clinical presentation, and you can't make the diagnosis without testing systematically. It's a once-in-a-lifetime targeted test alpha-1 levels at our medical center call $17 once in a lifetime to try and find those ZZ individuals. And if you have a low level, we then research the genotype testing to get the actual alleles involved.

The missed patients are those with asthma whose spirometry does not return to normal, which is the definition of COPD. And as we all know, a lot of primary care misses the opportunity to get a spirometry and that asthma has completely normal spirometry after therapy, and that's really the time to make sure that it's not COPD. And we truly believe that augmentation therapy is effective at decreasing progression of emphysema.

And thank everybody for attending today's webinar on alpha-1 antitrypsin deficiency. Thanks, Cheryl.

Dr. Pirozzi:
Thank you.

Announcer:
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