OCTOBER 2022

RARE NEUROLOGICAL DISEASE

SPECIAL REPORT

SELECTED ARTICLES

NORD® National Organization for Rare Disorders

NEUROLOGY REVIEWS

NOW APPROVED

amvuttra™ (vutrisiran) injection 25 mg/0.5 mL

AMVUTTRA™ (vutrisiran) is an RNAi therapeutic given once every 3 months as a subcutaneous injection to treat the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults.[1]

Visit **www.amvuttrahcp.com** for more information and to sign up for updates

Indication

AMVUTTRA™ (vutrisiran) is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Important Safety Information

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Adverse Reactions

The most common adverse reactions that occurred in patients treated with AMVUTTRA were arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).

Please see Brief Summary of full Prescribing Information following this ad.

RNA=ribonucleic acid; RNAi=RNA interference.

Reference: 1. AMVUTTRA Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.

Alnylam® PHARMACEUTICALS

AMVUTTRA™ (vutrisiran) injection, for subcutaneous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

AMVUTTRA is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of AMVUTTRA is 25 mg administered by subcutaneous injection once every 3 months.

Missed Dose

If a dose is missed, administer AMVUTTRA as soon as possible. Resume dosing every 3 months from the most recently administered dose.

Administration Instructions

AMVUTTRA is for subcutaneous use only and should be administered by a healthcare professional.

DOSAGE FORMS AND STRENGTHS

Injection: 25 mg/0.5 mL of vutrisiran as a clear, colorless-to-yellow solution in a single-dose prefilled syringe.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AMVUTTRA cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Study 1, a total of 122 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) received AMVUTTRA. Of these, 118 patients received at least 9 months of treatment and 34 patients received at least 15 months of treatment. The mean duration of treatment was 12.9 months (range: 1.7 to 19.3 months). The median patient age at baseline was 60 years and 65% of the patients were male. Seventy percent of AMVUTTRA-treated patients were Caucasian, 17% were Asian, 3% were Black, and 9% were reported as Other. Forty-four percent of patients had the Val30Met mutation in the transthyretin gene; the remaining patients had one of 21 other mutations. At baseline, 70% of patients were in Stage 1 of the disease and 30% were in Stage 2.

The most common adverse reactions (at least 5%) were arthralgia, dyspnea, and vitamin A decreased.

In Study 1, patients were instructed to take the recommended daily allowance of vitamin A *[see Warnings and Precautions]*. Seventy-four percent of patients treated with AMVUTTRA had normal vitamin A levels at baseline, and 98% of those with a normal baseline developed low vitamin A levels. In some cases, the decreased vitamin A level was reported as an adverse reaction.

Table 1: Adverse Reactions Reported in at least 5% of Patients Treated with AMVUTTRA (Study 1)

Adverse Reaction	AMVUTTRA N=122 (%)
Arthralgia*	11
Dyspnea*	7
Vitamin A decreased†	7

*Comprised of several similar terms

†Percentage only reflects those reported as an adverse reaction

Two serious adverse reactions of atrioventricular (AV) heart block (1.6%) occurred in patients treated with AMVUTTRA, including one case of complete AV block.

Injection site reactions were reported in 5 (4%) patients treated with AMVUTTRA. Reported symptoms included bruising, erythema, pain, pruritus, and warmth. Injection site reactions were mild and transient.

Immunogenicity

As with all oligonucleotides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In Study 1, 3 (2.5%) patients treated with AMVUTTRA developed anti-drug antibodies. Although anti-drug antibody development was not found to affect the pharmacokinetics, safety, or efficacy of AMVUTTRA in these patients, the available data are too limited to make definitive conclusions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on AMVUTTRA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. AMVUTTRA treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking AMVUTTRA. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effects on the fetus of a reduction in maternal serum TTR caused by AMVUTTRA and of vitamin A supplementation are unknown *[see Warnings and Precautions, and Clinical Pharmacology (12.2) in the full Prescribing Information]*.

In animal studies, subcutaneous administration of vutrisiran to pregnant rats resulted in developmental toxicity (reduced fetal body weight and embryofetal mortality) at doses associated with maternal toxicity *(see Data on the next page)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Subcutaneous administration of vutrisiran (0, 3, 10, or 30 mg/kg/day) to pregnant rats during the period of organogenesis resulted in embryofetal mortality at the high dose and reduced fetal body weight at the mid and high doses, which were associated with maternal toxicity.

Subcutaneous administration of vutrisiran (0, 3, 10, or 30 mg/kg/day) to pregnant rabbits resulted in no adverse effects on embryofetal development.

Subcutaneous administration of vutrisiran (0, 5, 10, or 20 mg/kg) to pregnant rats every 6 days throughout pregnancy and lactation resulted in no adverse developmental effects on the offspring.

Lactation

Risk Summary

There is no information regarding the presence of vutrisiran in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMVUTTRA and any potential adverse effects on the breastfed infant from AMVUTTRA or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No dose adjustment is required in patients ≥65 years of age *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. A total of 46 (38%) patients ≥65 years of age, including 7 (6%) patients ≥75 years of age, received AMVUTTRA in Study 1. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73m^2) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. AMVUTTRA has not been studied in patients with severe renal impairment or end-stage renal disease.

Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. AMVUTTRA has not been studied in patients with moderate or severe hepatic impairment.

Manufactured for: Alnylam Pharmaceuticals, Inc., Cambridge, MA 02142

Alnylam PHARMACEUTICALS

RARE NEUROLOGICAL DISEASE SPECIAL REPORT

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EDITOR'S NOTE

Thankfully, the COVID pandemic has not killed the spirit of innovation and the relentless search for answers in the rare disease community. There were several notable FDA approvals in 2021 and early 2022, emerging genetic therapies for monogenetic disorders, and recent advances in rare disease diagnosis and testing. This 7th annual issue of the Rare Neurological Disease Special Report highlights some of these developments.

For those of you who have been following the Rare Neurological Disease Special Report over the years, it is with great pride that I report that last year's issue won a prestigious B2B award. The 2021 issue, our 6th annual issue, won an American Society of Business Publication Editors (ASBPE) Silver Regional Award for excellence in an annual publication. It has been our honor over the years to partner with the National Organization for Rare Disorders (NORD) to serve the rare neurological disease community. That effort is rewarding enough. Winning an award is icing on the cake but much appreciated.

—Glenn S. Williams, VP, Group Editor
Neurology Reviews and MDedge Neurology

Peter L. Saltonstall

A NOTE FROM NORD

The National Organization for Rare Disorders (NORD) is tremendously grateful to the dedicated health care professionals who, despite long days and heavy workloads, continue to seek the latest information on medical advances that might be helpful to their patients. Please know that your commitment and support are tremendously important to the patients and families whom we serve.

As you may be aware, NORD is a nonprofit organization that was established in 1983 to provide advocacy, education, patient/family services, and research on behalf of all Americans affected by rare diseases and the medical professionals providing their care.

As we approach NORD's 40th anniversary, it is astonishing to realize how far we all have come since the early 1980s, when rare disease patients and their medical providers were essentially on their own to navigate the challenging waters of rare disease diagnosis and treatment.

Today, we are living in one of the most exciting periods in medical history, with innovative new diagnostics and treatments being developed or on the horizon. You'll find information about these medical advances, as well as resources for yourself and your patients, on the NORD website (www.rarediseases.org) including our Rare Disease Database, Video Library, CME programs and resources, and newsletter for medical professionals.

You'll also find information about the annual NORD Rare Diseases and Orphan Products Breakthrough Summit, the largest annual conference for professionals and patients in the rare community, along with our annual conference specifically for patients and families, the "Living Rare, Living Stronger Family Forum."

This issue of the Rare Neurological Disease Special Report features articles from rare disease medical experts on specific diseases, including spinal muscular atrophy, Pompe disease, and Rett syndrome, as well as more general topics such as genetic therapies for neuromuscular diseases.

Also in this issue are articles on new and exciting initiatives such as the "NORD Rare Disease Centers of Excellence." These 31 centers, geographically dispersed across the nation, represent an attempt to provide a strong, national network of support for both patients and medical professionals to promote earlier diagnosis and optimal care, regardless of location.

An interview in this issue with one of NORD's longtime medical advisors and a leading rare disease expert provides advice for community physicians and other HCPs related to diagnosing rare diseases and approaches that may help shorten the diagnostic odyssey for patients. In addition, you can read about how patient advocacy organizations are collecting and managing a precious asset – patient data – to advance understanding of diseases, even extremely rare ones, and support research.

We are grateful for the work you do and for your commitment to your patients, including those with extremely rare or newly identified diseases. We invite you to visit the NORD website often, sign up for our newsletter for medical professionals and contact NORD at any time if we can be helpful to you.

—Peter L. Saltonstall, president and CEO
National Organization for Rare Disorders (NORD)

Health care providers should have higher suspicion for rare diseases

Learning to recognize when a cluster of symptoms doesn't fit a pattern is important, as patients and their providers tend to gravitate toward diagnoses they are used to seeing, rather than suspecting a disease outside a usual pattern.

By Jeff Craven

The number of cataloged rare diseases continues to grow every day. According to the National Human Genome Research Institute, more than 6,800 rare diseases have been identified and between 25 million and 30 million Americans are living with rare diseases today.

Rare diseases have collectively emerged as a unique field of medicine with an "entirely new generation of conditions," said Marshall L. Summar, MD, chief of the division of genetics and metabolism at Children's National Hospital in Washington. He places the number of rare diseases closer to 8,000, and said it is "growing by a rate of 10 to 12 a week."

Although the field has made significant advancements in health care providers' ability to diagnose rare diseases, it has also highlighted what isn't known as well, said Dr. Summar, who is also past president and a former scientific advisory board member with the National Organization for Rare Disorders (NORD).

Keeping up to date on the latest rare diseases may seem like a daunting task to the average health care professional. However, while rare diseases remain the domain of the subspecialists, the generalist "can make a tremendous impact for their patients" early in the process by having a higher suspicion for rare diseases in their practice, said Dr. Summar.

Thinking of rare diseases in categories

Many patients with undiagnosed rare diseases undergo what's commonly referred to as a "diagnostic odyssey," moving from one provider to another to try to find an explanation for a condition they may or may not know is rare. For some patients, this process can take many years or even decades. From the patient's perspective, the main challenges are recognizing they have a problem that doesn't fit a common disease model. Once they recognize they have a potential rare disease, working with a provider to find the right diagnosis among the "vast number of disease diagnoses and designations, and actually sifting through it to find the one that's right for that patient" is the next challenge, said Dr. Summar.

Marshall L. Summar, MD

However, knowledge of rare diseases among health care professionals is low, according to a 2019 paper published in the Orphanet Journal of Rare Diseases.[1] In a survey from that paper asking general practitioners, pediatricians, specialists caring for adults, and specialists caring for children to evaluate their own knowledge of rare diseases, 42% of general practitioners said they had poor knowledge and 44% said they had a substandard understanding of rare diseases.

From a clinician's standpoint, diagnosing rare diseases in their patients can be challenging, with the potential for overreferral or overdiagnosis. However, it is also easy to underdiagnose rare diseases by missing them, noted Dr. Summar. This issue can vary based on the experience of the provider, he said, because while general practitioners who recently began practicing may have had more exposure to rare diseases, for health care professionals who have been practicing for decades, "this is a new arrival in their field."

During a busy day finding that extra time in an appointment to stop and question whether a patient might have a rare disease is another problem generalists face. "It is really tough for those general practitioners, because if you see 40 or 50 patients per day, how do you know which one of those [patients] were the ones that had something that wasn't quite fitting or wasn't quite ordinary?" he said.

When it comes to considering rare diseases in their patients, health care professionals in general practice should think in categories, rather than a particular rare disease, according to Dr. Summar. As the generalist is typically on the front

Jeff Craven is a freelance journalist specializing in medicine and health.

lines of patient care, they don't necessarily need to know everything about the rare disease they suspect a patient of having to help them. "You don't need to know the specific gene and the specific mutation to make the diagnosis, or to even move the patient forward in the process," he said.

The first steps a clinician can take include noticing when something with a patient is amiss, thinking about the disease category, and then creating a plan to move forward, such as referring the patient to a subspecialist. Learning to recognize when a cluster of symptoms doesn't fit a pattern is important, as patients and their providers tend to gravitate toward diagnoses they are used to seeing, rather than suspecting a disease outside a usual pattern.

The framing of rare diseases as categories is a change in thinking over the last decade, said Dr. Summar. Whereas rare disease diagnoses previously focused on fitting certain criteria, the development of more refined genetic sequencing has allowed specialists to focus on categories and genes that affect rare diseases. "Getting at a diagnosis has really been turned up on its head, so that by employing both next-generation sequencing, newborn screening, and other [tools], we can actually get to diagnoses faster than we could before," he said.

In terms of assessing for symptoms, health care professionals should be aware that "common" symptoms can be a sign of rare disease. What to look out for are the uncommon symptoms that create an "aha moment." Having a "good filter" for sensing when something isn't quite right with a patient is key. "It's like any time when you're screening things: You want high sensitivity, but you also have to have high specificity," he said.

Another clinical pearl is that good communication between patient and provider is paramount. "We're not always good listeners. Sometimes we hear what we expect to hear," said Dr. Summar.

Rare disease warning signs

Within the context of rare neurological diseases, Dr. Summar noted one major category is delays in neurological development, which is typically identified in children or adolescents. As the most complex organ in the body, "the brain probably expresses more genes than any other tissue on a regular basis, both in its formation and its function," said Dr. Summar. He said the single disease that rare disease specialists see most often is Down syndrome.

Another separate but overlapping major category is autism, identified in younger children through trouble with social interaction, lack of eye contact, and delays in speech and communication skills. A third major category is physical manifestations of neurological problems, such as in patients who have epilepsy.

A telltale sign in identifying a child with a potential rare neurological disease is when they are "not thriving in their development or not doing the things on track that you would expect, and you don't have a really good answer for it," said Dr. Summar. Generalists are normally on watch for developmental delays in newborns born premature or with a rough course in the nursery, but they should also be aware of delays in children born under otherwise typical circumstances. "If I have a patient who had normal pregnancy, normal labor and delivery, no real illnesses or anything like that, and yet wasn't meeting those milestones, that's a patient I would pay attention to," he said.

Another clue general practitioners can use for suspecting rare diseases is when a patient is much sicker than usual during a routine illness like a cold or flu. "Those are patients we should be paying attention to because it may be there's an underlying biochemical disorder or some disorder in how they're responding to stress that's just not quite right," said Dr. Summar. How a patient responds to stressful situations can be a warning sign "because that can often unmask more severe symptoms in that rare disease and make it a little more apparent," he said.

Learning more about rare diseases

Dr. Summar said he and his colleagues in the rare disease field have spent a lot of time working with medical schools to teach this mindset in their curricula. The concept is introduced in basic medical science courses and then reinforced in clinical rotations in the third or fourth year, he explained.

"One of the best places is during the pediatrics rotations in medical school," he said. "Remember, kids are basically healthy. If a child has a chronic illness or a chronic disease, more often than not, it is probably a rare disease."

For medical professionals not in pediatric practice, the concept is applied the same way for adult medicine. "You just want to make sure everyone takes a second when they have a patient and try not to assume. Don't assume it's exactly what it seems. Look at it carefully and make sure there's not something else going on," he said.

Health care professionals in general practice looking to learn more about rare diseases can increasingly find rare disease topics in their CME programs. Rare disease topics in CME programs are "one of the best places" to learn about the latest developments in the field, said Dr. Summar.

Will rare disease screening tools come to primary care?

Asking more doctors to refer out to rare disease specialists raises an issue: There simply aren't enough rare disease specialists in the field to go around.

Dr. Summar said partnering testing – where a general practitioner contacts a specialist to begin the process of testing based on the suspected condition – is a good stopgap solution. Telemedicine, which rose in popularity during the COVID-19 pandemic, can also play an important role in connecting patients and their providers with rare disease specialists, especially for generalists in remote communities. Dr. Summar noted he continues to see approximately 30% of his patients this way today. Telemedicine appointments can take place in the patient's home or at the provider's office.

"It actually provides access to folks who otherwise might not be able to either take off from work for a day – particularly some of our single parent households – or have a child who just doesn't travel well, or can't really get there, even if it's the patient themselves," he explained. "We can see patients that historically would have had trouble or difficulty coming in, so for me, that's been a good thing."

Telemedicine also helps give access to care for more medically fragile patients, many of whom have rare diseases, he added. While some aspects of care need to occur in person, "it's a good 80% or 90% solution for a lot of these things," he said.

Sharing educational videos is another way for health care providers in general practice to inform patients and their families about rare diseases. Children's National Medical Center has created a collection of these videos in a free app called GeneClips, which is available on major smartphone app stores. However, Dr. Summar emphasized that genetic counseling should still be performed by a rare disease specialist prior to testing.

"We're still at the point where I think having genetic counseling for a family before they're going into testing is really advisable, since a lot of the results have a probability assigned to them," he said. "I don't think we're really at the level where a practitioner is going to, first of all, have the time to do those, and I don't think there's enough general public awareness of what these things mean."

Although primary care providers may one day be able to perform more generalized sequencing in their own practice, that time has not yet come – but it is closer than you think. "The technology is there, and actually the cost has come down a lot," said Dr. Summar.

One potential issue this would create is an additional discussion to manage expectations of test results with family when the results are unclear, which "actually takes more time than counseling about a yes or no, or even an outcome that is unexpected," explained Dr. Summar.

"[W]e're in a midlife period right now where we're bringing forward this new technology, but we've got to continually prepare the field for it first," he said. "I think in the future we'll see that it has much greater utility in the general setting," he said. ■

REFERENCE

1. Vandeborne L et al. Information needs of physicians regarding the diagnosis of rare diseases: A questionnaire-based study in Belgium. Orphanet J Rare Dis. 2019;14(1):99.

The paradox of Pompe disease

For nearly 2 decades, patients with even the most severe genetic mutations have been surviving on therapy. But clinicians must now contend with previously unknown manifestations of this rare muscular disease.

By Jennie Smith

Until 2006, when a breakthrough therapy first made treatment possible, Pompe disease was a little-known metabolic myopathy fatal to infants. Those with later-onset disease experienced progressive, often severe disability into adulthood.

In this rare autosomal recessive disorder, which occurs in approximately 1 in 40,000 births worldwide, a deficiency or absence of the enzyme acid alpha-glucosidase causes glycogen to build up in the lysosomes of cells. While many tissues are affected, skeletal and cardiac muscle see the earliest involvement, with muscle hypotonia, cardiomyopathy, and breathing difficulties (mainly due to diaphragm weakness) composing the hallmark symptoms of the infantile form. Muscle weakness and progressive respiratory failure are prominent in later-onset disease.

The spectrum of severity and age of onset in Pompe disease is linked to combinations of mutations on the GAA gene, some of which destroy the body's ability to produce acid alpha-glucosidase whereas others merely hamper it. Less enzyme produced in the body generally corresponds with more severe disease activity.

The most severe end of the disease spectrum, or "classic infantile Pompe disease," presents at birth and is recognized in early infancy. Until treatment with enzyme replacement therapy (ERT) became available, patients usually died of cardiorespiratory failure within their first year of life. With therapy, patients have survived into their 20s and beyond. Late-onset disease is a far broader category in which patients can present at any time from their first year, including into middle age.

The emergence in 2006 of alglucosidase alfa (Lumizyme, Sanofi Genzyme), an ERT used long-term to improve survival and slow progression in children and adults, resulted in a boom of research interest, a push to timelier diagnosis, and – with patients living longer – a more thorough understanding of the natural history of Pompe disease. In addition to the usual clinical picture of progressive muscle weakness, difficulty breathing, and cardiomyopathy, investigators are seeing nervous system involvement in patients with Pompe disease.

A patient with Pompe, especially one with late-onset disease, may be diagnosed and even managed by his or her neurologist. To learn more, Neurology Reviews talked to two global experts in Pompe disease: Priya Kishnani, MD, of Duke University in Durham, N.C., and Antonio Toscano, MD, of the University of Messina (Italy).

Priya Kishnani, MD

Antonio Toscano, MD

Diagnosis: Still room to improve

"Most neurologists will encounter a patient with Pompe disease," said Dr. Kishnani, who has been working with Pompe for her entire career as a pediatrician and medical geneticist, treating patients of all ages and disease phenotypes.

"In newborns, diagnosis is more straightforward, because you've got an enlarged heart," she said. And thanks to efforts of researchers like Dr. Kishnani and Pompe advocacy groups, Pompe disease is now a part of the RUSP (Recommended Uniform Screening Panel) for newborns; currently 28 U.S. states are screening for Pompe disease.

"The challenge really is for the later-onset cases, which are 80% of all cases," Dr. Kishnani said.

Previously, muscle biopsies were the first step toward diagnosis. Dried blot spot assays to detect enzyme deficiency have since become the standard, along with other biochemical tests. Confirmation of the diagnosis is through gene sequencing panels to detect GAA mutations.

"Now that there is a treatment for Pompe disease and the availability of blood-based testing, many previously undiagnosed patients with limb girdle weakness are evaluated and the diagnostic odyssey ends," Dr. Kishnani said. "But there is still a diagnostic delay, and many cases remain undiagnosed."

Routine blood tests for creatine kinase and for liver enzymes can help point to Pompe disease. But elevated liver enzymes are

Jennie Smith is a freelance journalist and editor specializing in medicine and health.

often misinterpreted. "It's about the ratios," Dr. Kishnani said. "ALT is usually much more elevated if it is coming from a liver cause, and AST is usually higher than ALT if it is coming from muscle. But patients often end up getting a liver biopsy due to so-called elevated liver enzymes. As the workup continues, it is often later recognized that the source of the elevated enzymes is muscle involvement, and a referral to the geneticist or neurologist is made. Only then is appropriate testing to confirm a diagnosis initiated."

Dr. Toscano, a neurologist who specializes in Pompe disease and other myopathies and who has published on tools for diagnosing late-onset Pompe disease,[1] said that clinicians should be vigilant when evaluating any patient with limb girdle weakness and elevated creatine kinase (CK) – "especially if the CK is under 2,000," he said, "because it is very rare that patients with Pompe disease have a more elevated CK than that."

"Elevated CK, myalgia, and exercise intolerance" should prompt clinicians to suspect Pompe disease in a patient of any age, Dr. Toscano said. "When you come across this, you should be very persistent and get to the end of the story."

Dr. Toscano noted that the blood spot assay, while an important early step, is not fully diagnostic, "because you can have false positives." The molecular GAA assay is used to confirm Pompe disease. But detecting pathogenic variants on the GAA gene – of which there are more than 500 – can be more complicated than it sounds. Whereas two mutations are required for Pompe disease, sometimes only one can be detected. Dr. Toscano said he also treated some patients for Pompe with only one known mutation but with unequivocal clinical and biochemical aspects of Pompe disease.

While delays in diagnosis for late-onset Pompe disease remain significant – between 5 and 6 years on average for older patients, and up to 20 years for those with pediatric onset – both Dr. Kishnani and Dr. Toscano said they perceive them to be improving. With McArdle disease, another inherited glycogen storage disorder that is more common than Pompe disease but for which there is no treatment, "the delay is nearly 12 years," Dr. Toscano said.

ERT: The sooner the better

Enzyme replacement therapy is indicated for all patients with Pompe disease. Currently two are commercially available: alglucosidase alfa (Lumizyme, Sanofi Genzyme), indicated for all forms of Pompe disease, and avalglucosidase alfa-ngpt (Nexviazyme, Sanofi Genzyme), approved in 2021 for later-onset Pompe, though its indications have yet to be fully defined.

The semimonthly infusions represent, to date, the only disease-modifying therapies commercially available. Enzyme replacement therapy can reverse cardiac damage seen in infants and allow them to meet developmental milestones previously unthinkable. In adults, it can slow progression, though many treated patients will still develop chronic disability and require a wheelchair, respiratory support, or both.

"The phenotype of the patients we are seeing today is not as involved as it was prior to enzyme therapy," said Dr. Kishnani, who was part of the research team that developed ERT and launched the first clinical trials. "This is across the disease spectrum."

But optimal management means more than just getting a patient on therapy fast, Dr. Kishnani said.

"Very often the thinking is if the patient is on ERT, we've done right by the patient. Aspects we don't look at enough include: Are we monitoring these patients well? Are patients being followed by a multidisciplinary team that includes cardiology, physical therapy, and pulmonary medicine? Are we doing appropriate musculoskeletal assessments? They might have sleep hypoventilation. The BiPap settings may not be correct. Or they have not been assessed for antibodies," she said.

Many infants with severe phenotypes, notably those who produce no enzyme naturally, will develop immune reactions to the exogenous enzyme therapy. High antibody titers also have been seen and are associated with poor therapeutic response. While this is very clear in the infantile setting, late-onset patients also develop antibodies in response to ERT. In one study in 64 patients,[2] Dr. Toscano and his colleagues saw that antibodies may affect clinical response during the first 3 years of treatment, while a small study[3] by Dr. Kishnani's group saw clinical decline associated with high antibody titers in patients with late-onset disease.

While the relationship of specific titers to therapeutic response remains unclear, it is important to consider antibodies, along with other factors, in the monitoring of patients with Pompe disease. "We need to always ask, if a patient is falling behind, what could be the reason?" Dr. Kishnani said. "These are the things we as clinicians can do to improve or enhance the impact of ERT."

Dr. Toscano noted that a common misconception about late-onset Pompe disease is that cardiac manifestations are minimal or absent, whereas as many as about 20% of patients will have heart problems and need to be carefully monitored.

Neurological manifestations

With patients surviving longer on ERT, researchers have been able to develop a deeper understanding of the natural history of Pompe disease. Increasingly, they are seeing it as a multisystem disease that includes central nervous system involvement.

"Is Pompe an overt neurodegenerative disease? I would say no," Dr. Kishnani said. "But there is a neurological component that we've got to understand and follow more."

Glycogen accumulation, she noted, has been found in anterior horn cells, motor neurons, and other parts of the brain. "We have been doing MRIs on children with infantile Pompe, and we have seen some white matter hyperintensities. The clinical significance of this finding is still emerging. Sometimes it is present, but the child is cognitively intact. We have had college graduates who have white matter hyperintensities. So putting it in context will be important. But we know that glycogen is ubiquitous, and autopsy studies have shown that it is present in the brain."

In recent years, Dr. Toscano's group has investigated neurovascular complications of Pompe in late-onset patients. "This was something that really surprised us because for several years we have investigated mainly heart, muscle, or respiratory manifestations of the disease, but the central nervous system was really neglected," he said.

"Occasionally we did some brain MRIs and we found in even young patients some ischemic areas. We thought this was related to slowed circulation – that blood vessels in these patients are weak because they are impaired by glycogen accumulation." Dr. Toscano and his colleagues followed that observation with a study of late-onset patients,[4] in which they found that more than half had cerebrovascular abnormalities. "Even in, say, patients 30 to 35 years old we saw this – it's unusual to have a vascular disorder at that age."

Dr. Toscano and his colleagues also reported cerebral aneurysms[5] in patients with Pompe disease and have recommended that clinicians conduct MRI or cerebral angiograms on patients as part of routine follow-up. Blood pressure in Pompe patients should be carefully watched and managed with antihypertensive medication as needed, he said.

Part of the problem is that the proteins in ERT are not able to cross the blood-brain barrier, Dr. Toscano noted, adding that researchers are investigating other treatments that can.

Pompe disease as a research model

The successful development of ERT for Pompe disease marked a boom in research interest into not just Pompe – for which several experimental therapies are currently in the pipeline – but for other myopathies and glycogen storage disorders.

"I think that Pompe has served as a template both as a muscle disease and a lysosomal storage disease, and so some of our learnings from Pompe have been applied across different diseases," Dr. Kishnani said.

Studies in spinal muscular atrophy, for example, "in some ways mirrored what was done for Pompe – treatment trials were initiated in babies at the most severe end of the disease population with infantile disease, and used similar clinical trial endpoints," Dr. Kishnani said. "Even for the later-onset end of the spectrum, the endpoints we used in Pompe for muscle strength and function have been relevant to many other neuromuscular disorders."

Pompe disease research also ushered in a new appreciation of immune responses in protein replacement therapies, Dr. Kishnani noted.

"In the field today, you hear the term cross-reactive immunological material, or CRIM, all the time," she said. "But when we first started talking about it in the space of Pompe disease, there was a lot of scientific debate about what the significance of CRIM-negative status was in relationship to the risk for development of high and sustained antibody titer and a poor clinical response. To understand this involved a lot of going back to the data and digging into the small subset of nonresponders. One of the powers of rare disease research is that every patient matters, and it's important to understand what's going on at the patient level rather than just the group data level."

A robust pipeline

The decade and a half since the advent of ERT has seen what Dr. Toscano described as "an explosion of interest" in Pompe disease.

"We're seeing an extraordinary number of papers on everything from clinical, biomarkers, genetics, and rehabilitation – this disease is now considered from every point of view, and this is very important for patients," Dr. Toscano said. Alongside this has come industry interest in this rare disease, with several companies investigating a range of treatment approaches.

The existence of a treatment, "while not perfect," he said, "has interested the patient associations and doctors to try and improve service to patients. Patients with Pompe disease are well attended, probably more so than patients with degenerative disorders in which there is no therapy."

Last year the second ERT – avalglucosidase alfa – was approved by the U.S. Food and Drug Administration to treat

"I think that Pompe has served as a template both as a muscle disease and a lysosomal storage disease, and so some of our learnings from Pompe have been applied across different diseases."

late-onset Pompe disease. The drug, currently being investigated in infants as well, was designed to improve the delivery of the therapeutic enzyme to muscles and enhance glycogen clearance, and results from ongoing trials suggest some functional and clinical benefit over standard ERT.

Other drugs in development for Pompe disease include substrate reduction therapies, which aim to reduce the storage of glycogen in cells, and therapies that improve residual function of mutant GAA enzyme in the body. These and other therapies in development have the potential to modify nervous system manifestations of Pompe disease.[6]

Because a single gene is implicated in Pompe disease, it has long been considered a good candidate for gene therapies that prompt the body to make stable enzyme. Seven companies are now investigating gene therapies in Pompe disease.[7] Some of these deliver to skeletal muscles and others aim for the liver, where proteins are synthesized and secreted and adverse immune responses might be more easily mitigated. Other gene therapies use an ex vivo approach, removing and replacing cells in bone marrow.

Dr. Kishnani's research group at Duke University is leading a small clinical trial in late-onset patients of a GAA gene transfer to the liver using adeno-associated virus (AAV) vectors.[8]

"We have started AAV gene therapy trials in adults with Pompe disease and will later evaluate children because ERT is available as a standard of care, and so from a safety perspective this makes the most sense," Dr. Kishnani said. "We do have challenges in the field of gene therapy, but I think if we are able to overcome the immune responses, and … to treat at a lower dose, there's a very good pathway forward."

Dr. Toscano and Dr. Kishnani have received reimbursement from Sanofi and other manufacturers for participation on advisory boards and as speakers. ■

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Rett syndrome: Looking to the future and the promise of gene therapy

Like many monogenic disorders, Rett syndrome is entering an exciting stage – at which the words "treatment" and "cure" can be spoken with intent and conviction, not just hopeful optimism.

By Courtney S. Ambrose and Barbara J. Bailus, PhD

The dream of curing genetic disorders has been a persistent but elusive goal, even before the human genome was mapped. Once mapping of the human genome was complete in 2001, an entirely new avenue of potential treatments and cures for genetic diseases and disorders was opened.[1,2]

The disorders best suited for targeted gene therapy are monogenic; however, tools and delivery methods for editing the human genome were limited and difficult to apply, until the advent of the CRISPR system in 2012.[3] CRISPR (an acronym of clustered regularly interspaced short palindromic repeats) has changed the way in which gene therapy strategies are pursued, with dozens of companies leveraging a variety of platforms to create potentially life-changing therapies for devastating rare diseases and disorders.

One of the rare monogenic disorders that is embracing multiple gene therapy approaches is Rett syndrome, a rare, debilitating neurodevelopmental disorder. In this review, we explore the molecular cause of Rett syndrome, disease presentation, current treatments, ongoing clinical trials, and therapies that are on the horizon.

Underlying molecular cause

Rett syndrome is caused by mutations in, or the absence of, the MECP2 gene, which produces methyl-CpG binding protein 2 (MECP2). The syndrome was first described clinically in 1954 by the Austrian physician Andreas Rett; it would take until 1982 before the disorder was officially named, eponymously, in a seminal paper by Hagberg.[4] After Hagberg's characterization, Rett syndrome became the predominant global clinical diagnosis identified among cognitively impaired females, with an incidence of 1 in every 10,000 to 15,000.[4]

In 1999, mutations in, and deletions of, MECP2 were identified as the cause of Rett syndrome.[4,5] MECP2 is located on the X chromosome, in the Xq28 region, making Rett syndrome an X-linked dominant disorder.[6] Rett syndrome is seen predominantly in females who are mosaic for mutant or deleted MECP2. Random X chromosome inactivation results in some cells expressing the mutant MECP2 allele and other cells expressing the normal functioning MECP2 allele; the percentage of cells expressing the normal allele correlates with the degree of syndrome severity.[7-9]

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The incidence of Rett syndrome is much lower in males, in whom the syndrome was originally thought to be lethal; many observed male cases are either mosaic or occur in XXY males.[10,11]

Approximately 95% of cases of Rett syndrome are due to de novo mutations in MECP2, with a handful of specific mutations and large deletions accounting for more than 85% of cases.[12] The fact that Rett syndrome is monogenic and most cases are caused by, in total, only a handful of mutations or deletions makes the syndrome a promising candidate for gene therapy.

At the molecular level, it has been observed that the MECP2 mutations of Rett syndrome lead to loss of gene function, thus disrupting the ability of the MECP2 nuclear protein to regulate global gene transcription through its binding to methylated DNA sites.[12] A large percentage of these missense and nonsense mutations lead to a truncated or nonfunctional protein.[12]

One of the ways in which MECP2 regulates transcription is as a component of heterochromatin condensates and by separation of heterochromatin and euchromatin.[13-15] It has been observed that the cells of Rett syndrome patients have an altered chromatin state, potentially contributing to transcriptional dysregulation.[16,17] Several mutations observed in Rett

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syndrome patients occur in crucial domains for heterochromatin condensate formation, which helps explain this cellular phenotype.[13] Introduction of a engineered "mini" MECP2 in a murine model of Rett syndrome has resulted in partial rescue of heterochromatin condensate formation and transcriptional regulation – fostering the hypothesis that correcting those genetic changes could lead to a potential therapy.[18]

Beyond the role of MECP2 in heterochromatin condensate formation, the gene interacts with more than 40 proteins that have diverse roles in cellular function, epigenetic modulation, and neuronal development. This volume of interactions contributes to MECP2 being a global gene regulatory protein that has far-reaching effects on transcriptional regulation across the genome.[19-22]

Epigenetic dysregulation has been associated with neurodevelopmental and neuropsychiatric disorders.[23] Both insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor are transcriptional targets of MECP2, and are involved in neuronal differentiation, synaptic function, and neurite outgrowth.[12] This helps explain the neurodevelopmental phenotypes observed in MECP2-mutated patients.

Notably, although Rett syndrome patients experience neurodevelopmental phenotypes at the cellular level, neuronal death is not readily observed. That observation provides hope that an interventional therapy after onset of symptoms might prove beneficial.

Presentation

Early neurotypical development. A hallmark of Rett syndrome is neurotypical physical and mental development until 6 to 24 months of age.

Stagnation is the first stage of the syndrome, involving a small but rapid decline in habitual milestones, such as motor and language skills.[12] Subtle signs, such as microcephaly and hypotonia, can also arise at this time but might be missed.[24]

Rapid regression follows stagnation. Speech and motor delays and impaired gait and breathing occur;[12,25] purposeful hand skills are lost, replaced by repetitive hand-wringing movements that are a hallmark of the syndrome.[12,24] Seizures are observed; they become more common during the next stage.[12]

Plateau. Language advances can be observed, but further deficits are seen in motor skills and hand coordination.[12]

Late motor deterioration stage. Late physical deficits develop, leading to lifelong impairments. The physical deficits observed are the result of severe muscle weakness, usually resulting in wheelchair dependency.[12]

Plateau. Patients then reach a second plateau. Regression stops; deficient physical and cognitive states stabilize and are maintained.[25]

At all stages of Rett syndrome, the following are observed:

- Gastrointestinal problems.
- Sleep disturbances.
- Abnormal cardiorespiratory coupling.
- Greater-than-expected mortality.[12]

Final regression. The patient is fully dependent for the rest of their lifespan, partially due to seizure activity.[26,27]

A life-changing diagnosis

A diagnosis of Rett syndrome is life-changing for a patient's family; access to supportive groups of other patients and their families is extremely beneficial. Two helpful organizations – the Rett Syndrome Research Trust[28] and International Rett Syndrome Foundation[29] – offer patient support and community and fund research.

Because X chromosome inactivation is random in Rett syndrome, the individual patient can present with a wide variety of phenotypic combinations – making the patient, and their needs, unique.[12] During stages of regression, patients often experience emotional dysregulation and anxiety, which is attributable to their increasing physical difficulties.[30] They often exhibit combinations of uncontrolled movements, including repetitive rocking, scratching, and self-injurious behavior.[30] For most, regression subsides after the first 5 years of alternating development and regression; after that, their ultimate symptoms persist for life.[25]

As patients mature, they need to be monitored for proper nutrition and scoliosis.[25] As adults, they are at risk of pneumonia, respiratory distress, status epilepticus, osteopenia, and lack of adequate food or water because of impaired ability to feed.[25]

The lifespan of Rett syndrome patients has increased, thanks to improvements in health care, advances in technology, and early genetic testing, which allows for earlier diagnosis, intervention, and management of symptoms.

Current treatments

When a female patient presents with regression and loss of milestones, sequencing of MECP2 is performed to verify whether Rett syndrome is the cause, by detecting any of the known mutations. Multiplex ligation-dependent probe amplification is also performed to detect major deletions.[25]

All available treatments for Rett syndrome are symptomatic; intensive early intervention is practiced.[31] Multidisciplinary management – medical, psychiatric, and physical – is introduced almost immediately after diagnosis. Following diagnosis, patients are prescribed antiseizure, sleep, and anxiety medications.[31] Electroencephalography can be performed to identify seizure type. Neuromuscular blockage drugs can be prescribed to help with gait and stereotypic hand movements.[25]

Handguards or splints to the elbows can be prescribed by an occupational therapist to improve hand movement.[25] Physical therapy can improve mobility; hydrotherapy and hippotherapy have been successful in helping to maintain mobility and muscle support.[32,33] Nutritional management is implemented to control caloric intake and maintain the vitamin D level.[31] Some patients experience constipation and urinary retention, putting them at risk of nephrolithiasis.

Once the signs and symptoms of Rett syndrome progress, and milestones regress to a certain point, patients need constant, full-time care for the rest of their lives.[34] Symptomatic interventions have greatly improved patient outcomes, it has been shown that about 70% reach adulthood with a potential lifespan of about 50 years.[25]

Although there is no cure for Rett syndrome and treatments are symptomatic, ongoing studies – both clinical and preclinical – offer promise that treatments will be developed that work at molecular and genetic levels.

Clinical trials

Advances in understanding of Rett syndrome have led to many therapies entering clinical trials, several of which show promise.

Trofinetide. One of the most promising targets for downstream therapy, mentioned earlier, is IGF-1, which was the target of a successful phase 3 clinical trial, LAVENDER (sponsored by Acadia Pharmaceuticals).[35,36] This trial studied trofinetide, a synthetic IGF-1 analog that inhibits neuroinflammation, restores glial function, corrects synaptic deficiencies, and regulates oxidative stress response.[12,37,38] Initial results from phase 2 and phase 3 trials indicate improved scores for treated patients in the Rett syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) scores, while also showing improvements in the Communication and Symbolic Behavior Scales Developmental Profile Infant–Toddler Checklist–Social composite score.[36,39]

Although there is no cure for Rett syndrome and treatments are symptomatic, ongoing studies – both clinical and preclinical – offer promise that treatments will be developed that work at molecular and genetic levels.

The most common adverse events seen with trofinetide were diarrhea and vomiting.

Acadia Pharmaceuticals has filed for approval of a new drug application for trofinetide with the U.S. Food and Drug Administration, for which the company has been granted Fast Track Status and orphan drug designations. Most (95%) subjects in the phase 3 LAVENDER trial elected to continue taking trofinetide in the subsequent open-label Lilac and Lilac-2 extension studies.[36] A current open-label phase 2/3 trial is recruiting patients 2 to 5 years of age to evaluate trofinetide.[40] It is expected that, in the near future, this could be an FDA approved treatment for Rett syndrome.

Blarcamesine. Another small molecule drug, blarcamesine (also known as ANAVEX2-73), a sigma-1 receptor agonist, produced promising results in phase 2 clinical trials in adult Rett syndrome patients. The drug is in a phase 2/3 clinical trial for pediatric Rett syndrome patients (sponsored by Anavex Life Sciences).[41-43]

Phase 2 results indicated statistically significant and clinically meaningful improvement in RSBQ and CGI-I scores with blarcamesine. Improvement was initially observed within 4 weeks after the start of treatment and was sustained throughout the study. The drug was shown to be well tolerated, with minimal adverse effects. These results were observed in adult patients, demonstrating that improvements in Rett syndrome are possible even after regression.

Blarcamesine activates the sigma-1 receptor, which is pivotal to restoring cellular homeostasis and restoring neuroplasticity – deficiencies of which have been linked to autophagy and glutamate toxicity. The drug has also been explored as a potential treatment for other neurological disorders.[44-47] Improvements in blarcamesine-treated patients further correlated with lower levels of glutamate in cerebrospinal fluid, which is a Rett syndrome biomarker, supporting the proposition that behavioral improvements were due to drug intervention.[48,49] The phase 2 trial was modified into a phase 3 trial and additional endpoints were added.[41-43]

All patients in the phase 2 adult trial elected to continue in the extension study.

Based on these promising data, Anavex is pursuing an approval pathway for adult patients, while continuing dosage optimization phase 2/3 trials and recruitment for a pediatric trial.[42,43]

Is the future about gene therapy?

TSHA-102 (miniMECP2). Taysha Gene Therapies is developing a promising gene therapy, TSHA-102, for Rett syndrome, and is aiming to begin phase 1/2 clinical trials in 2022.[50] The technology for this therapy relies on the delivery of a fragment

of MECP2 (known as miniMECP2), which is regulated by a built-in microRNA regulator (miR-responsive auto-regulatory element, or miRARE) to help ameliorate MECP2 dosage toxicity. Overexpression of MECP2 is toxic to neurons, which has made traditional [so to speak] gene replacement therapy difficult in Rett syndrome. Levels of MECP2 need to be tightly regulated, and the Taysha microRNA technology regulates levels of miniMECP2, thus reducing toxicity.

The Taysha microRNA technology has yielded promising results in mouse studies for Rett syndrome; results indicate a lengthening of lifespan and delayed onset of gait abnormalities.[51] TSHA-102 is in the preclinical stage but offers promise that it will be the first gene therapy for Rett syndrome to enter clinical trials.

As the field of gene therapy advances, several promising technologies are on the horizon that could potentially have disease-altering impacts on Rett syndrome. These therapies are divided into two broad categories: those at the gene level and those at the transcription and protein level. A few of these approaches are highlighted below.

Gene replacement involves adding a full or partial copy of MECP2 to neuronal cells. This type of therapy presents challenges, from delivery of the new gene to dosage concerns, because MECP2 can be toxic if overexpressed.[52-54] Groundbreaking work was done in mouse models involving truncated MECP2, exhibiting phenotypic rescue and validating the gene-replacement approach.[18] This strategy is being pursued by Neurogene, which has a unique technology that allows for tuning of the gene's expression to get the correct protein levels in the patient. Promising data was presented this year at the American Society of Gene and Cell Therapy conference.[55]

Early gene replacement therapy studies also laid the foundation for the minMECP2 and microRNA approach being used by Taysha Gene Therapies (discussed above).[51]

"Correcting" DNA mutations. A different approach at the genetic level involves "correcting" mutations in MECP2 at the DNA level. This is possible because, in a large subset of Rett syndrome patients who have the same missense or nonsense mutations, by using CRISPR, a gene editing tool (discussed above) a single base pair can be corrected.[56,57] Previous research, in a Rett syndrome-model of induced pluripotent stem cells, showed that this type of editing is possible – and effective.[52] An approach with particular promise involves use of a class of CRISPR proteins known as base editors that are able to specifically alter a single base of DNA.[57] The technique has the potential to address many of the mutations seen in Rett syndrome; research on this type of technology is being pursued by Beam Therapeutics.[58]

Another promising "correction" approach is exonic editing, in which a much larger section of DNA – potentially, exons 3 and 4, which, taken together, comprise 97% of known MECP2 mutations seen in Rett syndrome – is replaced.[59]

In both CRISPR and exonic editing therapeutic approaches, endogenous levels of MECP2 expression would be maintained. Of note, both approaches are being pursued for use in treating other genetic disorders, which provides a boost in scaling-up work on addressing safety and efficacy concerns that accompany gene-editing approaches.[58] One advantage to the DNA correction approach is that it has the potential to be a "one-and-done" treatment.

"Correcting" RNA. Beyond directly editing DNA, several therapeutic approaches are exploring the ability to edit RNA or to provide the protein directly to cells as an enzyme replacement therapy. Such an RNA correction strategy leverages a technology that takes advantage of cells' natural RNA editor, known as adenosine deaminase acting on RNA (ADAR), which corrects errors in cells' RNA by providing specific guides to the cell. ADAR can be targeted to fix mutations in the MECP2 RNA transcript, resulting in a "corrected" MECP2 protein.[60,61] This technology has delivered promising proof-of-concept evidence in cells and in murine models, and is in the therapeutic pipeline at VICO Therapeutics.[62]

Shape Therapeutics has also leveraged ADAR to "correct" mutated RNA; Rett syndrome is among the top priorities in the company's pipeline.

Worth noting is that there are several advantages to the "correction" approach:

Leveraging internal repair mechanisms minimizes the immune response.

The flexibility of correction means that it can be used to address many of the mutations that cause Rett syndrome.[63]

Enzyme replacement therapy, in which the MECP2 protein produced by MECP2 would be directly replaced, is being explored in Rett syndrome patients. This technology has been used successfully in Pompe disease; however, Rett syndrome presents its own challenge because MECP2 needs to be delivered to the brain and neuronal cells.[64]

Where does this work stand? The technologies described in this section are in preclinical stages of study. Nonetheless, it is expected that several will enter human clinical trials during the next 5 years.

Conclusion

A diagnosis of Rett syndrome is a life-altering event for patients and their families. But there is more hope than ever for effective therapies and, eventually, a cure.

Continued on page 18

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FIRDAPSE can cause seizures. Do not use FIRDAPSE in patients with a history of seizures, or with a hypersensitivity to amifampridine or another aminopyridine.

Please see Brief Summary of full Prescribing Information on the next page.

References: 1. Yoon CH, Owusu-Guha J, Smith A, Buschur P. Amifampridine for the management of Lambert-Eaton myasthenic syndrome: a new take on an old drug. *Ann Pharmacother*. 2020;54(1):56-63. **2.** Full Prescribing Information for FIRDAPSE (amifampridine). Catalyst Pharma; 2021. **3.** Shieh P, Sharma K, Korhman B, Oh SJ. Amifampridine phosphate (FIRDAPSE) is effective in a confirmatory phase 3 clinical trial in LEMS. *J Clin Neuromuscul Dis*. 2019;20(3):111-119. **4.** Oh SJ, Scherbakova N, Kostera-Pruszczyk A, et al; LEMS Study Group. Amifampridine phosphate (FIRDAPSE®) is effective and safe in a phase 3 clinical trial in LEMS. *Muscle Nerve*. 2016;53(5):717-725.

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FIRDAPSE is a potassium channel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults.

DOSAGE AND ADMINISTRATION

- The recommended starting dosage is 15 mg to 30 mg daily taken orally in divided doses (3 to 4 times daily)
  - Starting dosage is 15 mg daily for patients with renal impairment, hepatic impairment, and in known N-acetyltransferase 2 (NAT2) poor metabolizers
- Dosage can be increased by 5 mg daily every 3 to 4 days
- Dosage is not to exceed a maximum of 80 mg daily
- The maximum single dose is 20 mg

CONTRAINDICATIONS

FIRDAPSE is contraindicated in patients with:

- A history of seizures
- Hypersensitivity to amifampridine phosphate or another aminopyridine

WARNINGS AND PRECAUTIONS

Seizures

FIRDAPSE can cause seizures. Seizures have been observed in patients without a history of seizures taking FIRDAPSE at the recommended doses, at various times after initiation of treatment, at an incidence of approximately 2%. Many of the patients were taking medications or had comorbid medical conditions that may have lowered the seizure threshold. Seizures may be dose-dependent. Consider discontinuation or dose-reduction of FIRDAPSE in patients who have a seizure while on treatment. FIRDAPSE is contraindicated in patients with a history of seizures.

Hypersensitivity

In clinical trials, hypersensitivity reactions and anaphylaxis associated with FIRDAPSE administration have not been reported. Anaphylaxis has been reported in patients taking another aminopyridine; therefore, it may occur with FIRDAPSE. If anaphylaxis occurs, administration of FIRDAPSE should be discontinued and appropriate therapy initiated.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Seizures
- Hypersensitivity

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials (Study 1 and 2) in patients with LEMS, 63 patients were treated with FIRDAPSE, including 40 patients treated for more than 6 months, and 39 patients treated for more than 12 months. In an expanded access program, 139 patients with LEMS were treated with FIRDAPSE, including 102 patients treated for more than 6 months, 77 patients treated for more than 12 months, and 53 patients treated for more than 18 months.

Study 1 was a double-blind, placebo-controlled, randomized discontinuation study in adults with LEMS. Following an initial open-label run-in phase (up to 90 days), patients were randomized to either continue FIRDAPSE treatment or transition to placebo for a 14-day double-blind phase. Following final assessments, patients were allowed to resume FIRDAPSE treatment for up to 2 years (open-label, long-term safety phase of the study).

During the open-label run-in phase of Study 1, 53 patients received FIRDAPSE for an average of 81 days at an average daily dosage of 50.5 mg/day. The average patient age was 52.1 years and 66% were female. There were 42 patients who had no prior exposure to FIRDAPSE at the initiation of this study. Table 1 shows adverse reactions with an incidence of 5% or greater occurring in the 42 LEMS patients newly initiated on treatment with FIRDAPSE during the run-in phase of the study.

Table 1. Adverse Reactions in ≥5% of LEMS Patients Newly Treated with FIRDAPSE in Study 1

ADVERSE REACTION	FIRDAPSE N=42 %
Paresthesia*	62
Upper respiratory tract infection	33
Abdominal pain	14
Nausea	14
Diarrhea	14
Headache	14
Elevated liver enzymes**	14
Back pain	14
Hypertension	12
Muscle spasms	12
Dizziness	10
Asthenia	10
Muscular weakness	10
Pain in extremity	10
Cataract	10
Constipation	7
Bronchitis	7
Fall	7
Lymphadenopathy	7

*Includes paresthesia, oral paresthesia, oral hypoesthesia

**Includes elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and gamma-glutamyl transferase (GGT)

Other Adverse Reactions

In the overall population treated in Study 1 (n=53), including the double-blind phase and the 2-year open-label long-term safety phase, additional adverse reactions occurring in at least 5% of the patients included: dyspnea, urinary tract infection, gastroesophageal reflux, insomnia, peripheral edema, pyrexia, viral infection, blood creatine phosphokinase increase, depression, erythema, hypercholesterolemia, and influenza. These patients received an average daily dosage of 66 mg of FIRDAPSE.

DRUG INTERACTIONS

Drugs that Lower Seizure Threshold

The concomitant use of FIRDAPSE and drugs that lower seizure threshold may lead to an increased risk of seizures. The decision to administer FIRDAPSE concomitantly with drugs that lower the seizure threshold should be carefully considered in light of the severity of the associated risks.

Drugs with Cholinergic Effects

The concomitant use of FIRDAPSE and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of FIRDAPSE and of those drugs and increase the risk of adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FIRDAPSE during pregnancy. Physicians are encouraged to enroll pregnant patients, or pregnant women may register themselves in the registry by calling 855-212-5856 (toll-free), using the Fax number 877-867-1874 (toll-free), by contacting the Pregnancy Coordinating Center at firdapsepregnancyregistry@ubc.com or by visiting the study website at www.firdapsepregnancystudy.com.

Risk Summary

There are no data on the developmental risk associated with the use of FIRDAPSE in pregnant women. In animal studies, administration of amifampridine phosphate to rats during pregnancy and lactation resulted in developmental toxicity (increase in stillbirths and pup deaths, reduced pup weight, and delayed sexual development) at doses associated with maternal plasma drug levels lower than therapeutic drug levels (see Animal Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Oral administration of amifampridine phosphate (0, 7.5, 22.5, or 75 mg/kg/day) to female rats prior to and during mating and continuing throughout organogenesis produced no adverse effects on embryofetal development. Plasma amifampridine exposure (AUC) at the highest dose tested is approximately 7 times that in humans at the maximum recommended human dose (MRHD) of 80 mg amifampridine/day. Oral administration of amifampridine phosphate (0, 9, 30, or 57 mg/kg/day) to pregnant rabbits throughout organogenesis produced no adverse effects on embryofetal development. The highest dose tested is approximately 7 times the MRHD (80 mg/day amifampridine) on a body surface area (mg/m^2) basis.

Oral administration of amifampridine phosphate (0, 7.5, 22.5, or 75 mg/kg/day) to female rats throughout pregnancy and lactation resulted in an increase in stillbirths and pup deaths, reduced pup weight, and delayed sexual development in female pups at the mid and high doses tested. The no-effect dose (7.5 mg/kg/day amifampridine phosphate) for adverse developmental effects is associated with a plasma amifampridine exposure (AUC) less than that in humans at the MRHD.

Lactation

Risk Summary

There are no data on the presence of FIRDAPSE in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FIRDAPSE and any potential adverse effects on the breastfed infant from FIRDAPSE or from the underlying maternal condition.

In lactating rat, amifampridine was excreted in milk and reached levels similar to those in maternal plasma.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of FIRDAPSE did not include sufficient numbers of subjects aged 65 and over (19 of 63 patients in Studies 1 and 2) to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Renal clearance is an elimination pathway for amifampridine and the inactive metabolite, 3-N-acetyl amifampridine, and exposure of amifampridine is higher in subjects with renal impairment. Therefore, in patients with renal impairment, FIRDAPSE should be initiated at the lowest recommended starting dosage (15 mg/day), and patients should be closely monitored for adverse reactions. Consider dosage modification or discontinuation of FIRDAPSE for patients with renal impairment as needed based on clinical effect and tolerability. The safety, efficacy, and pharmacokinetics of amifampridine have not been studied in patients with end-stage renal disease (CLcr <15 mL/min or patients requiring dialysis). No dosage recommendation for FIRDAPSE can be made for patients with end-stage renal disease.

Hepatic Impairment

The effects of FIRDAPSE have not been studied in patients with hepatic impairment. FIRDAPSE is extensively metabolized by N-acetyltransferase 2 (NAT2) and hepatic impairment may cause an increase in exposure. Therefore, initiate FIRDAPSE in patients with any degree of hepatic impairment at the lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions. Consider dosage modification or discontinuation of FIRDAPSE for patients with hepatic impairment as needed based on clinical effect and tolerability.

NAT2 Poor Metabolizers

Exposure of FIRDAPSE is increased in patients who are N-acetyltransferase 2 (NAT2) poor metabolizers. Therefore, initiate FIRDAPSE in patients who are known NAT2 poor metabolizers at the lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions. Consider dosage modification of FIRDAPSE for patients who are known NAT2 poor metabolizers as needed based on clinical effect and tolerability.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Risk of Seizures

Inform patients that FIRDAPSE can cause seizures, and to notify their healthcare provider if they experience a seizure.

Hypersensitivity

Instruct patients to inform their healthcare provider if they have signs or symptoms of hypersensitivity, and to seek emergency help if symptoms of anaphylaxis occur.

FIRDAPSE Dosing

Instruct patients to take FIRDAPSE exactly as prescribed. Patients should carefully follow the dose escalation schedule provided by their healthcare provider to safely achieve the therapeutic dosage. Inform patients that the tablets may be divided in half at the score, if needed. Instruct patients not to take a double dose to make up for a missed dose.

Drug Interactions

Instruct patients to notify their healthcare provider prior to starting any new medication, including over-the-counter drugs.

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking FIRDAPSE they should inform their healthcare provider. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to FIRDAPSE during pregnancy and encourage them to enroll if they become pregnant while taking FIRDAPSE *[see Use in Specific Populations (8.1) of full Prescribing Information]*.

Storage

Advise patients to store FIRDAPSE at 68°F to 77°F (20°C to 25°C).

Catalyst pharmaceuticals

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Continued from page 15

Multiple late-stage clinical trials in progress are demonstrating promising results from therapeutic products, with minimal adverse events. Remarkably, these interventions have delivered improvements to adult patients after regression has stabilized. With rapid progress being made in the field of gene therapy, a hopeful picture is emerging: that therapeutic intervention will be possible before regression, thus effectively treating and, potentially, even curing Rett syndrome.

The landscape is broadening. Add to this hope for approved therapies is the fact that Rett syndrome isn't the only target being pursued with such strategies; in fact, researchers in the larger field of neurodevelopmental disorder study are working together to find common solutions to shared challenges – from how therapies are designed and delivered to how toxicity is minimized. Much of what is being explored in the Rett syndrome field is also under investigation in other neurodevelopmental syndromes, including Angelman, Prader-Willi, chromosome 15q11.2-13.1 duplication (Dup15q), and Fragile X syndrome. This kind of parallel investigation benefits all parties and optimizes a treatment platform so that it can be applied across more than a single disorder.

Like many monogenic disorders, Rett syndrome is entering an exciting stage – at which the words "treatment" and "cure" can be spoken with intent and conviction, not just hopeful optimism. These words portend real promise for patients with Rett syndrome, and for their families. ■

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Rare disease patient advocacy groups empowered by data

On the IAMRARE platform, patient advocacy organizations are trained to conduct observational research and host natural history.

By Theodore Bosworth

With the goal of advancing treatment of rare neurological diseases – or rare diseases of any type – the National Organization for Rare Disorders (NORD) has launched innovative new research initiatives in recent years to help patient advocacy organizations develop a precious asset: data to support better understanding of diseases and research that might lead to life-altering diagnostics or treatments.

"Most rare diseases still don't have approved therapies, and the problem is often a lack of the basic information needed to advance research," explained Aliza Fink, DSc, the director of research programs at NORD. "Our goal is to help patient organizations play a key role in the collection, analysis, and sharing of data to support better understanding of how a disease presents, its natural history, the types and severity of symptoms, and other unanswered questions."

Over the past 2 decades, the Internet, social media, and other communications resources have provided patient organizations with unprecedented reach. As a result, these organizations are in a unique position to connect patients and caregivers around the world – those dealing with even the rarest of rare diseases – and become a repository of information on the disease and the patient experience.

Since the late 1980s, NORD has had a research grants program, and the grants this program provides to academic researchers have led to numerous significant discoveries and publications, as well as to two products that ultimately were approved by the U.S. Food and Drug Adminstration (FDA). More recently, however, NORD's research programs have been expanded to include an initiative known as IAMRARE, in which patient advocacy organizations are trained to conduct observational research and host natural history studies and registries on a platform developed by NORD.

"We work with the patient groups to determine what types of data would be most important to drive research, help develop the methodology for data collection, and advise them on protocols for supporting the quality and integrity of the data," Dr. Fink said. "By systematically collecting data from the patients and families they serve, these groups are in a position to contribute enormously to understanding the disease and advancing research."

Aliza Fink, DSc

NORD also helps with the practical aspects of conducting research of sufficient quality to be publishable, such as providing groups with guidelines and best practices for developing medical advisory committees, creating templates and materials to streamline their project's submission to institutional review boards, ensuring data security and privacy in accordance with Health Insurance Portability and Accountability Act criteria, and developing other expected standards for data collection and analysis.

Unlike even academic medical centers with an interest in a given rare disease, leading patient advocacy groups for these specific disorders have unmatched access to affected patients and families. This includes patients being managed in diverse settings or those not yet receiving care at all. By harnessing this patient population to record the signs, symptoms, disease course, and other information, the patient advocacy groups can contribute greatly to the pool of available data and ultimately what is known about the disease.

Data empowers research

While NORD helps groups through the IAMRARE program to become research-ready and guides them in developing research protocols and goals, the data are ultimately owned by the patient advocacy groups themselves. This helps to ensure that the patient voice is heard. By controlling data collection and dissemination, the advocacy groups can take a leading role in defining the goals of research, including what outcome measures are important to them and what they

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agree are the most promising avenues for research to achieve those goals.

"By collecting the data to understand the disease, it sets the stage for the next steps in research," explained Debbie Drell, the director of membership for NORD. She noted that IAMRARE has grown steadily since its inception in 2014 and that there are now close to 40 advocacy groups participating.

The value of this initiative is not difficult to grasp. Even though direct participation in research was not generally part of the agenda for some advocacy groups when IAMRARE was conceived, Ms. Drell said that this initiative is a compelling perk of becoming involved with NORD. Groups that elect to become research-ready in order to participate in IAMRARE fall into a category of membership that requires specific organizational structures – such as a medical advisory board – and NORD provides templates and guidance to help them meet these qualifications to successfully become research-ready.

Collaboration leads to progress

NORD was founded by an ad hoc committee of patient organizations that played a key role in enactment of the Orphan Drug Act nearly 40 years ago. Shortly after the Orphan Drug Act was passed by Congress and signed into law by President Ronald Reagan in 1983, the ad hoc committee formally united to create NORD to continue the momentum of this initial collaboration and support the rare disease community. According to Mary Dunkle, a senior advisor at NORD, passage of the Orphan Drug Act, which is widely considered a major driver of progress in development of treatments for rare diseases, made the advantages of their cooperation clear.

"The groups had so many issues in common across the spectrum of diseases that they decided to continue their collaboration," she explained. "They realized that, while each disease is rare, the challenges they present to patients, families, clinicians, and researchers have many similarities."

The definition of rare disease, according to the National Institutes of Health, is a disorder that affects fewer than 200,000 people in the United States. More than 7,000 such disorders have been identified. Approximately one-third of rare diseases are neurological. Whether neurological or affecting different or multiple organ systems, most – perhaps 75%-80% – involve a genetic component, according to Ms. Dunkle.

Research reaps rewards

Altogether, today there are more than 1,000 patient organizations that provide various types of support and services for patients and caregivers affected by rare diseases. Approximately one-third of these organizations are members of NORD. For organizations that don't yet meet the membership criteria or for other reasons have not yet formally joined NORD, there are still many opportunities to get involved and to learn best practices to strengthen their governance, infrastructure, and capacity to support their members.

Of these, the IAMRARE program is one of the best examples of ways to get involved. Beyond the many other ways these groups help patients and families cope with challenging diseases, participation in research takes rare disorder advocacy to a different level. Objective data can attract the attention of those with the resources to further study the disease, while also giving advocacy groups a seat at the table when researchers or industry become interested.

"Why create a registry? It removes competition between academic centers or industry working on their own. It creates one central source for data sharing, and the advantage is that advocacy groups have a trusted relationship with the patient community because they are not-for-profit, community-run, and patient-driven," Ms. Drell explained.

The registry platforms developed for IAMRARE are customizable. With guidance from NORD, the advocacy groups themselves decide what data to collect and what questions they wish to answer, according to Dr. Fink. Once the registries are created, patients and caregivers participate by responding to survey questions on disease onset, progression over time, types and severity of symptoms, and other topics. The data can be de-identified for research purposes. The advocacy groups decide how and when to share the data, including whether to publish findings.

"Some of the groups have been very successful in getting the data published and leveraging their results to drive research forward, but there is variability in the extent of dissemination across the groups," said Dr. Fink. She noted that many of the registries that NORD has helped set up involve groups whose officers have had little or no prior research experience.

"We have advocacy groups that have had biomedical researchers on staff and other groups that are coming to research completely new," Dr. Fink said. In trying to get them up to speed on quality data collection, "We try to meet them where they are," she added, indicating that leading groups to a research-ready status is not just about logistics but can sometimes involve an organizational reorientation.

The examples of peer-reviewed publications that can be directly traced to IAMRARE registries are growing. One example is a registry on Prader-Willi syndrome, which is a complex neurodevelopmental disorder characterized by failure to thrive and by multiple endocrine abnormalities. The registry was developed in NORD's IAMRARE program by the Foundation for Prader-Willi Research, a nonprofit created in 2003 by parents of children with this disorder.

By 2019, when the first data from the Global Prader-Willi Syndrome Registry were published, they drew from 23,550 surveys completed for 1,696 separate cases of the disorder in 37 countries. The surveys provided some preliminary findings on demographics and on the genetic subtypes most commonly encountered, as well as simply proof that the registry was viable. From its inception in 2015, a significant proportion of the Prader-Willi population in the United States had been enrolled, according to the study authors. With time, the serial accumulation of more data on more cases will be invaluable for documenting disease characteristics. It will be a constantly maturing resource even after fundamental questions on disease impact and prognosis are addressed.

Data accumulation

Only about 10% of rare diseases currently have approved treatments, but there is widespread belief in the rare community that collecting and analyzing the data that can promote understanding of the biology of the disease and identify therapeutic targets could accelerate the development of treatments for diseases that currently have none.

Therefore, data accumulation has become central to the mission of NORD. In addition to IAMRARE, the organization has embarked on several other important initiatives in data accumulation for rare diseases. One is the Rare Disease Cures Accelerator – Data and Analytics Platform (RDCA-DAP), an initiative in which NORD is partnering with the Critical Path Institute. The goal of this program is to gather disparate pools of existing data in a standardized format to increase their power.

"With funding from the FDA, we have helped to support this platform, which is designed specifically to provide a centralized structure for combining and sharing of data," according to Dr. Fink. In RDCA-DAP, patient-level data is being assembled from a variety of resources, including academic centers, industry, registries, observational studies, and clinical trials. The program was launched in September 2021. In some cases, gaining access to data includes resolving privacy issues or addressing the proprietary concerns of those who currently have the data, but the value of the combined data is a compelling argument for participation.

"What we are trying to do is pull together the data from their current silos into one platform, and then make it generally available," said Dr. Fink. As with IAMRARE, RDCA-DAP offers enormous potential.

"The primary challenge for those studying rare diseases is the small numbers of patients. Randomized clinical trials for some of these diseases are simply not feasible because there are not enough subjects to power two study arms," said Dr. Fink in explaining why NORD has turned to novel strategies for data generation. One strategy for maximizing the potential value of data from these small populations of patients is data-sharing. For RDCA-DAP, data access will be open to all stakeholders after scientific review and approval. "Anyone can get an account and request data from the platform," said Dr. Fink, who expects this to spur more and novel types of research in rare disorders.

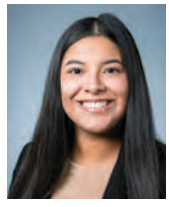
Another example of recent NORD initiatives to advance research and understanding of rare diseases is a study of metachromatic leukodystrophy (MLD) that is now enrolling patients, which also represents a partnership with the FDA. For this study, which is known as the HOME study, NORD hosts a platform where patients and caregivers enter data to capture the natural history of this disease. All MLD patients, even if they are already participating in a clinical trial or another registry, are invited. As with the IAMRARE registries, surveys capture patient or caregiver responses entered from a computer or smart device.

"We have always believed that the fact that so many rare diseases don't have treatments or are not even being studied by researchers doesn't reflect a lack of interest among academic or industry researchers. Rather, it reflects a lack of data to support research and to provide a fundamental understanding of the disease," Dr. Fink said. "If NORD's expanded research programs can draw the patient community together to provide that crucially needed data, we will have provided an important and essential service to patients, patient organizations, and researchers alike." ■

Myasthenia gravis: Finding strength in treatment options

Although the treatment of myasthenia gravis might have once been considered stagnant, newer expert consensus and novel research are generating optimism for innovative therapies.

By Peter van der Eb; Scarlet Toruno, MS; and Jason Laird, DMSc, MHS, MBA, PA-C


Peter van der Eb; Scarlet Toruno, MS; Jason Laird, DMSc, MHS, MBA, PA-C

The term myasthenia gravis (MG), from the Latin "grave muscle weakness," denotes the rare autoimmune disorder characterized by dysfunction at the neuromuscular junction.[1] The clinical presentation of the disease is variable but most often includes ocular symptoms, such as ptosis and diplopia, bulbar weakness, and muscle fatigue upon exertion.[2,3] Severe symptoms can lead to myasthenic crisis, in which generalized weakness can affect respiratory muscles, leading to possible intubation or death.[2,3]

Onset of disease ranges from childhood to late adulthood, and largely depends on the subgroup of disease and the age of the patient.[4] Although complications from MG can arise, treatment methods have considerably reduced the risk of MG-associated mortality, with the current rate estimated to be 0.06 to 0.89 deaths for every 1 million person-years (that is, approximately 5% of cases).[3,5]

Pathophysiology

MG is caused by binding of autoimmune antibodies to postsynaptic receptors and by molecules that prevent signal transduction at the muscle endplate.[2,4,6,7] The main culprit behind the pathology (in approximately 85% of cases) is an autoimmune antibody for the acetylcholine receptor (AChR); however, other offending antibodies – against muscle-specific serine kinases (MuSK), low-density lipoprotein receptor-related protein 4 (LRP4), and the proteoglycan agrin – are known, although at a lower frequency (in approximately 15% of cases).[4,8] These antibodies prevent signal transmission by blocking, destroying, or disrupting the clustering of AChR at the muscle endplate, a necessary step in formation of the neuromuscular junction.[4,8,9]

The activity of these antibodies is key to understanding the importance of subgrouping the types of MG on the basis of antigen-specific autoimmune interactions. Specifically, the four categories of disease following a diagnosis of MG[2,7] are:

- AChR antibody-positive.
- MuSK antibody-positive.
- LRP4 antibody-positive.
- Seronegative MG.

Classifying MG into subgroups gives insight into the functional expectations and potential treatment options for a given patient, although expectations can vary.[2]

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Regrettably, the well-understood pathophysiology, diagnosis, and prognosis of MG have limited investigation and development of new therapies. Additionally, mainstay treatments, such as thymectomy and prednisone, work to alleviate symptoms for most patients, and have also contributed to periods of slowed research and development. However, treatment of refractory MG has, in recent years, become the subject of research on new therapeutic options, aimed at treating heterogeneous disease populations.[10]

In this review, we discuss the diagnosis of, and treatment options for, MG, and provide an update on promising options in the therapeutic pipeline.

Diagnosis

Distinguishing MG from other neuromuscular junction disorders is a pertinent step before treatment. Although the biomarkers discussed in this section are sensitive for making a diagnosis of MG, additional research is needed to classify seronegative patients who do not have circulating autoantibodies that are pathognomonic for MG.[11]

Upon clinical examination of observable myasthenic weakness, next steps would require assays for anti-AChR and anti-MuSK.[1] If either of those tests are inconclusive, assays for anti-LRP4 are available (although the LRP4 antibody is also a marker in other neurological disorders).[12]

In the MG diagnostic algorithm, next steps include an electromyography repetitive stimulation test, which, if inconclusive, is followed by single-fiber electromyography.[1] If any of these tests return positive, computed tomography or magnetic resonance imaging is necessary for thymus screening.

What follows this diagnostic schema is pharmacotherapeutic or surgical intervention to reduce, or even eliminate, symptoms of MG.[1]

Consensus on treatment standards

A quantitative assessment of best options for treating MG was conducted by leading experts,[13] who reached consensus that primary outcomes in treating MG are reached when a patient presents without symptoms or limitations on daily activities; or has only slight weakness or fatigue in some muscles.[13]

Pyridostigmine, an acetylcholinesterase inhibitor, is recommended as part of the initial treatment plan for MG patients. Pyridostigmine prevents normal breakdown of acetylcholine, thus increasing acetylcholine levels and allowing signal transmission at the neuromuscular junction.[14] Not all patients reach the aforementioned treatment goals when taking pyridostigmine, however; some require corticosteroids or immunosuppressive agents, or both, in addition.

Onset of disease ranges from childhood to late adulthood, and largely depends on the subgroup of disease and the age of the patient. Although complications from MG can arise, treatment methods have considerably reduced the risk of MG-associated mortality.

Steroids, such as prednisone and prednisolone, occupy the second line in MG patients because of their ability to produce a rapid response, availability, and economy.[1,15] Initial dosages of these medications are gradually adjusted to a maintenance dosage and schedule, as tolerated, to maintain control of symptoms.[15]

In MG patients who are in respiratory crisis, it is recommended that high-dosage prednisone be given in conjunction with plasmapheresis or intravenous immunoglobulin (IVIg).[15] When the response to steroids is inadequate, adverse effects cannot be tolerated, or the patient experiences symptomatic relapse, nonsteroidal immunosuppressive agents are started.

Immunosuppressives are used to weaken the immune response or block production of self-antibodies. Several agents have been identified for use in MG, including azathioprine and mycophenolate mofetil; their use is limited, however, by a lack of supporting evidence from randomized clinical trials or the potential for serious adverse effects.[13]

Referral and specialized treatments. Patients who are refractory to all the aforementioned treatments should be referred to a physician who is expert in the management of MG. At this point, treatment guidelines recommend chronic IVIg infusion or plasmapheresis, which removes complement, cytokines, and antibodies from the blood.[14] Additionally, monoclonal antibody therapies, such as eculizumab, have been shown to have efficacy in severe, refractory AChR antibody–positive generalized MG.[16]

Thymectomy has been a mainstay and, sometimes, first-line treatment of MG for nearly 80 years.[15] The thymus has largely been implicated in the immunopathology of AChR-positive MG. Models suggest that increased expression of inflammatory factors causes an imbalance among immune cells, resulting in lymphofollicular hyperplasia or thymoma.[17]

Despite the growing body of evidence implicating the thymus in the progression of MG, some patients and physicians are reluctant to proceed with surgical intervention. This could be due to a disparity in surgical treatment options offered by surgeons, and facilities, with varying experience or ability to conduct newer techniques. Minimally invasive approaches, such as video-assisted thoracoscopic surgery and robotic thymectomy, have been found to be superior to traditional open surgical techniques.[18,19] Minimally invasive techniques result in significantly fewer postoperative complications, less blood loss, and shorter length of hospital stay.[19]

In addition to the reduced risk offered by newer operative techniques, thymectomy has also been shown to have a beneficial effect by allowing the dosage of prednisone to be reduced in MG patients. In a randomized clinical trial conducted by Wolfe and coworkers,[20] thymectomy produced improvement in two endpoints after 3 years in patients with nonthymomatous MG: the Quantitative MG Score and a lower average prednisone dosage. Although thymectomy is not a necessary precursor to remission in MG patients, it is still pertinent in reducing the adverse effects of long-term steroid use – providing objective evidence to support thymectomy as a treatment option.

Emerging therapies

Although conventional treatments for MG are well-established, 10% to 20% of MG patients remain refractory to therapeutic intervention.[21] These patients are more susceptible to myasthenic crisis, which can result in hospitalization, intubation, and death.[21] As mentioned, rescue therapies, including plasmapheresis and IVIg, are imperative to achieve remission of refractory MG, but such remission is unsustainable. Risks associated with these therapies, including contraindications and patient comorbidity, and their limited availability have prevented plasmapheresis and IVIg from being reliable interventions.[12]

These shortcomings, along with promising results from randomized clinical trials of newer modes of pharmacotherapeutic intervention, have increased interest in new therapies for MG. For example, complement pathway and neonatal Fc receptor (FcRn) inhibitors have recently shown promise in removing pathogenic autoimmune antibodies.[18]

Efgartigimod. FcRn is of interest in treating generalized MG because of its capacity to recycle and extend the half-life of IgG.[22] Efgartigimod is a high-affinity FcRn inhibitor that simultaneously reduces IgG recycling and increases its degradation.[22] This therapy is unique: It is highly selective for IgG, whereas other FcRn therapies are nonspecific, causing an undesirable decrease in other immunoglobulin and albumin levels.[22] In December 2021, the U.S. Food and Drug Administration approved efgartigimod for the treatment of AChR-positive generalized MG.[23]

Zilucoplan is a subcutaneously administered complement inhibitor that has completed phase 3 clinical trials.[18,24] The drug works by inhibiting cleavage of proteins C5a and C5b in the terminal complement complex, a necessary step in forming cytotoxic pores on targeted cells.[18,24] Zilucoplan also prevents tissue damage and destruction of signal transmission at the postsynaptic membrane.[25] Clinical trials have already established improvement in the Quantitative MG Score and the Myasthenia Gravis Activities of Daily Living Score in patients with generalized MG.[18,24]

Zilucoplan is similar to eculizumab, but targets a different binding site, allowing for treatment of heterogeneous MG populations who have a mutation in the eculizumab target antigen.[26] Additionally, because of specific drug-body interactions, parameters for treatment using zilucoplan are broader than for therapies such as eculizumab. In a press release of zilucoplan trial results, the complement inhibitor showed statistically significant improvement in the treatment group of generalized, AChR-positive MG patients compared to the placebo group. Tolerability and safety were also favorable findings in this study. However, a similar rate of treatment-emergent adverse events were recorded between the treatment group (76.7%) and placebo group (70.5%), which could indicate that the clinical application of this treatment is still forthcoming.[27] If zilucoplan is approved by the FDA, it will be used earlier in disease progression and for a larger subset of patients.[26]

Nipocalimab is another immunoglobulin G1, FcRn antibody that reduces IgG levels in blood.[27,28] A phase 2 clinical study in patients with AChR-positive or MuSK antibody–associated MG showed that 52% of patients who received nipocalimab had a significant reduction in the Myasthenia Gravis Activities of Daily Living Score 4 weeks after infusion.[28] Phase 3 studies for adults with generalized MG are underway and are expected to conclude in April 2026.[29]

Looking forward

Despite emerging therapies aimed at treating IgG in both refractory and nonrefractory MG, there is still a need for research into biomarkers that further differentiate disease. Developing research into new biomarkers, such as circulating microRNAs, gives insight into the promise of personalized medicine, which can shape the landscape of MG and other disorders.[30] As of August 2022, only two clinical trials are slated for investigation into new biomarkers for MG.

Although the treatment of MG might have once been considered stagnant, newer expert consensus and novel research are generating optimism for innovative therapies in coming years. ■

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Spinal muscular atrophy: Patient care in the age of genetically targeted therapy

Newly available treatments have changed the natural history of SMA. Newborn screening, updated treatment guidelines, and treatment algorithms have likewise changed what can be clinically done for patients with SMA, but still questions remain.

By Kelli Whitlock Burton

In 2016, the U.S. Food and Drug Administration approved nusinersen, the first treatment for spinal muscular atrophy (SMA). Until then, SMA had a mortality rate nearly double that of the general population.[1] Two-thirds of patients were symptomatic within 6 months of birth and, in the absence of mechanical ventilation and other support, had a nearly 100% mortality rate by age 2.[2]

Five years later, there are three approved treatments for SMA, all of which have been shown to slow or even halt disease progression in many patients. These new therapies, coupled with expanded newborn screening and advancements in optimizing patient care, are changing the natural history of the disease and offering a prognosis that extends well beyond adolescence. Neurologists, whose SMA patient population once consisted almost entirely of children, are now treating more adults with the disease. Indeed, more than half of all people alive with SMA in the United States today are adults, according to Cure SMA.

"Managing SMA used to be clinic follow-ups where we were doing our best supportive care and watching people fall apart before our eyes," said John Brandsema, MD, a physician and neuromuscular section head at the Children's Hospital of Philadelphia. "Today, what we see in the vast majority of people is that they are either the same as they were before – which is completely against the natural history of this disease and something to be celebrated – or that people are really better with their function. It totally changes everything in the clinic."

Among those changes are a more proactive approach to rehabilitation and an even greater emphasis on personalized medicine and multidisciplinary care. But there is also a need for updated treatment guidelines, a new classification system to measure disease severity, specific biomarkers to guide therapy choices, more data on long-term efficacy of existing therapeutics, new medications to complement those therapies, and a deeper understanding of a disease that may have treatment options but still has no cure.

John Brandsema, MD

Mary Schroth, MD

Advances in early diagnosis

Patients with SMA lack a working copy of the survival motor neuron 1 (SMN1) gene, which provides instructions for producing a protein called SMN that is critical for the maintenance and function of motor neurons. Without this protein, motor neurons eventually die, causing debilitating and progressive muscle weakness that affects the ability to walk, eat, and breathe. SMA is rare, affecting about 1 in 10,000 newborns.

In approximately 96% of patients, SMA is caused by homozygous loss of the SMN1 gene. People with SMA have at least one copy of the SMN2 gene, sometimes called a "backup" gene, that also produces SMN protein. However, a single nucleotide difference between SMN2 and SMN1 causes about 90% of the protein produced by SMN2 to be truncated and less stable. Even with multiple copies of SMN2 present, as is the case with many infants with SMA, the amount of functional protein produced isn't enough to compensate for the loss of SMN1.[3]

All three approved medications are SMN up-regulators and work to increase the amount of functional SMN protein. Starting these medications early, even before symptoms present, is critical to preserve motor function. Early treatment depends on early diagnosis, which became more widespread after 2018 when SMA was added to the federally Recommended Uniform Screening Panel for newborns. As of July 1, 2022, 47 states have incorporated SMA newborn screening into their state panel,

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ensuring that 97% of all infants born in the United States undergo SMA screening shortly after birth. Screening in the remaining states – Hawaii, Nevada, and South Carolina – and Washington, D.C., is expected by mid-2023.

SMA newborn screening is a PCR-based assay that detects homozygous SMN1 gene deletion found in about 95% of all people with SMA. The remaining 5% of cases are caused by various genetic mutations that can only be detected with gene sequencing. In these cases, and in children who don't undergo SMA newborn screening, the disease is usually identified when symptoms are noticed by a parent, pediatrician, or primary care provider. But a study found that in 2018 only 52.7% of pediatricians correctly identified genetic testing as a requirement for a definitive diagnosis of SMA; in 2019, with a larger sample size, that number decreased to 45%.[4] The lack of awareness of diagnostic requirements for SMA could contribute to delays in diagnosis, said Mary Schroth, MD, chief medical officer for Cure SMA and a coauthor of the study.

"In our world, suspicion of SMA in an infant is an emergency situation," Dr. Schroth said. "These babies need to be referred immediately and have genetic testing so that treatment can begin as soon as possible."

Based on the study findings, Dr. Schroth and others with Cure SMA launched a new tool in 2021 designed to help pediatricians, primary care physicians, and parents identify early signs of SMA, so that a referral to a pediatric neurologist happens quickly. Called SMArt Moves, the educational resource features videos and a checklist to help increase early detection in infants who had a negative SMA newborn screening result or did not receive SMA screening at birth.[5]

Who to treat, when, and with which treatment

For many patients, having multiple effective treatment options means that SMA is no longer a fatal disease in early childhood, but one that can be managed into adolescence and adulthood. The question for clinicians is, who do they treat, when, and with which treatment?

Studies have long shown that the number of copies of the backup gene that a patient has is inversely associated with disease severity.[6] In 2018, a group of SMA experts published a treatment algorithm to help guide decision-making following a positive SMA newborn screening.[7] The treatment guidelines were updated in 2020 based on clinical trial data for presymptomatic infants, and current recommendations include immediate treatment for infants with two to four copies of the SMN2 gene.[8] For patients with only one copy of SMN2, most of whom will likely be symptomatic at birth, the guidelines recommend that treatment decisions be made jointly between the clinician and the family.[7,8]

Two deaths from liver failure linked to spinal muscular atrophy drug

Two children taking the gene therapy drug onasemnogene abeparvovec (Zolgensma, Novartis) for spinal muscular atrophy (SMA) have died from acute liver failure, according to a statement issued by the drug's manufacturer.

The patients were 4 months and 28 months of age and lived in Russia and Kazakhstan. They died 5-6 weeks after infusion with Zolgensma and approximately 1-10 days after the initiation of a corticosteroid taper.

These are the first known fatal cases of acute liver failure associated with the drug, which the company notes was a known side effect included in the product label and in a boxed warning in the United States.

"Following two recent patient fatalities, and in alignment with health authorities, we will be updating the labeling to specify that fatal acute liver failure has been reported," the statement reads.

"While this is important safety information, it is not a new safety signal," it adds.

Rare genetic disorder

SMA is a rare genetic disorder that affects about 1 in 10,000 newborns. Patients with SMA lack a working copy of the survival motor neuron 1 (SMN1) gene, which encodes a protein called SMN that is critical for the maintenance and function of motor neurons.

Without this protein, motor neurons eventually die, causing debilitating and progressive muscle weakness that affects the ability to walk, eat, and breathe.

Zolgensma, a one-time gene replacement therapy delivered via intravenous infusion, replaces the function of the missing or nonworking SMN1 gene with a new, working copy of the SMN1 gene.

The first gene therapy treatment for SMA, it was approved by the U.S. Food and Drug Administration in 2019 for patients with SMA up to 2 years of age. It is also the most expensive drug in the world, costing about $2.1 million for a one-time treatment.

"We have notified health authorities in all markets where Zolgensma is used, including the FDA, and are communicating to relevant healthcare professionals as an additional step in markets where this action is supported by health authorities," the manufacturer's statement says.

Studies have suggested that the treatment's effects persist more than 5 years after infusion.

Clinical trials currently underway by Novartis are studying the drug's long-term efficacy and safety and its potential use in older patients.

The company is also leading the phase 3 clinical trial STEER to test intrathecal (IT) administration of the drug in patients ages 2-18 years who have Type 2 SMA.

That trial began late last year after the FDA lifted a 2-year partial hold on an earlier study. The FDA halted the STRONG trial in 2019, citing concerns from animal studies that IT administration may result in dorsal root ganglia injury. The partial hold was released last fall following positive study results in nonhuman primates.

None of the current trials will be affected by the two deaths reported, according to a Novartis spokesperson.

Some suggest that the number of SMN2 copies a patient has should also be a factor in determining phenotype, which has started a conversation on the development of a new classification system.[9] The original classification system for disease severity – Types 0-4 – was based on age of onset and degree of motor function achieved, with Type 0 developing prenatally and being the most severe and Type 4 developing in adulthood. Type 1 is the most common, affecting more than half of all people with SMA, followed by Types 2-4. In 2018, updated consensus care guidelines offered a revised classification system that better reflected disease progression in the age of therapy. The functional motor outcomes include nonsitters (historically Type I), sitters (historically Type 2/3), and walkers (historically Type 3/4).[10,11] These guidelines are a start, but clinicians say more revision is needed.

"Types 1, 2, 3, 4 were based on function – getting to a certain point and then losing it, but now that we can treat this disease, people will shift categories based on therapeutic response or based on normal development that is possible now that the neurologic piece has been stabilized," Dr. Brandsema said. "We need to completely change our thinking around all these different aspects of SMA management."

While discussions of a new classification system for SMA are underway, another effort to update treatment recommendations is closer to completion. Led by Cure SMA, a group of about 50 physician experts in the United States and Europe who specialize in SMA are revising guidelines for diagnosis and treatment, the first time the recommendations have been updated since 2018. The updated recommendations, which should be published later this year, will focus on diagnosis and treatment considerations.

"We have three treatments that are available, and there are specific FDA indications for each of those, but it's not totally clear just how those medications should be used or applied to different clinical situations," said Dr. Schroth. "We're in a rapid phase of learning right now in the SMA community, trying to understand how these treatments alter physiology and disease outcomes and how to best use the tools that we now have available to us. In parallel with clinical treatments, we have to be doing the best care we can to optimize the outcomes for those treatments."

Research advances in 2021

Although all three drugs approved to treat SMA – nusinersen (Spinraza; Biogen), onasemnogene abeparvovec-xioi gene replacement therapy (Zolgensma; Novartis Gene Therapies), and risdiplam (Evrysdi, Genentech/Roche) – are highly effective, there are still unanswered questions and unmet needs. New research findings from 2021 focused on higher dosing, different drug-delivery methods, combination therapy, and complementary therapeutics to address SMA comorbidities.

Higher-dose nusinersen. The first drug approved to treat SMA, nusinersen is an antisense oligonucleotide approved for all ages and all SMA types. It works by altering splicing of the SMN2 gene pre-mRNA to make more complete SMN protein. Given as an intrathecal (IT) injection, four "loading doses" are administered within the first 2 months of treatment, followed by a maintenance dose every 4 months for the duration of the individual's life.

Reports from patients of waning effects of nusinersen just prior to follow-up treatment have led some clinicians to ask if a higher dose may be needed. A study underway seeks to address that issue.

DEVOTE is a phase 2/3 trial to study the safety and efficacy of high-dose nusinersen in patients with SMA. Preliminary findings reported in 2021 found no adverse events among patients treated with 28 mg of nusinersen for 161-257 days.[12] Another analysis from this trial found that higher doses are associated with greater decrease of plasma phosphorylated neurofilament heavy chain (pNF-H) levels in patients with SMA and may lead to clinically meaningful improvement in motor function beyond that observed with the approved 12 mg dose.[13] The trial is ongoing.

Another trial, ASCEND, is a phase 3B study assessing higher dose nusinersen in patients previously treated with risdiplam. Recruitment for that trial began in October 2021.

Long-term efficacy and IT administration of SMA therapy. Several studies are looking at the long-term efficacy and alternate routes of administration of onasemnogene abeparvovec and other SMA therapies.

A one-time gene replacement therapy delivered via an IV infusion replaces the function of the missing or nonworking SMN1 gene with a new, working copy of the SMN1 gene. FDA approved in 2019, it is authorized for use in patients with SMA up to 2 years of age.

The latest data from an ongoing, long-term follow-up safety study of onasemnogene abeparvovec, published in May 2021, suggest that the treatment's effects persist more than 5 years after treatment. Researchers followed 13 infants with symptomatic SMA Type 1 since the beginning of the phase 1 clinical trial of the gene transfer therapy. All patients who received the therapeutic dose maintained their baseline motor function, and two of the patients actually improved without other SMN-targeted treatment. At a median 6.2 years after they received treatment, all were alive and none needed permanent ventilation.[14]

After a 2-year hold by the FDA, a study of IT administration of onasemnogene abeparvovec is now enrolling patients. Citing concerns from animal studies that IT administration

might result in dorsal root ganglia injury, the FDA issued a partial hold on the STRONG trial in 2019. Following positive study results in nonhuman primates, the FDA announced the trial can continue. Novartis is launching a new phase 3 STEER trial to test the drug delivered intrathecally in patients aged 2-18 years with Type 2 SMA. IT administration could allow the gene therapy to be used safely and effectively in more patients with SMA.

Efficacy of risdiplam in more patients. The first oral treatment for SMA was approved by the FDA in 2020. It's given once per day in patients with SMA of all ages and disease types. The drug increases functional SMN protein production by the SMN2 gene.

A July 2021 publication of the results of the FIREFISH study found that infants with Type I SMA treated with risdiplam for 12 months were significantly more likely to achieve motor milestones, such as sitting without support, compared with untreated infants with Type 1 SMA.[15] Risdiplam is also effective in older patients with Type 2 or 3 SMA, according to results published in December from the SUNFISH clinical trial.[16] Another study, RAINBOWFISH, is studying safety and efficacy at 24 months in presymptomatic infants started on treatment at up to 6 weeks of age.

The efficacy of risdiplam in previously treated patients is the subject of JEWELFISH, an ongoing study in patients 6 months to 60 years with SMA. Preliminary data presented at the 2020 Virtual SMA Research and Clinical Care Meeting suggest treatment with risdiplam led to a median two-fold increase in the amount of blood SMN protein levels after 4 weeks, which was sustained for at least 24 months.[17]

Combination therapy. Among the more eagerly awaited results are those from studies of combination therapies, including those that combine approved SMN up-regulators with new non–SMN-targeted therapeutics.

"We're seeing that while these three approved therapies have dramatic results, especially for infants who are treated presymptomatically, there are still unmet medical needs in those patients, particularly for older teens and adults whose disease may have progressed before they were able to start therapy," said Jackie Glascock, PhD, vice president of research for Cure SMA.

Of particular interest are studies of myostatin inhibitors, therapeutics that block the production of the protein myostatin. Myostatin acts on muscle cells to reduce muscle growth. Animal studies suggest that inhibiting myostatin increases muscle mass, which could be important in patients with muscle loss due to SMA.

Three experimental myostatin inhibitors are currently in clinical trials. MANATEE is a global phase 2-3 trial that aims to evaluate the safety and efficacy of the antimyostatin antibody GYM329 (RO7204239) in combination with risdiplam. SAPPHIRE is a phase 3 trial of apitegromab (SRK-015) in combination with nusinersen or risdiplam. RESILIANT is a phase 3 trial of tadefgrobep alfa in combination with other treatments.

A trial is underway to study the efficacy and safety of nusinersen in patients with persistent symptoms of SMA after treatment with the gene therapy. The phase 4 study, RESPOND, is enrolling children aged 2-36 months.

What's needed next

Despite the advances in treatment and patient care, Dr. Brandsema, Dr. Schroth, and Dr. Glascock note that there remain unmet needs in the SMA community in a variety of areas.

Increased focus on adults with SMA. Before nusinersen, treatment of SMA mainly involved treating its symptoms. Many patients stopped seeing their neurologist, relying more heavily on pulmonary care specialists and/or primary care providers to address breathing, nutrition, and mobility problems. "Now with the approval of these treatments, they're coming back to see their neurologists and are becoming more visible in the SMA community," Dr. Schroth said.

Despite this re-emergence, a 2020 meta-analysis of studies on adults with SMA found a paucity of data on physical and occupational therapy, respiratory management, mental health care, and palliative care.[18]

"There is just so much work we need to do in the area of adult clinical care of SMA."

Treatment algorithms. While the development of the newborn screening algorithm and revised patient care guidelines are helpful resources, clinicians still face uncertainty when choosing which therapy will work best for their patients. Treatment algorithms that help clinicians figure out what therapy or combination of therapies will offer the best outcomes for individual patients are desperately needed, Dr. Brandsema said.

"Each person's experience of this disease is so unique to the individual based partly on their genetics and partly on the factors about what got them into care and how compliant they are with everything we're trying to do to help them," he said. "Biomarkers would help clinicians create personalized treatment plans for each patient."

More basic science. While scientists have a good understanding of the SMN gene, there are many unanswered questions about the function of the SMN protein and its relationship to motor neuron loss. SMN is a ubiquitously expressed protein, and its function in other cell types is largely unknown. Despite all of the research advances, there is much basic science left to be done.

"We are strongly advocating to regulatory authorities that these aren't cures and we need to continue to invest in the basic research," Dr. Glascock said. "These biological questions that pertain to SMN and its function and expression really drive drug development. I really think that understanding those pathways better will lead us to more druggable targets." ■

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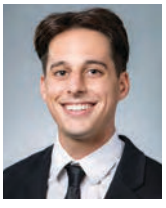
The broad and challenging – but promising – landscape of peripheral neuropathy

This review of peripheral neuropathy summarizes the more common causative entities, diagnostic tools that can potentially be employed to identify the disorder, and treatments that are in use or being tested to prevent, slow, or reverse its effects.

By Yun Seo Lee; Jonathan Kosacki; Kanika Bhandari, PharmD; and Amanda Tran, PharmD

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Peripheral neuropathy is becoming an increasing focal point for clinicians when treating patients, because of the plethora of causes to which the disorder has been attributed. Characterized by damage to the peripheral nervous system, peripheral neuropathy causes sharp, burning pain; numbness of the extremities that can travel proximally; muscle weakness; and an overall diminished quality of life. Rather than being a self-developing disease, peripheral neuropathy has mostly been identified as a symptom of causative disorders and therapeutic agents – making prevention and treatment extremely important for patients and providers.

In this review, we summarize the landscape of peripheral neuropathy, including the more common causative entities; diagnostic tools that can potentially be employed to identify the disorder; and treatments that are in use or being tested to prevent, slow, or reverse the effects of peripheral neuropathy.

DIABETIC PERIPHERAL NEUROPATHY

The most common cause of peripheral neuropathy is diabetes mellitus. Diabetic peripheral neuropathy (DPN) is a symmetrical, length-dependent neuropathy that affects more than 50% of type I and type II diabetes patients.[1] Not only is DPN an initiating factor of foot ulcers and nontraumatic lower-limb amputation, but it also leads to a severely lower quality of life, financial burden, and increased risk of death after major surgical procedures.[2]

Once DPN has progressed significantly, its effects are irreversible; there are no agents capable of reversing or halting DPN past initial stages of disease.[3] It is important to detect and treat DPN early on, as it has a favorable prognosis and most DPN-related amputations are preventable.

Diagnosis

Nerve-conduction studies are the preferred diagnostic tool for DPN; however, these studies are costly and difficult to conduct in a clinical setting.[2] Currently, such diagnostic tools as the 10-g monofilament and tuning fork are more commonly utilized to detect loss of protective foot sensation to decrease the risk of foot ulceration.[2] In addition, other common aspects of diagnosing DPN include assessment of symptoms in the patient's hands or feet and patient-reported symptoms.

Several diagnostic devices are in experimental stages and have shown potential for utilization in clinical settings.

DPNCheck is a handheld device, with a turnaround time of 3 minutes, that measures sural nerve conduction velocity, which can identify DPN early in asymptomatic cases; and amplitude of sensory-nerve action potentials, which decrease with the degeneration of axons, a clinical characteristic of DPN. In a study of

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patients with diabetes (n = 162 [type 1, n = 80; type 2, n = 82]) and healthy controls (n = 80), a comparative analysis of DPNCheck and reference techniques showed a strong linear relationship between clinical neuropathy scores and LDI_{FLARE} (r = 0.64-0.84; $P < .03$), which suggests that the device might be viable in clinical settings.[4] LDI_{FLARE} is a method developed to assess axon reflex to detect neuropathy in type 2 diabetes.[4]

Neuropad, a 10-minute test, measures foot plantar-surface sweat production, indicated by a cobalt compound color change on the device. The test is advantageous because it is highly sensitive – 73% more sensitive than DPNCheck – and does not rely on patient response or require operator training.[5] A study of Neuropad showed that a drier foot and, therefore, increased risk of foot ulceration correlated with greater abnormal readings on the device, which might indicate onset of more severe DPN in the future.[6]

Sudoscan measures sudomotor function in 3 minutes through an electrochemical reaction between stimulated sweat glands and electrodes.[2] A study performed in China in patients with type 2 diabetes (n = 394) showed that electrical conductance in the feet is associated with increasing risk and severity of symptoms of DPN in asymptomatic patients (r = 0.98 [95% confidence interval, 0.962-0.993]; $P < .01$) and might serve as a biomarker of DPN.[7]

Although these three techniques present favorable data, each is a nerve conduction study that can access only small-fiber nerves. Additional testing is required for larger-fiber nerves that are also affected by DPN.[2] Also, some of the studies of these devices have high heterogeneity and a small sample size. Further research utilizing these three methods should include larger sample sizes to appropriately assess any clinically significant patient outcomes.

Corneal confocal microscopy (CCM), another potential technique for DPN screening, is a noninvasive ophthalmic device for assessing corneal small-fiber nerves. A study of patients with diabetes or obesity or both (n = 35) showed high reproducibility of corneal-nerve pathology identification using CCM.[8] A larger-scale study showed that CCM can detect a reduction in corneal-nerve parameters in DPN patients, as well as in patients who have yet to develop DPN – thus demonstrating the technique's ability to detect both early subclinical and established DPN.[9] Once CCM is approved as a point-of-care device, it might provide a reliable, sensitive screening method for DPN as an early-intervention tool.

Therapeutic options

The three principal types of treatment for DPN are tricyclic antidepressants, anticonvulsants, and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs). Only three medications are U.S. Food and Drug Administration approved for the treatment of DPN: pregabalin, duloxetine, and the recently approved capsaicin patch. Some opioid analgesics, including extended-release tapentadol, are FDA approved for DPN-associated neuropathic pain; however, evidence of their efficacy is questionable, and they present a risk of addiction.[10] Here, we focus on potential treatments for DPN and DPN-associated neuropathic pain.

Cinacalcet. Several potential treatments have been studied for alleviating DPN symptoms after progression. Cinacalcet is a calcimimetic agent that activates the adenosine monophosphate-activated protein kinase–endothelial nitric oxide synthase pathway, which mediates DPN development. The drug has shown evidence of improving sensorimotor function and restoring nerve function in human Schwann cells expressed in diabetes-induced mice.[11] In these animal models, cinacalcet improved tactile response when interventional mice were compared with a control group ($P < .01$).[11] Further research is necessary to determine similar efficacy in human subjects.

Traditional Chinese medicine. Recent studies have focused on traditional Chinese medicine and practice, such as acupuncture and moxibustion, for DPN.

Moxibustion is the technique of burning moxa floss (a plant also known as mugwort) on different points on the body, which is thought to alleviate disease. In a study performed on rats, moxibustion increased nerve velocity ($P < .05$) and preserved sciatic-nerve ultrastructure.[12] Research on the use of moxibustion is preliminary. A meta-analysis of available data found that all clinical studies took place in China, and results were therefore subject to high heterogeneity and small sample size.[13] Previously, a lack of high-quality data prevented moxibustion from being considered a potential treatment.[3] The technique has demonstrated potential benefit, but larger-scale and more rigorous studies must be utilized to verify its clinical efficacy.

Quercetin. This common dietary flavonoid is in development. In rat models with induced DPN, treatment produced significant neuroprotective effects, such as rescued mechanical withdrawal threshold, lowered nerve densities ($P = .0378$), and rescued lowered levels of reactive O_2 species ($P < .0001$), which contribute to neurotoxicity in many peripheral neuropathies.[14] Another study of the anti-inflammatory effects of quercetin in rat models found significant lowering of inflammatory factors, including proteins encoded by toll-like receptor 4 and MyD88, and protein transcription factor nuclear factor kappa B ($P < .001$), which can be beneficial in the treatment of DPN.[15] Future testing in human subjects might reveal similarly positive effects.

Vitamin B. A systematic review examined the therapeutic effects of vitamin B supplementation on DPN. Through a meta-analysis on 14 studies (n = 997), it was revealed that statistically

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significant improvements in pain and electrophysiological sensory outcomes were observed after vitamin B supplementation. However, the majority of the studies included in the analysis utilized combination therapies with different vitamins (such as vitamin D) and other vitamin B types. Furthermore, deficiencies in B vitamins – especially folic acid and vitamin B_{12} – have been observed in diabetic patients, and may be the potential cause of DPN in them. The validity of the studies and their findings are weakened by this observation. Therefore, the clinical efficacy of individual B vitamin supplements must be evaluated in long-term, larger-scale future studies that exclude those with B vitamin deficiency and DPN to minimize potential error.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Platinum-based agents have been widely accepted as an ideal solution for slowing tumor progression; however, it has been established that platinum adducts within DNA are the cause of neuronal degeneration – specifically in dorsal-root ganglion neurons of the peripheral nervous system. In a 2010 meta-analysis in the United States, the prevalence of chemotherapy-induced peripheral neuropathy (CIPN) was observed to range from 65% to 75%, depending on the platinum-based agent.[16] This problem is often dose-limiting and can lead to cessation of treatment, causing patients physical and financial harm. CIPN can be acute or chronic, and symptoms affect motor, sensory, and autonomic function, which can lead to reduced quality of life.[17]

Diagnostic tools and strategies

A variety of avenues can be taken to assess whether a patient has CIPN. Because peripheral neuropathy is often subjective, it has been recommended that clinicians use patient-reported outcome measures in this setting, in the form of a questionnaire.

Common toxicity criteria. The most conventional measure of CIPN is the National Cancer Institute's Common Toxicity Criteria, which grades severity of adverse effects on a scale of 1 to 5 and has been found to be statistically valid.[18] This questionnaire assesses a patient's neuropathic pain score and sensory deficits, and can detect other potential adverse findings, such as neutropenia.

Total neuropathy score. This commonly used questionnaire measures subjective autonomic, sensory, and motor symptoms on a scale of 0 to 4 for each item, with the individual item scores then summed. A score > 5 indicates CIPN.[19] The tested validity of this measure shows that it has an inter-rater reliability of 0.966 and an intra-rater reliability of 0.986.[19]

Other questionnaires. The Neuropathy Screening Questionnaire, Treatment-Induced Neuropathy Assessment Scale, and Chemotherapy-Induced Peripheral Neuropathy Assessment Tool have been identified as means of understanding what a patient experiences following neurotoxic chemotherapy.[18]

Pain caused by CIPN can also be assessed with one of several general scales, such as the Neuropathic Pain Scale for Chemotherapy-Induced Neuropathy (NPS-CIN), which identifies a patient's level of pain on a scale from 0 to 4 on six items: intensity, unpleasantness, sharpness, depth, numbness, and tingling. This scale has been found to be reliable.[18]

Other scales that can be used are the Neuropathic Pain Symptom Inventory, Patient-Reported Outcomes Measurement Information System: Pain Quality Neuro, and Leeds Assessment of Neuropathic Symptoms and Signs.[18]

Other diagnostic tests. Tests to determine a chemotherapy patient's functional ability regarding their extremities include postural stability tests, the Timed Up and Go (TUG) test, the Fullerton Advance Balance (FAB) Scale, the 6-minute walk test, and the grooved pegboard test.

Nerve conduction studies have been identified as useful tools to assess the physiologic function of fibers, but are costly and used most often in research settings.[18] Quantitative sensory testing and the Bumps test are used to assess threshold capacities for varying sensations. Nerve-imaging tools, such as high-resolution ultrasonography, magnetic resonance neurography, and positron emission and computed tomography, have been found to be successful in identifying nerve damage.[18]

Additionally, the accumulation of mitochondrial DNA (mtDNA) in the blood has been identified as a potential biomarker for CIPN following animal trials on rats. Researchers conducted a double-blind trial where healthy rats were given doses of paclitaxel, oxaliplatin, and bortezomib and compared to vehicle-treated rats. Researchers found that there was a correlation between the onset of CIPN and levels of mtDNA, with one- to twofold increases of mtDNA found in paclitaxel- and oxaliplatin-treated patients ($P < 0.01$). Dysfunctional mitochondria can cause an increase in the activity of reactive oxygen species, which results in damage to mtDNA; and abnormal bioenergetics, which may lead to irregular ATP production and result in cellular damage.

Navitoclax. The antineoplastic agent cisplatin is used to treat a variety of cancers, including ovarian, lung, head and neck, testicular, and bladder.[20] Using single-cell RNA sequencing of dorsal-root ganglion cells in mouse models that have been given human equivalent doses of cisplatin to induce peripheral neuropathy, a study identified that the drug was upregulating the cyclin-dependent kinase inhibitor 1A gene (CDKN1A) and leading to overproduction of its product, the p21 protein.[21] This

is because of a cellular response to DNA damage that causes the dorsal-root ganglion sensory neuron to change into a senescence-like state to survive. Subsequently, accumulation of senescent sensory neurons correlates with induction of neuropathic pain and peripheral neuropathy. It has been established, in mouse models, that removing senescent cells has the potential to reduce or reverse peripheral neuropathy associated with cisplatin treatment.[21]

A study induced irreversible CIPN using cisplatin in mice that were subsequently treated with antineoplastic agent navitoclax (n = 5) or vehicle (n = 10). Using navitoclax, a broad-spectrum senolytic agent, the study examined the dorsal-root ganglia of the mice and found that CIPN was reversed following clearance of senescent cells, with baseline mechanical thresholds able to be reestablished without difference, compared with the control group (P = .7734).[22] The investigators found that clearance of senescent cells using navitoclax proved a promising avenue toward mitigating CIPN. More studies should be completed to validate this treatment as an effective preventive.

NGF monoclonal antibody (tanezumab). Tanezumab has been identified as a potential analgesic for CIPN having observed success during animal trials. This monoclonal antibody targets the NGF-TrkA pathway in a dose-dependent manner which results in a reduction of neuronal sensitivity and subsequently neuropathic pain (P < .05). NGF is a peripheral pain mediator that has functional properties relating to inflammation and neuropathy. Therefore, by targeting this protein and inhibiting its activation, patients could potentially see a dramatic improvement in their quality of life following a CIPN diagnosis. This potential analgesic was observed to be successful for a variety of chemotherapeutic agents including cisplatin, vincristine, and paclitaxel.

SASP inhibitors. A second possible approach to neutralizing senescent cells would be by inhibiting the senescence-associated secretory phenotype (SASP). This could be accomplished through the use of nuclear factor kappa B inhibitors, mammalian target of rapamycin (mTOR) inhibitors, bromodomain and extra-terminal (BET) inhibitors, and inhibitors of secretory factors, such as interleukin (IL)-6 and tumor necrosis factor (TNF) alpha.[23] Rapamycin, an mTOR inhibitor that is already used in clinical settings, has been found to reduce the inflammatory effects of senescent cells, expanding the lifespan of mice.[24] JQ1, OTX015, and ARV825 are BET inhibitors that have been found to block bromodomain-containing protein 4, thus inducing senescent cell death.[25] IL-6 inhibitors (for example, tocilizumab) and TNF alpha inhibitors (for example, adalimumab) are already used clinically and can mitigate the effects of SASP.[23,26] However, further studies are needed to examine potential adverse effects of this type of therapy.

Mitigation of oxaliplatin adverse effects. This platinum-based chemotherapeutic agent associated with peripheral neuropathy is primarily used to treat colorectal cancer and digestive-tract malignancies.[27] Oxaliplatin-induced peripheral neuropathy (OIPN) can be acute or chronic, and causes neuropathic pain, autonomic nerve dysfunction, and hypersensitivity to cold, which lead to abnormal nervous system effects, such as peripheral paresthesia.

These symptoms derive from oxaliplatin's effects on a variety of cellular mechanisms, and differ in chronic and acute OIPN. Acute OIPN includes abnormal changes to sodium, potassium, calcium, and transient receptor potential channels, which lead to dysregulation and dysfunction in peripheral neurons; glia activation associated with dysregulation of pain modulation, by reducing thresholds; and upregulation of the octamer-binding transcription factor (OCT) protein.

Chronic OIPN has been associated with damage to nuclear DNA by platinum adducts, mitochondrial dysfunction (due to oxidative stress), and neuroinflammation caused by glia activation and gut microbiota.[28]

With increased understanding regarding cellular mechanisms affected in OIPN, treatment options are being established to prevent or reduce its effects. A treatment being tested for the treatment of OIPN is the serotonin and norepinephrine reuptake inhibitor (SSNRI) antidepressant duloxetine.[29] In a clinical trial of 40 patients with gastrointestinal cancer, duloxetine was found to reduce cold sensitivity (P = .001), tingling or discomfort of hands (P < .002) and feet (P = .017), and peripheral neuropathic pain (P = .001), and was found to prevent paresthesia (P = .025).[29] The SNRI antidepressant venlafaxine has also shown that it can alleviate neuropathic pain and motor neuropathy in clinical trials.[30]

Antioxidant agents, such as amifostine and calmangafodipir, have also been identified as possible preventive measures against OIPN. Amifostine prevents neuronal hyperactivation and nitrosative stress, while calmangafodipir modulates reactive O_2 species, regulates ion channels, and protects axons and the myelin sheath.[31,32]

Treatments such as riluzole, lidocaine, and pregabalin have all shown promise in reducing the effects of OIPN by their action on potassium, sodium, and calcium channels, respectively.[28] A study conducted on mice (n = 565) with OIPN found that riluzole effectively mitigated motor and sensory deficits associated with the use of oxaliplatin.[33]

TREK-1 and TRAAK, potassium channels that are important for thermal and motor sensitivity, and that act as silencing mechanisms to excitatory stimuli, were shown to degenerate following oxaliplatin treatment, leading to hypersensitivity. Riluzole performs its therapeutic function by activating TREK-1

and TRAAK channels and blocking excessive accumulation of glutamate. Following riluzole treatment, mice were observed to show a significant reduction in sensorimotor deficits. Interestingly, riluzole also aided in reducing depression associated with oxaliplatin ($P < .01$).[33] However, more studies are necessary to ensure the safety and efficacy of riluzole in humans.

Pyridoxine, pyridostigmine for vincristine-induced peripheral neuropathy. Vinca alkaloids have also been identified as chemotherapeutic agents that induce peripheral neuropathy. One such agent, vincristine, which is used primarily to treat leukemia and brain cancer, has been observed to cause peripheral neuropathy, including motor, autonomic, and sensory symptoms, such as abnormal gait, mechanical allodynia, paresthesia, ptosis, and obstipation, and altered perception of stimuli.[34,35] These symptoms are caused primarily by the ability of vincristine to activate neuroinflammatory mechanisms in dorsal-root ganglia. This is caused by activation of nucleotide-binding oligomerization domain 3 (NLRP3)-dependent release of IL-1b and subsequent cleavage of gasdermin D and caspase-1 in macrophages (observed in mouse models). Vincristine activates the NLRP3 signaling cascade that results in production of proinflammatory cytokines, thus inducing symptoms of peripheral neuropathy.[36]

Pyridoxine and pyridostigmine have been introduced as potential treatments for vincristine-induced peripheral neuropathy. Following a clinical trial of pediatric acute lymphoblastic leukemia patients, a study of 23 patients with vincristine-induced peripheral neuropathy found statistical validity for using pyridoxine and pyridostigmine because the drugs improved the neuropathy score ($P < .001$).[37] However, more research is needed before implementing their use in point-of-care settings.

AUTOIMMUNE PERIPHERAL NEUROPATHY

Autoimmune peripheral neuropathies (APNs) occur when the immune system targets the peripheral nervous system and its various cells. Although there is a wide range of conditions in this category of peripheral neuropathy, the two most common types – Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) – have been targeted for clinical research.

Guillain-Barré syndrome: Diagnosis

Guillain-Barré syndrome encompasses a variety of acute inflammatory polyneuropathies, including axonal motor, sensory, and autonomic neuropathies and Miller Fisher syndrome (MFS).[38] In particular, the anti-GQ1b ganglioside antibody is considered archetypical in APNs because it is detected in MFS patients and not found in normal and disease-control samples, which makes it a good clinical marker.[39]

It is difficult to distinguish GBS from CIDP because the time frame of onset of maximum deficit of neuropathy – 4 weeks – can overlap with subacute CIDP symptoms.[40] Current diagnosis is based on elevated levels of cerebrospinal fluid (CSF) proteins, which can increase fourfold 6 weeks into the early phase of disease, and nerve conduction studies.[40] However, electrodiagnostic readings and CSF protein levels are normal in 30% to 50% of patients in the first week after onset of disease and must be repeated in weeks that follow.[41] A major disadvantage in the workup of suspected GBS is that the syndrome can be confirmed only several weeks after onset of symptoms.

Ultrasonography. A potential new diagnostic tool is serial peripheral nerve ultrasonographic (US) imaging. A pilot study of GBS patients (n = 16) showed that US can detect enlarged nerve cross-sections in median, ulnar, and sural nerves in the first 3 weeks of disease. Imaging performance was consistent with that of nerve conduction studies, and was advantageous because US is easier to perform and for patients to undergo.[42]

Spinal inflammation. Another study hints at the importance of spinal-root inflammation as an early indicator of disease, especially when nerve conduction study readings are normal.[43] Further research is needed to demonstrate the clinical efficacy of this diagnostic method in larger population groups.

Guillain-Barré syndrome: Therapeutic options

The standard of care for GBS in the United States is intravenous immunoglobulin (IVIG) therapy and plasmapheresis, but there is no FDA-approved treatment.[44] Although the two treatments have been shown to be equally effective in early stages of disease, early relapses can occur with both. One study found that 20% of patients who underwent plasmapheresis relapsed.[40] Because nearly 50% of GBS patients do not respond to IVIG or plasmapheresis, the need is urgent for new therapies to decrease the risk of permanent disability.[45]

Antibody therapy. Recent developments include the use of monoclonal antibodies against GBS. ANX005 is an immunoglobulin G4 recombinant antibody that inhibits complement component 1q (C1q). Activation of this protein triggers the classical complement cascade, a natural part of the innate immune system that is nonetheless inappropriately activated in some autoimmune diseases, leading to neurodegeneration as a consequence of tissue damage.

ANX005 was found to have high-binding affinity to C1q in human, rat, cynomolgus monkey, and dog sera in nonclinical trials, and demonstrated low cross-reactivity despite being a plasma protein present throughout human tissue. Furthermore, studies show that ANX005 can deplete C1q completely in the CSF of monkeys.[46] Phase 1b clinical trials in Bangladesh with GBS patients (n = 23) 18-58 years of age against a pla-

cebo group (n = 8) indicate that treatment is well tolerated. Drug-related serious adverse events were lacking and subjects' GBS-Disability Score improved compared with placebo controls at week 1 ($r^2 = 0.48$; $P < .0001$) and week 8, when an improvement of three or more in the score was observed.[40]

ANX005 is entering phase 2 trials, which are expected to be completed in 2023.[47]

Eculizumab. This promising treatment is a monoclonal antibody against C5 convertase, an enzyme that catalyzes formation of C5b-9, a membrane attack complex in nerve membranes. Studies in mouse models showed that treatment could significantly improve symptoms of terminal motor neuropathy and completely block formation of membrane attack complexes.[48] Rats in this study were paralyzed by anti-GQ1b antibodies to emulate GBS pathogenesis.

A double-blind, placebo-controlled phase 2 clinical trial in Japan enrolled 34 patients (23 assigned to receive eculizumab; 11, to placebo); all were 18 years old or older and could not walk independently (3-5 on the GBS functional grading scale). Results showed the following:

- Sixteen percent more patients receiving eculizumab treatment (n = 14; 42-78 years) than in the placebo group (n = 5; 20-73 years) could walk independently after 4 weeks.
- Fifty-six percent more patients in the functional group (n = 17; 52-90 years) than in the placebo group (n = 2; 20-52 years) could run after 6 months.[49] While it is noted that the first portion of the trial failed to meet the predefined significance level, its long-term effects are observed to have therapeutic potential.

Eculizumab is in phase 3 clinical trials with primary data to be released in October 2022.[50]

Alemtuzumab, which inhibits the CD52 gene, was found to alleviate symptoms and restore strength in a rapidly deteriorating patient with MFS and chronic lymphocytic leukemia. By week 4 of treatment, anti-GQ1B antibodies were eliminated. However, the cause of this patient's MFS is unclear; recovery might have been the result of multiple factors.[51]

IgG inhibition. Additional ongoing studies include therapies geared toward the neonatal Fc receptor as a potential clinical target for IgG inhibition.[52]

Chronic inflammatory demyelinating polyneuropathy (CIDP): Diagnosis

CIDP is the most common chronic APN and shares many similarities with GBS but differs in its responsiveness to corticosteroids, prognosis, and more. Lack of consensus on diagnostic criteria for CIDP has led to reliance on nerve conduction studies and clinical findings for making the diagnosis.[53]

Guidelines. European Federation of Neurological Societies/Peripheral Nerve Society guidelines have high sensitivity (81%) and specificity (96%) and are utilized as diagnostic criteria for CIDP; however, a survey found that these criteria may be underutilized in clinical practice – which might contribute to a high misdiagnosis rate.[54] Furthermore, although current diagnostic methods are dependent on CSF proteins, this disease is lacking a diagnostic biomarker, leading to easy overdiagnosis and unnecessary immunotherapy.[55]

Electrodiagnostic testing, which is often used, is limited because it cannot evaluate small-fiber nerves, cannot access the CNS adequately, and does not provide a specific diagnosis.[56]

Sphingomyelin in CSF. Recently, a study in Italy explored the potential of CSF sphingomyelin as a biomarker for CIDP and for GBS. Findings reveal that sphingomyelin levels can be used to diagnose more than 80% of APN cases in the clinical setting. Different levels were identified in GBS, acute inflammatory demyelinating polyneuropathy, and typical and atypical CIDP patients. Additionally, sphingomyelin showed potential to diagnose the correct stage of disease. An increase in sphingomyelin in relapsing CIDP patients was noted, compared with what was seen in controls and stable CIDP patients.[57] Larger-scale studies are needed to further test the efficacy of this method.

CIDP: Therapeutic options

First-line therapy for CIDP comprises prednisone, 60-100 mg/d, plasmapheresis, and IVIG, all of which have proved effective. Some patients respond better to one treatment than to others4[0]; some have subpar response to all these treatments and are categorized as having refractory CIDP.[45]

Although there are no newly approved treatments for CIDP, several agents show promise in ongoing clinical trials.

Rituximab is an anti-CD20 monoclonal antibody being studied in two phase 2 clinical trials of efficacy for refractory CIDP with IgG4 autoantibodies, after showing potential efficacy.[58,59]

Efgartigimod is an Fc fragment that blocks the neonatal Fc receptor, prevents lysosome degradation of IgGs, and thus allows them to be "recycled."[60] These autoantibodies are crucial in disease pathology because lowering their concentration provides effective therapy.[61] Phase 1 trials showed that repeated doses of efgartigimod reduced IgG levels in healthy volunteers by 50%. Repeated dosing lowered IgG levels, on average by 75% in serum, which was an effect that was sustained for an 8-week period.[62] Phase 2 trials are recruiting, with a projected primary completion in 2023.

INFECTION-INDUCED PERIPHERAL NEUROPATHY

Infections have been identified as a primary cause of peripheral neuropathy. Infection-induced peripheral neuropathy has

been associated with Lyme disease, Epstein-Barr and human immunodeficiency virus (HIV) infection, shingles, hepatitis B and C, diphtheria, leprosy, and rabies.[63] Extensive research on peripheral neuropathy has not been completed for most of the diseases, highlighting an unmet need for patients who experience this sequela of infection.

HIV is a well-documented viral cause of peripheral neuropathy. The most common symptom is distal sensory polyneuropathy, which affects more than 50% of patients with HIV.[64] The incidence of distal sensory polyneuropathy in HIV has been correlated with the use of antiretroviral therapy – specifically, tenofovir disoproxil fumarate – and with certain proteins secreted by the virus.[65] Symptoms include loss of sensory properties, neuropathic pain, and allodynia.[66]

Diagnostic tools and strategies

Nerve conduction studies have primarily been used to diagnose HIV-induced peripheral neuropathy, as well as electrophysiological testing and noninvasive CCM. These assays can detect changes or abnormalities in large- and small-fiber nerves in HIV infection patients.[66]

Therapeutic options

Studies in mouse models have illustrated how the Tat protein correlates with induction of motor and sensory distal symmetric polyneuropathy. Expression of Tat can lead to mitochondrial disruption, resulting in degeneration of sensory dorsal root ganglia and subsequent neuropathic pain.[67]

Pirenzepine. Studies on mice have identified a potential treatment for HIV infection–induced peripheral neuropathy with pirenzepine, targeting the muscarinic subtype-1 receptor. Pirenzepine activates a molecular pathway that promotes neurite growth and mitochondrial function. Researchers found that, following treatment with pirenzepine (n = 6), there was marked reduction in mitochondrial degeneration and HIV-induced distal sensory neuropathy.[66] This outcome was due to the ability of pirenzepine to block the effects of Tat protein expression, leading to reversal of its neurodegenerative effects.

Exercise combined with analgesics has also been identified as a potential treatment for alleviating distal sensory polyneuropathy in HIV infection–induced peripheral neuropathy. In a 12-week study, researchers instructed subjects who were receiving a combination of HIV treatments, including tenofovir, lamivudine, and efavirenz, to perform aerobic and resistance exercises. This regimen was intended to improve peripheral nerve-conduction velocity and increase the density of nerve fibers and neurogenic branching.

The study identified baseline pain scores and divided participants into three groups: aerobic exercise (n = 45), resistance exercise (n = 44), and controls (n = 47), for whom the average level of pain was 2 on an ascending scale of 1 to 10. There was significant reduction in pain score in the experimental groups by the end of the study, as well as an increased sensory profile.[64] This study has elucidated a pain management therapy for HIV-induced peripheral neuropathy that can prove beneficial for patients.

CRYPTOGENIC SENSORY POLYNEUROPATHY

Also known as idiopathic neuropathy or small-fiber sensory peripheral neuropathy, cryptogenic sensory polyneuropathy (CSPN) affects one-third of patients with peripheral neuropathy, in whom (despite extensive testing) no known cause of their condition is revealed.

Diagnostic tools and strategies

Applicable clinical and laboratory tests of any potential known underlying causes of neuropathy, including diabetes, hereditary disorders, and autoimmune disease, must be performed to rule out those causes and suggest an idiopathic cause.[68]

Therapeutic options

There are no FDA-approved treatments for CSPN, as most treatments are geared toward neuropathic pain management, rehabilitation, and supportive care.[68] Because of a lack of research and data regarding these types of peripheral neuropathies, various studies suggest different first-line therapies. For example, anticonvulsants (pregabalin, gabapentin), antidepressants (duloxetine), and opioid-like compounds (tramadol) are all therapy options to treat DPN.[3]

Adequate data are lacking to support the efficacy of immunosuppressive therapy in CSPN.

Summary

An increasing incidence of peripheral neuropathy, coupled with the fact that one-third of patients with peripheral neuropathy experience idiopathic neuropathy, indicates that extensive studies must be undertaken to identify mitigation and prevention strategies for peripheral neuropathy. To summarize the landscape of treatment for peripheral neuropathy:

Diabetic peripheral neuropathy. Treatment for DPN comprises three FDA-approved products: pregabalin, duloxetine, and a higher (8%)-strength capsaicin patch.[3] Pain-management therapies also exist to reduce diabetes-induced neuropathic pain, including gabapentin, amitriptyline, and extended-release tapentadol.[10]

Chemotherapy-induced peripheral neuropathy has yet to be effectively treated in humans; however, many trials are being completed in animals with promising results. Treat-

ment for CIPN has been identified using senolytic agents, such as navitoclax,[22] and through inhibition of SASP by a variety of agents, including ARV825, tocilizumab, and adalimumab.[23-26]

Oxaliplatin-induced peripheral neuropathy. Research has identified a potential preventive agent in duloxetine, with human trials already showing efficacy and safety.[29] Animal models have shown progress studying antioxidant agents, such as amifostine[31] and calmangafodipir,[32] which target ion channels. In a similar mechanism of action, riluzole has been observed to reduce motor and sensory deficits and depression resulting from treatment with oxaliplatin.

Vincristine-induced peripheral neuropathy. Progress has been seen in treating vincristine-induced peripheral neuropathy with pyridoxine and pyridostigmine, which have improved neuropathy scores in trial subjects;[37] more studies must be completed before these agents can be established as effective therapy.

Autoimmune PN. There are no FDA-approved drugs to mitigate the peripheral neuropathy induced by GBS and CIDP; however, studies are being conducted to resolve this impediment. Potential treatments, such as ANX005, a recombinant antibody, and eculizumab, a monoclonal antibody, have both shown efficacy in human trials and provide a potential path toward treatment against peripheral neuropathy caused by GBS.[47,50] CIDP is currently treated using prednisone, plasmapheresis, and IVIG.[40] Clinical trials are studying the efficacy of rituximab and efgartigimod for CIDP.[58-60]

Infection-induced peripheral neuropathy. Although many infections can induce peripheral neuropathy, HIV is most well documented and therefore was singled out for discussion in this article. Pirenzepine has been shown to promote neurite growth and reduce mitochondrial degeneration – both of which factors are associated with reduction of neuropathic pain.[66] Exercise and analgesics have also been found to mitigate the effects of HIV-induced distal sensory neuropathy, with pain scores being reduced.[61]

Cryptogenic sensory polyneuropathy. Research has yet to identify a causative agent of, or subsequent potential therapy for, CSPN. Increased knowledge about this neuropathy will, it is hoped, bring patients closer to a cure – beyond current pain mitigation strategies with anticonvulsants, antidepressants, and opioid-like compounds.[3] ■

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NORD Rare Disease Centers of Excellence: A new network seeks to break down barriers in rare disease care

"The goal was to find places that could help with unanswered questions, whether diagnostic questions or treatment questions. To identify places where a patient could reasonably expect to go and have a deeper dive – maybe an interdisciplinary deep dive."

By Jennie Smith

In November 2021, the National Organization for Rare Disorders (NORD) announced that it had designated 31 institutions across the United States as "NORD Rare Disease Centers of Excellence." More than just a stamp of approval, the new NORD network aims to change the way rare diseases are diagnosed and treated, creating more efficient pathways for collaboration among physicians, while helping patients get better care closer to home.

To understand better how the nascent network can benefit patients and clinicians, Neurology Reviews spoke with Ed Neilan, MD, PhD, NORD's chief scientific and medical officer. Dr. Neilan, a pediatrician and geneticist, is a former president of the medical staff at Boston Children's Hospital and also served as head of global medical affairs for rare neurology at Sanofi Genzyme.

How did NORD choose its 31 centers?

We were looking for places that had both broad capabilities and deep expertise, where it was reasonable to expect that a patient with almost any condition could go and, without too many missteps or delays, get the right diagnosis or the right treatment. We also sought sites that were educating the next generation of rare disease specialists across departments. The sites had to be involved in research, because that moves the field forward, and sometimes it's the only way to get a really impactful treatment for the 95% of rare diseases that don't have an FDA-approved treatment. NORD sent a letter inviting different centers to apply, along with an application that had 120 questions. Most of the questions sought information about what kinds of expertise or services were available on-site, so that patients don't have to go elsewhere to get, let's say, a brain MRI scan or to see an immunologist. We wanted each site to be a place where you could go for almost any problem, at any age, and expect that while you're being seen, and receiving treatment, it can also contribute to the education of the next generation of rare disease specialists and to research.

Ed Neilan, MD, PhD

Several of the members of the network comprise more than one institution: They're a children's hospital combined with another facility.

Children's hospitals, which are highly specialized and able to care for rare things in children, couldn't apply by themselves. They had to apply in partnership with a center that could provide adult care as patients got older; otherwise, their care model would be incomplete. We've had some small victories already just by asking these questions and outlining this sort of approach. At one institution in the Great Plains, the director told us that he had been trying for years to get permission to hire someone who could make appointments across three different hospitals – a children's hospital and two adult hospitals. He'd wanted to ensure that patients with rare and genetic diseases were seen in the appropriate places, and thanks to the NORD designation, he finally can. Now, regardless of age, the same office staff can handle the arrangements, and the patient will be scheduled in the right place.

You make clear that these are different from disease-specific centers of excellence – you specifically chose the 31 centers for their breadth of expertise.

There's no way to represent all 7,000 rare diseases equally, and disease-specific centers of excellence, which already exist for hemophilia, muscular dystrophy, cystic fibrosis, and some other

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conditions, have a very important role. We're not aiming to compete with any other existing resources. What we are seeking to do is to fill the unmet need of, "What if there are no such designations for the disease that you're concerned about?" Our goal was to find places that could help with unanswered questions, whether diagnostic questions or treatment questions. To identify places where a patient could reasonably expect to go and have a deeper dive – maybe an interdisciplinary deep dive.

The delay to diagnosis can be years in rare diseases. How can the network help speed up diagnoses?

With all these experts on different diseases, we hope to develop some better diagnostic algorithms within the network. Another thing we can do is to share resources. With 31 sites, everybody's seeing patients with unknown diagnoses. Everyone is seeing patients for whom they would maybe like to get a whole genome done, or a whole exome done, but they are often encountering stiff resistance from insurance companies.

Meanwhile some sites, but not all 31, have multimillion-dollar grants to do sequencing and other kinds of advanced diagnostic tests to solve unknown cases. And there are people at those sites who say, "We need more samples. Can you get us samples from the other sites?"

One of the main things we aim to do is share information, including information about available diagnostic resources. We want all 31 sites to know which sites have funding and programs that enable them to study samples for other sites. We also want to know what criteria they're putting on it. Someone might say: "I've got a grant to sequence genomes for people with unexplained seizures. Send me all your unexplained seizures." Somebody else might have a grant for unexplained GI diseases. So, we want to put on our intranet a resource for the 31 sites, kind of a cookbook for – when if you can't get it paid for by insurance, but you really think you need a particular special test – who might be able to do it for you within the network.

This would seem to benefit research across sites as well.

Yes, but we also want to share clinical advice and expertise for direct patient benefit. So, it doesn't always have to fulfill the goals of a specific research project. For example, we might be able to create an undiagnosed patient quality improvement database across all 31 sites that could compliantly let Drs. X and Y know that they're each seeing a patient with the same rare thing.

But let's say you want to move the field forward by discovering a new disease. Rare genetic diseases are now being discovered at the rate of about 250 a year, so about 5 per week across the world. With two or three unrelated patients who have the same disease and a whole exome sequence, you can potentially discover a disease. Maybe you've found one unique patient with a genetic variant of possible significance, but you can't be 100% sure, and you may not be able to convince your colleagues, or journal editors, until you find other cases. You need those two or three ultrarare patients. Within this network, a lot of sites want to share information about their ultrarare patients and be able to put together additional instances of the same thing, to prove that it is a real disease, to learn more about it and how to diagnose, manage, and treat it.

More than just a stamp of approval, the new NORD network aims to change the way rare diseases are diagnosed and treated, creating more efficient pathways for collaboration among physicians, while helping patients get better care closer to home.

Part of the idea with a nationwide network is that patients aren't going to have to move around among these centers of excellence, is that correct? They're going to be seen at the closest ones, and it's the expertise that is mobile.

Yes, that's right. While we can't eliminate the need for travel, what we are trying to do is increase the sharing of expertise, to improve results for patients while limiting the need for traveling very long distances. As a geneticist I've been on both the requesting and the receiving end of consultations with doctors at other sites, sometimes very far away, especially for ultrarare conditions for which any one physician's experience is limited. We all try to honor these sorts of requests, but insurance doesn't reimburse it and so hospitals don't give doctors much credit for it.

We want to ultimately find ways to incentivize this type of collaboration. Hopefully we can get agreements with insurance companies to allow intersite consultations within our network, recognizing that they don't want to pay for the patient to be seen out of state, but you also want the patient to get the best possible medical advice. This might require legislative changes

in the long run. But what we can do more readily is create a culture within this network of mutual consultation and sharing of clinical experience. Outside of such a network, the idea of "cold calling" somebody, whom you may never have met, and asking them for help and free advice is a little bit of a bar, right? We want to lower that bar.

Can patients get telemedicine consults with physicians across the network?

NORD supports having telemedicine options for everybody regardless of diagnosis, rare or not, and we support legislation that would continue access and reimbursement for telemedicine post pandemic. I hope we can get that, or at least preserve telemedicine for rare diseases, for which there are often not enough, or sometimes not any, expert providers in the same state. Ultimately, we want patients to be able to get the expert assessments and advice they need. For rare diseases, that sometimes means battling back and forth with an insurance provider, seeking permission to see an expert clinician a thousand miles away. By sharing medical expertise, and through telemedicine when that's allowed, we hope to reduce the need for that. But the telemedicine environment is still evolving and somewhat uncertain.

How will the network's physician collaborations take place?

One of the important things NORD is providing to the network is an information technology setup and intranet across the 31 sites. That intranet is where center staff will go to access the network's internal resources, including live and recorded case conferences. In those case conferences you can present a case you haven't been able to solve. Experts you may have only heard of by reputation will now be streamed to your computer as part of the nationwide network. It benefits the patient because you get additional expert opinions, but it also benefits the physicians because we have this collegial space for discussion and learning. We'll be linked by frequent meetings – some in person, most virtual – a common culture, and a common intranet.

On the intranet, we will also have a growing set of useful databases, links, and documents that are available to all members. These will be progressively updated with help from experts at the centers, so that clinicians can more directly learn from each other, instead of separately reinventing the wheel. The way things usually work, when you see a patient with an ultrarare condition that you're not that familiar with, is that you tell them what little you can, then schedule them to come back in a few weeks. In the meantime, usually in your off time, you spend hours searching PubMed and other sources and you try to piece things together, to figure out what's known that might help your patient. But imagine that this has already been figured out by someone else in the network. You can see on the network a list of articles the other expert read and found helpful in addressing this problem. And you then reach out directly to that other expert.

In recent months you've had one-on-one meetings with all 31 directors at the sites, and after that you convened 11 working groups. What are you trying to achieve?

Once the sites were chosen, we aimed to talk quickly and honestly about what everyone needed, what everyone saw as the biggest problems to tackle in rare diseases. Two things were very rewarding about those phone calls: one, all the centers were very enthusiastic, and two, they pretty much all agreed on what the key unmet needs are for rare disease patients and the practitioners trying to help them. So, we empaneled working groups of expert volunteers enthusiastic to work on each of those problems. These groups collectively comprise more than 200 volunteers – faculty, staff, and trainees – from the different sites nationwide. Each group is working on a key unmet need in rare diseases, and each group will be given its own space on our file-sharing platform, where they can share information and co-develop new ideas and documents. When something they produce is good enough to start to be a practice resource, such as a draft treatment guideline that the working group now wants to try in the real world, but it's not yet ready to be published, they can share it and have it tested by all 31 sites through the dedicated intranet we are building for the network. ■

Staying alert for patients with narcolepsy

The chronic neurologic disorder entails not only excessive sleepiness but also social and professional challenges.

By Erik Greb



Michael J. Thorpy, MB, ChB; Thomas E. Scammell, MD; Kiran Maski, MD, MPH

Almost half of Americans report feeling daytime sleepiness on at least 3 days per week. For most patients, this sleepiness results from insufficient nighttime sleep. But a minority of these patients have narcolepsy, a chronic neurologic disorder that impairs the brain's control of sleep-wake cycles. This disorder often goes undiagnosed, but neurologists can make a significant difference by learning how to recognize and treat it.

What is narcolepsy?

Narcolepsy is characterized by excessive daytime sleepiness (EDS) and sudden attacks of sleep. Patients have difficulty staying awake for long periods of time, and the disorder can make performing daily tasks difficult. Problems with concentration and alertness are common.

Narcolepsy is considered to have two subtypes. Patients with narcolepsy type 1 also have cataplexy, a sudden loss of muscle tone. Attacks of cataplexy are triggered by strong, usually positive, emotions. These attacks have manifestations ranging from slurred speech to complete weakness of most muscles. Patients with narcolepsy type 2, however, do not have cataplexy.

Dysregulation of rapid eye movement (REM) sleep, which is when most dreaming occurs, is another symptom of narcolepsy. The transition to REM sleep is quicker in patients with narcolepsy and usually occurs within 15 minutes of sleep onset. A related symptom is sleep paralysis, an inability to move while falling asleep or waking up. This symptom resembles a state that normally occurs during REM sleep.

Hallucinations also are common in patients with narcolepsy and can be especially vivid. Hypnagogic hallucinations occur during the transition to sleep, and hypnopompic hallucinations arise while the patient is waking up. Patients may think they see a stranger in their bedroom, and children sometimes report seeing animals.

Although it is easy for patients with narcolepsy to fall asleep at night, they often have disrupted sleep. Patients have frequent, brief arousals throughout the night that may become disturbing. Dream content often is affected in narcolepsy, too. Patients have described lucid dreams of flying or out-of-body experiences. After such intense dreams, patients often feel that their sleep has not been restful.

Criteria and diagnosis

To receive a diagnosis of narcolepsy type 1, a patient must have EDS that persists for at least 3 months and at least one of the following two features: cataplexy and objective evidence of quick sleep onset and early start of REM sleep or low cerebrospinal fluid (CSF) levels (that is, less than 110 pg/mL) of hypocretin. Hypocretin, also known as orexin, is a neuropeptide that regulates wakefulness and arousal.

Patients must meet five criteria to receive a diagnosis of narcolepsy type 2. They must have EDS that persists for at least 3 months. They must have test results that show quick sleep onset and early start of REM sleep. They must have no cataplexy. Their CSF levels of hypocretin must be normal or unknown. Finally, they must have no other conditions that provide a better explanation for their symptoms and test results.

"The diagnosis of narcolepsy is made primarily by history on the clinical features of the disorder," said Michael J. Thorpy, MB,

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ChB, professor of neurology at Albert Einstein College of Medicine and director of the Sleep–Wake Disorders Center at Montefiore Medical Center in New York. When narcolepsy is suspected, testing is required to confirm the diagnosis. The patient should undergo all-night polysomnographic (PSG) testing, followed by a daytime multiple sleep latency test (MSLT). Measurement of CSF hypocretin can be diagnostic but is performed mainly in the research setting and is not common in the clinical setting, said Dr. Thorpy.

Patients with narcolepsy typically fall asleep in an average of less than 8 minutes during the nap opportunities of the MSLT. They also have at least two sleep-onset REM periods. "A new change in the diagnostic classification is that a sleep-onset REM period on the preceding night's PSG can count as one of the two sleep-onset REM periods required for diagnosis," said Dr. Thorpy.

"In the case of type 1 narcolepsy, the history is usually pretty clear, and the MSLT is usually positive, in the sense that it is consistent with a narcolepsy pattern," said Thomas E. Scammell, MD, professor of neurology at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston. "The PSG is also important, because other factors that disrupt the patient's nighttime sleep (such as obstructive sleep apnea and periodic limb movements) must be ruled out, especially in type 2 narcolepsy," said Dr. Scammell.

Early sleep onset, late diagnosis

Diagnostic delay is a common problem for patients with narcolepsy. Although the median age of onset is 16 years, a patient typically does not receive the appropriate diagnosis until adulthood. "It takes, on average, somewhere between 8 and 12 years for a patient to get a diagnosis of narcolepsy," said Dr. Thorpy. Growing awareness and an increase in the number of sleep disorder centers have reduced but not eliminated the diagnostic delay.

Children with narcolepsy are often misdiagnosed. "One of the most common misdiagnoses in childhood is ADHD, because sleepiness in children differs from that in adults," said Dr. Thorpy. Sleepy children often become hyperactive and display increased impulsivity, he explained. Stimulants prescribed for ADHD tend to mask the symptoms of narcolepsy and delay the correct diagnosis. Mood disorders, behavioral disorders, and psychogenic disorders are other common misdiagnoses for children with narcolepsy.

But when it comes to adults, sometimes patients themselves contribute to the diagnostic delay. EDS is "such a pervasive feeling that I think a lot of people just don't make much of it," said Dr. Scammell. The symptom is easily ascribed to insufficient sleep or a difficult work schedule. "It may take them months to get to see a doctor," said Dr. Scammell.

Behavioral treatments

Nonpharmacologic treatments are one component of care for patients with narcolepsy. Patients must maintain a regular sleep-wake schedule and ensure that they are in bed for no less than 8 hours per night, said Dr. Thorpy. Taking no more than two daytime naps of less than 20 minutes each can help relieve some of the sleepiness, he added.

In addition to ensuring an adequate amount of sleep, it is important to promote good quality sleep, said Dr. Scammell. To do this, clinicians should address any conditions such as sleep apnea that disrupt patients' sleep, he added.

Patients also tend to avoid situations that are likely to entail the emotional stimuli that could precipitate cataplexy. Some avoid laughter or try to suppress their emotions. "That's not good," said Kiran Maski, MD, MPH, assistant professor of neurology at Harvard Medical School and neurologist and sleep physician at Boston Children's Hospital. "We worry that that might be a risk factor for depression or social isolation." Cognitive-behavioral therapy can help patients with narcolepsy gradually increase their comfort with and exposure to social situations.

Although behavioral treatments are helpful, they are not sufficient to control all the symptoms of narcolepsy. Most patients require pharmacologic treatments, which are the most effective treatments for narcolepsy, said Dr. Thorpy.

Pharmacologic treatments

Previously, neurologists relied on the stimulants methylphenidate and amphetamine, which primarily treated patients' EDS. But the field is moving away from these drugs because of their tendency to induce side effects and their potential for abuse, said Dr. Thorpy. In this context, modafinil and armodafinil became the mainstay for promoting alertness in patients with narcolepsy.

In recent years, newer medications have emerged that have slightly greater efficacy and better safety profiles than modafinil and armodafinil. Solriamfetol (Sunosi, Jazz Pharmaceuticals), for example, is effective for EDS but does not affect cataplexy. Pitolisant (Wakix, Harmony Biosciences), on the other hand, effectively treats EDS and cataplexy.

Sodium oxybate (Xyrem, Jazz Pharmaceuticals) is the only medication that treats all the symptoms of narcolepsy, said Dr. Thorpy. "That treats the sleepiness, the cataplexy, and the disturbed nocturnal sleep," he added. Sodium oxybate also appears to reduce sleep paralysis, hallucinations, and disturbed dreams.

A potential concern about sodium oxybate, which has been used since approximately 2000, is its high sodium load. A new formulation called low-sodium oxybate (Xywav, Jazz Pharmaceuticals) "has a slightly better safety profile, particularly in people who have cardiovascular or renal disease," said Dr. Thorpy. "This is tending to take over the role of regular sodium oxybate."

Many clinicians who treat patients with narcolepsy develop their own approaches, but the choice of treatment generally depends on the patient's symptoms, said Dr. Scammell. Modafinil is a good first choice for patients with mild to moderate sleepiness, he added. Pitolisant is another good choice for these patients but is more expensive. Both drugs are well tolerated.

Clinicians can consider solriamfetol and amphetamine for patients with moderate to severe sleepiness. "I generally consider the oxybates to be a second line," said Dr. Scammell. Although these drugs may be the most effective, and they do help patients a great deal, they have a higher prevalence of side effects and are more expensive, he added. "If we can get good results with something gentle and simple like modafinil, that would be great."

"There are differences of opinion as to what the first-line treatments are," said Dr. Thorpy. Some patients prefer to use the traditional stimulants as first-line treatments, but others prefer to avoid them because of their adverse effects. They favor the newer, and unfortunately more expensive, medications instead. But there is no consensus among clinicians about which of the newer medications to use. "There's no standard treatment, and it's very hard to develop an algorithm that is acceptable to most physicians treating patients with narcolepsy," said Dr. Thorpy.

Treatment response varies, as well. Some patients respond extremely well to treatment, but clinical trials indicate that even optimal therapy helps patients achieve about 70% of the normal level of alertness. "If they're sedentary, sitting in a boring meeting or at the computer, they can still fall asleep, even with our current medications," said Dr. Scammell.

"The hardest symptom of all to treat is the EDS," agreed Dr. Thorpy. Most patients cannot be treated with one medication alone, and polypharmacy tends to be necessary, he added. Typically, this means the addition of another medication to the regimen to maximize alertness. For other patients, cataplexy is difficult to control, and adding an anticataplectic medication is appropriate. Still, most patients can control their cataplexy with one drug, either oxybate or pitolisant, said Dr. Thorpy.

Investigational treatments

Researchers are trying to develop new medicines with greater potency, and several medications are under investigation. Early studies have shown that reboxetine, an antidepressant medication that affects dopamine and norepinephrine activity, is an effective treatment for EDS and cataplexy. Ongoing phase 3 studies are examining reboxetine for EDS. Another drug known as FT-218 is a once-nightly formulation of sodium oxybate, unlike the twice-nightly formulations of the drug that currently are available. In a phase 3 trial, the drug was associated with significant improvements in wakefulness and reductions in attacks of cataplexy. Avadel, which is developing the drug, submitted it to the U.S. Food and Drug Administration for approval in 2021, but the agency has not yet made a decision about it.

Researchers and patients alike have high hopes for medications that activate the orexin receptors. Orexin stimulates the wake-promoting neurons in the brain. Narcolepsy, and particularly narcolepsy type 1, is characterized by a loss of hypocretin cells in the central nervous system. The loss of these cells promotes sleepiness and disturbed REM sleep. To counteract this loss of cells, several companies are investigating new orexin agonists.

One such medication is TAK-994, which was developed by Takeda. The drug showed great promise for treating EDS and cataplexy, said Dr. Thorpy. But when phase 3 studies suggested that TAK-994 was associated with hepatotoxicity, the company terminated the studies. Nevertheless, other orexin agonists, including Takeda's TAK-861, are under investigation.

"If we can restore orexin signaling, it could be like giving insulin to type 1 diabetics," said Dr. Scammell. This class of medications could provide substantial improvements in sleepiness and other symptoms, he added. "I think when orexin agonists become available, it's going to be quite transformative." But these drugs are still in early development and will not be available in clinical practice for several years.

Common psychological comorbidities

Certain comorbidities are prevalent among patients with narcolepsy, and psychiatric disorders tend to be the most common. These comorbidities may complicate the management of narcolepsy. Nevertheless, they often are significant enough to require management in their own right, said Dr. Thorpy.

Depression is likely twice as common among patients with narcolepsy than among the general population, said Dr. Scammell. "Whether this is an actual neurobiologic feature of the disease, or whether it is just a reaction to having a challenging disorder isn't entirely clear," he added. "But it doesn't get the attention or treatment that it deserves."

Partnering with a psychologist or psychiatrist is important because many treatments can exacerbate mood disorders, said Dr. Maski. In general, stimulants, for example, can worsen depression and anxiety and are associated with increased suicide risk. "We oftentimes are using high-dose stimulants in patients, so mood has to be really carefully monitored and managed," Dr. Maski added.

Cases of depression and suicidal ideation were reported in clinical trials of sodium oxybate. Although these serious adverse events were rare, patients must be monitored very closely even on treatments specifically approved for narcolepsy, said Dr. Maski. Mood disturbances are reported less frequently with modafinil and pitolisant than with stimulants, she noted.

Many times, patients need to take an antidepressant medication, but these drugs could affect the medicines administered for narcolepsy, said Dr. Thorpy. Pitolisant, in particular, may be adversely affected by current antidepressant medications. The only remedies are to change from pitolisant to another narcolepsy medication or to use an antidepressant that does not have histamine 1 receptor antagonism or affect the QTc interval.

Anxiety also is prevalent among patients with narcolepsy, and it can be worsened by traditional stimulants. These drugs also can increase the likelihood of irritability or obsessive-compulsive tendencies. "Traditional stimulants would be best avoided in these patients who have significant anxiety," said Dr. Thorpy.

The social burden of narcolepsy

The burden of narcolepsy extends beyond psychiatric comorbidities into the social sphere. "Patients with narcolepsy do have greater difficulties in terms of social and interpersonal relationships," said Dr. Thorpy. The disorder reduces patients' quality of life, and educational difficulties and job loss are common in this population. "It's a lifelong, incurable disorder, and these patients suffer an immense burden throughout their life because of the sleepiness that … affects their cognitive abilities," said Dr. Thorpy.

"There's an increased reporting of what probably amounts to social isolation," said Dr. Maski. Patients often report that they must prioritize activities or events because they do not have the energy or alertness to participate in all of them. For instance, adolescents with narcolepsy frequently say that they must forgo after-school extracurricular activities because they need to prioritize studying and getting enough sleep. "Those priorities take away from their normal social life and events that they would like to participate in," said Dr. Maski.

Another problem is that patients have the impression that others do not understand their condition. They are afraid that they will be perceived as lazy, uninterested, or unmotivated if they fall asleep. "Sometimes they withdraw from social events because they don't want to be perceived in such a way," said Dr. Maski. She and her colleagues encourage patients to participate in selected after-school events and to engage in social activities they find meaningful to maintain social networks.

An unpublished study of more than 300 patients with narcolepsy examined the effect of the disorder on patients' social lives. At the end of the day, many patients "crash and burn," said Dr. Scammell. Consequently, they do not have as much energy for social activities.

This lack of energy affects patients' social relationships. The study suggests that patients with narcolepsy do not have as many friends as the general population does. Nevertheless, the frequency of close relationships and marriage was similar between patients with narcolepsy and the general population. "What people are doing is putting their energy into these close relationships, rather than having lots of friends and socializing a lot," said Dr. Scammell. "I found that heartening, that people were doing their best and developed those close relationships," which are vitally important for many reasons, he added.

The study, which has been submitted for publication, also asked patients about their sex lives. Many patients reported having had cataplexy during sex, and others reported that their medications caused problems with their sex lives. "Their doctors never ask about these things, and many patients actually would like their doctor to ask about them more," said Dr. Scammell.

In addition, narcolepsy significantly affects a patient's ability to drive. Patients with narcolepsy have a three- to fourfold increased risk of car accidents, said Dr. Scammell. This increased risk likely results from patients' EDS.

But as important as this issue is for patients' lives, there is no consensus on how to counsel patients about driving, said Dr. Maski. "For instance, it is not really clear if there is value in doing a maintenance of wakefulness test before allowing patients with narcolepsy to drive," she said. The test is not validated in children or adolescents, which raises questions about how to advise beginning drivers with narcolepsy. "It's not really clear that passing your maintenance of wakefulness test increases your safety behind the wheel," said Dr. Maski.

"It's the rare person with narcolepsy who can easily and safely do a 2-hour drive by themselves," said Dr. Scammell. Patients must determine what their own limits are, and it is important for clinicians to discuss reasonable limits honestly with their patients. "I almost never would push to have somebody's license taken away," said Dr. Scammell. "But there are patients who only can drive around town for short errands, and if it's anything more than half an hour, they start getting drowsy."

There is a need for a public awareness campaign about narcolepsy, Dr. Scammell added. Such a campaign was carried out in Italy several years ago, and it included cartoons and TV segments. "It got a lot of people's attention, and there was a real spike in new and correct diagnoses of narcolepsy," said Dr. Scammell. But such a broad campaign is expensive, while narcolepsy is rare, and it might not be feasible to reach out to the general population. "But I certainly think it's worth targeting doctors who are likely to see patients with sleepiness: neurologists, psychiatrists and psychologists, and primary care doctors," said Dr. Scammell. ■

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