RARE RHEUMATOLOGIC DISEASES

SPECIAL REPORT

Rheumatology News

NORD® National Organization for Rare Disorders

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Rheumatology News

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The *Rare Rheumatologic Diseases Special Report* is a supplement to Rheumatology News, an independent newspaper that provides the practicing rheumatologist with timely and relevant news and commentary about clinical developments in the field and about the impact of health care policy on the specialty and the physician's practice.

Jeff Evans

EDITOR'S NOTE

Rare rheumatologic diseases strike the young and old and men and women alike with disabling and sometimes life-threatening consequences, but their infrequent occurrence and heterogeneous presentations make them challenging to study without collecting large number of patients into registries. Read this report to learn about how registries for rare pediatric diseases, including polyarticular juvenile idiopathic arthritis, as well as scleroderma and myositis, have led to important insights into treatments and disease characteristics.

While treatments based on rapidly evolving genetic engineering technology such as CRISPR/Cas9 might be on the distant horizon, we learn how cell-based treatments such as autologous hematopoietic stem cell transplantation are already in use and becoming the standard of care for selected patients with systemic sclerosis.

In the report, we also learn about updated recommendations on the management of large-vessel vasculitis from the European League Against Rheumatism and recent efforts to establish classification criteria for chronic nonbacterial osteomyelitis/chronic recurrent multifocal osteomyelitis, and we also gain insight on how to diagnose and manage pediatric localized scleroderma.

I hope you enjoy this special report!

—Jeff Evans, Group Editor, Rheumatology News

Sika Dunyoh

A NOTE FROM NORD

Welcome to our first issue of the *Rare Rheumatologic Diseases Special Report*! NORD is proud to collaborate with *Rheumatology News* and medical experts to bring you information on timely and important topics related to caring for individuals affected by rare rheumatologic diseases.

We value this opportunity to speak directly to the professionals who play such a critically important role in the lives of the patients and families whom we represent.

Topics covered in this issue—such as how disease registries are providing data to generate new insights, hematopoietic stem cell transplantation, and research on pediatric rheumatologic diseases such as polyarticular JIA—reflect that this is a time of incredible momentum in rare disease knowledge and research.

More than half of the new medical treatments approved by the U.S. Food and Drug Administration in 2018 were for rare diseases, and many of these new products represent significant advances over previously available treatment options. This includes, for instance, products that employ precision medicine to help identify the patients most likely to benefit from specific therapies.

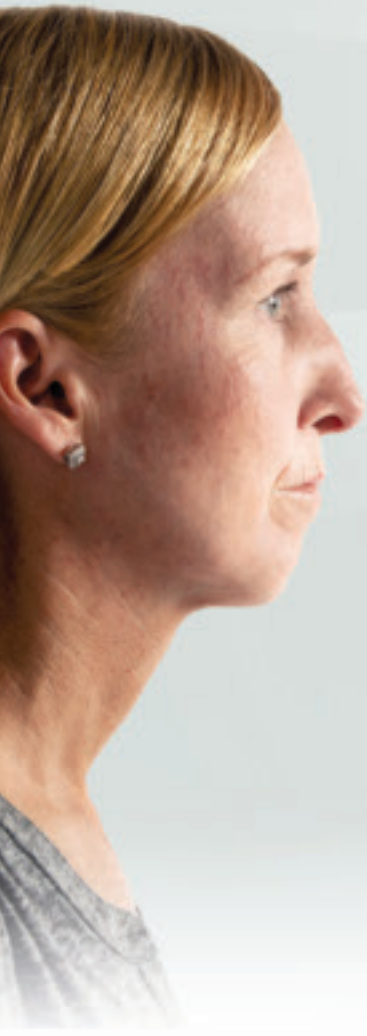
With more than 7,000 medical conditions now recognized as rare diseases by the National Institutes of Health (NIH)—and new ones being identified on a regular basis—it is increasingly difficult for the busy clinician to stay abreast of the latest thinking and advances related to these conditions. NIH and NORD provide resources, described in this issue, to help physicians and other medical professionals provide up-to-the-minute care for their patients who are affected by these rare medical conditions.

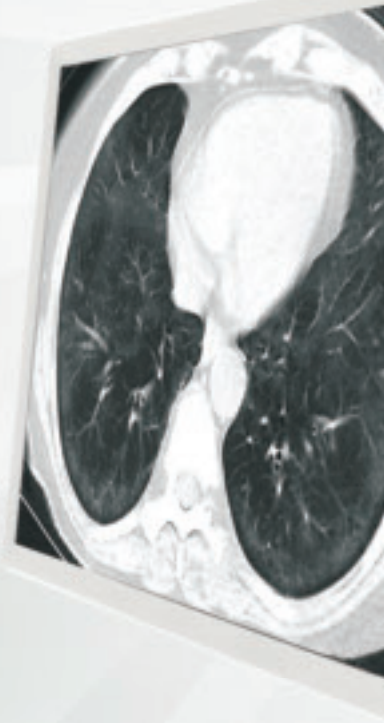
NORD is grateful for this opportunity to present information about the current status of rare disease management, new tools for generating better understanding of diseases, and new treatment options for adults and children affected by rare rheumatologic diseases.

We invite you to visit the NORD website often (www.rarediseases.org) for ongoing updates, including research funding opportunities. We also encourage you to watch for other educational resources provided by NORD for medical professionals, including free webinars, CME resources, and our annual NORD Rare Diseases and Orphan Products Breakthrough Summit, which takes place in Washington, D.C., each year in October.

—Sika Dunyoh, Director, Educational Initiatives, National Organization for Rare Disorders (NORD)

NOW APPROVED
to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)[1]





FACE SSc-ILD HEAD ON

OFEV (nintedanib) is proven to reduce lung function decline in patients with SSc-ILD[1,2]

OFEV®
(nintedanib)
capsules 150mg

INDICATION

OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hepatic Impairment: OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dosage (100 mg twice daily). Consider treatment interruption or discontinuation for management of adverse reactions.

Please see additional Important Safety Information on the following pages and accompanying Brief Summary of Prescribing Information.

NOW APPROVED

Studied in the largest phase 3 trial in SSc-ILD to date

580 patients with SSc-ILD were randomized in a double-blind, placebo-controlled, 52-week trial. The primary endpoint was the annual rate of decline in FVC over 52 weeks[1-3]

Proven to reduce lung function decline in patients with SSc-ILD

OFEV reduced the annual rate of FVC decline by 41 mL/year (44% relative reduction) compared with placebo (*P*=.04; 95% CI=3, 79)[1,2]

FDA, Food and Drug Administration; FVC, forced vital capacity.

*Diarrhea was reported in 76% of patients receiving OFEV vs 32% on placebo.[1]

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

Elevated Liver Enzymes and Drug-Induced Liver Injury

- Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and post-marketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the post-marketing period. The majority of hepatic events occur within the first three months of treatment. OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, and GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In the SSc-ILD study, a maximum ALT and/or AST greater than or equal to 3 times ULN was observed in 4.9% of patients treated with OFEV.
- Patients with low body weight (less than 65 kg), patients who are Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may result in increased liver enzymes.
- Conduct liver function tests prior to initiation of treatment, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modifications, interruption, or discontinuation may be necessary for liver enzyme elevations.

Gastrointestinal Disorders

Diarrhea

- In the SSc-ILD study, diarrhea was the most frequent gastrointestinal event reported in 76% versus 32% of patients treated with OFEV and placebo, respectively. Events were primarily mild to moderate in intensity and occurred within the first 3 months. Diarrhea led to permanent dose reduction in 22% and discontinuation in 7% of OFEV patients versus 1% and 0.3% in placebo patients, respectively.
- Dosage modifications or treatment interruptions may be necessary in patients with diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists, discontinue treatment.

OFEV is the **FIRST AND ONLY** FDA-approved therapy to slow the rate of decline in pulmonary function in patients with SSc-ILD[1,3]

Demonstrated safety and tolerability profile

The most common adverse reactions were gastrointestinal in nature and generally of mild or moderate intensity[1*]

One capsule, twice daily with food[1]

See Brief Summary of Prescribing Information for complete dosing recommendations

Learn more at OFEVhcp.com

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Disorders (cont'd)

Nausea and Vomiting

- In the SSc-ILD study, nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively. Events were primarily of mild to moderate intensity. Nausea and vomiting led to discontinuation of OFEV in 2% and 1% of patients, respectively.
- If nausea or vomiting persists despite appropriate supportive care including anti-emetic therapy, consider dose reduction or treatment interruption. OFEV treatment may be resumed at full dosage or at reduced dosage, which subsequently may be increased to full dosage. If severe nausea or vomiting does not resolve, discontinue treatment.

Embryofetal Toxicity: OFEV can cause fetal harm when administered to a pregnant woman and patients should be advised of the potential risk to a fetus. Women should be advised to avoid becoming pregnant while receiving OFEV and to use highly effective contraception during treatment and at least 3 months after the last dose of OFEV. As the impact of nintedanib on the effectiveness of hormonal contraception is unknown, advise women using hormonal contraceptives to add a barrier method. Verify pregnancy status prior to starting OFEV and during treatment as appropriate.

Arterial Thromboembolic Events: In the SSc-ILD study, arterial thromboembolic events were reported in 0.7% of patients in both the OFEV-treated and placebo-treated patients. There were 0 cases of myocardial infarction in OFEV-treated patients compared to 0.7% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk, including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia.

Risk of Bleeding: OFEV may increase the risk of bleeding. In the SSc-ILD study, bleeding events were reported in 11% of OFEV versus 8% of placebo patients. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. There have been post-marketing reports of non-serious and serious bleeding events, some of which were fatal.

Please see additional Important Safety Information on the following page and accompanying Brief Summary of Prescribing Information.

OFEV®
(nintedanib)
capsules 150mg

OFEV is available through partnering specialty pharmacies

DOWNLOAD AND COMPLETE THE PRESCRIPTION FORM AT OFEVHCP.COM

FAX THE PRESCRIPTION FORM TO ONE OF THE SPECIALTY PHARMACIES

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS (CONT'D)

Gastrointestinal Perforation: OFEV (nintedanib) may increase the risk of gastrointestinal perforation. In the SSc-ILD study, no cases of gastrointestinal perforation were reported in either OFEV or placebo-treated patients. In the post-marketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, have a previous history of diverticular disease, or who are receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

ADVERSE REACTIONS

- Adverse reactions reported in the SSc-ILD study in greater than or equal to 5% of OFEV patients, and more than placebo, included diarrhea, nausea, vomiting, skin ulcer, abdominal pain, liver enzyme elevation, weight decreased, fatigue, decreased appetite, headache, pyrexia, back pain, dizziness and hypertension.
- In the SSc-ILD study, the most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% vs. 1.7%) and pneumonia (2.8% vs. 0.3%). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm.

DRUG INTERACTIONS

- **P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers:** Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib.
- **Anticoagulants:** Nintedanib may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary.

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment.
- **Reproductive Potential:** OFEV may reduce fertility in females of reproductive potential.
- **Smokers:** Smoking was associated with decreased exposure to OFEV, which may affect the efficacy of OFEV. Encourage patients to stop smoking prior to and during treatment.

CL-OF-100021 09.06.19

Please see accompanying Brief Summary of Prescribing Information on the following pages.

References: 1. OFEV® (nintedanib) Prescribing Information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2019. **2.** Distler O et al. *N Engl J Med.* 2019;380(26):2518-2528. **3.** Distler O et al. *Clin Exp Rheumatol.* 2017;35 Suppl 106(4):75-81.

Boehringer Ingelheim

OFEV® (nintedanib) capsules 150mg

OFEV® (nintedanib) capsules, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

Please see package insert for full Prescribing Information, including Patient Information

1 INDICATIONS AND USAGE: 1.1. Idiopathic Pulmonary Fibrosis: OFEV is indicated for the treatment of idiopathic pulmonary fibrosis (IPF). **1.2 Systemic Sclerosis-Associated Interstitial Lung Disease:** OFEV is indicated to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD).

2 DOSAGE AND ADMINISTRATION: 2.1 Testing Prior to OFEV Administration: Conduct liver function tests in all patients and a pregnancy test in females of reproductive potential prior to initiating treatment with OFEV *[see Warnings and Precautions]*. **2.2 Recommended Dosage:** The recommended dosage of OFEV is 150 mg twice daily administered approximately 12 hours apart. OFEV capsules should be taken with food and swallowed whole with liquid. OFEV capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of OFEV is missed, the next dose should be taken at the next scheduled time. Advise the patient to not make up for a missed dose. Do not exceed the recommended maximum daily dosage of 300 mg. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily approximately 12 hours apart taken with food. **2.3 Dosage Modification due to Adverse Reactions:** In addition to symptomatic treatment, if applicable, the management of adverse reactions of OFEV may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with OFEV *[see Warnings and Precautions and Adverse Reactions]*. Dose modifications or interruptions may be necessary for liver enzyme elevations. Conduct liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Discontinue OFEV in patients with AST or ALT greater than 3 times the upper limit of normal (ULN) with signs or symptoms of liver injury and for AST or ALT elevations greater than 5 times the upper limit of normal. For AST or ALT greater than 3 times to less than 5 times the ULN without signs of liver damage, interrupt treatment or reduce OFEV to 100 mg twice daily. Once liver enzymes have returned to baseline values, treatment with OFEV may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily) *[see Warnings and Precautions and Adverse Reactions]*. In patients with mild hepatic impairment (Child Pugh A), consider treatment interruption, or discontinuation for management of adverse reactions.

4 CONTRAINDICATIONS: None

5 WARNINGS AND PRECAUTIONS: 5.1 Hepatic Impairment: Treatment with OFEV is not recommended in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment *[see Use in Specific Populations]*. Patients with mild hepatic impairment (Child Pugh A) can be treated with a reduced dose of OFEV *[see Dosage and Administration]*. **5.2 Elevated Liver Enzymes and Drug-Induced Liver Injury:** Cases of drug-induced liver injury (DILI) have been observed with OFEV treatment. In the clinical trials and postmarketing period, non-serious and serious cases of DILI were reported. Cases of severe liver injury with fatal outcome have been reported in the postmarketing period. The majority of hepatic events occur within the first three months of treatment. In clinical trials, administration of OFEV was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in the majority of cases. In IPF studies (Studies 1, 2, and 3), the majority (94%) of patients with ALT and/or AST elevations had elevations less than 5 times ULN and the majority (95%) of patients with bilirubin elevations had elevations less than 2 times ULN. In the SSc-ILD study (Study 4), a maximum ALT and/or AST greater than or equal to 3 times ULN was observed for 4.9% of patients in the OFEV group and for 0.7% of patients in the placebo group *[see Use in Specific Populations]*. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes. Conduct liver function tests (ALT, AST, and bilirubin) prior to initiation of treatment with OFEV, at regular intervals during the first three months of treatment, and periodically thereafter or as clinically indicated. Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. Dosage modifications or interruption may be necessary for liver enzyme elevations. *[see Dosage and Administration]*. **5.3 Gastrointestinal Disorders:** Diarrhea: In clinical trials, diarrhea was the most frequent gastrointestinal event reported. In most patients, the event was of mild to moderate intensity and occurred within the first 3 months of treatment. In IPF studies (Studies 1, 2, and 3), diarrhea was reported in 62% versus 18% of patients treated with OFEV and placebo, respectively [*see Adverse Reactions*]. Diarrhea led to permanent dose reduction in 11% of patients treated with OFEV compared to 0 placebo-treated patients. Diarrhea led to discontinuation of OFEV in 5% of the patients compared to less than 1% of placebo-treated patients. In the SSc-ILD study (Study 4), diarrhea was reported in 76% versus 32% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. Diarrhea led to permanent dose reduction in 22% of patients treated with OFEV compared to 1% of placebo-treated patients. Diarrhea led to discontinuation of OFEV in 7% of the patients compared to 0.3% of placebo-treated patients. Dosage modifications or treatment interruptions may be necessary in patients with adverse reactions of diarrhea. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues *[see Dosage and Administration]*. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe diarrhea persists despite symptomatic treatment, discontinue treatment with OFEV. Nausea and Vomiting: In IPF studies (Studies 1, 2, and 3), nausea was reported in 24% versus 7% and vomiting was reported in 12% versus 3% of patients treated with OFEV and placebo, respectively. In the SSc-ILD study (Study 4), nausea was reported in 32% versus 14% and vomiting was reported in 25% versus 10% of patients treated with OFEV and placebo, respectively *[see Adverse Reactions]*. In most patients, these events were of mild to moderate intensity. In IPF studies (Studies 1, 2, and 3), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. In the SSc-ILD study (Study 4), nausea led to discontinuation of OFEV in 2% of patients and vomiting led to discontinuation of OFEV in 1% of the patients. For nausea or vomiting that persists despite appropriate supportive care including anti-emetic therapy, dose reduction or treatment interruption may be required *[see Dosage and Administration]*. OFEV treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If severe nausea or vomiting does not resolve, discontinue treatment with OFEV. **5.4 Embryo-Fetal Toxicity:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose (MRHD) in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV and to use highly effective contraception during treatment and at least 3 months after the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, therefore advise women using hormonal contraceptives to add a barrier method. Verify pregnancy status prior to treatment with OFEV and during treatment as appropriate *[see Use in Specific Populations]*. **5.5 Arterial Thromboembolic Events:** Arterial thromboembolic events have been reported in patients taking OFEV. In IPF studies (Studies 1, 2, and 3), arterial thromboembolic events were reported in 2.5% of patients treated with OFEV and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of OFEV-treated patients compared to 0.4% of placebo-treated patients. In the SSc-ILD study (Study 4), arterial thromboembolic events were reported in 0.7% of patients in both treatment arms. There were 0 cases of myocardial infarction in OFEV-treated patients compared to 0.7% of placebo-treated patients. Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Consider treatment interruption in patients who develop signs or symptoms of acute myocardial ischemia. **5.6 Risk of Bleeding:** Based on the mechanism of action (VEGFR inhibition), OFEV may increase the risk of bleeding. In IPF studies (Studies 1, 2, and 3), bleeding events were reported in 10% of patients treated with OFEV and in 7% of patients treated with placebo. In the SSc-ILD study (Study 4), bleeding events were reported in 11% of patients treated with OFEV and in 8% of patients treated with placebo. In the postmarketing period non-serious and serious bleeding events, some of which were fatal, have been observed. Use OFEV in patients with known risk of bleeding only if the anticipated benefit outweighs the potential risk. **5.7 Gastrointestinal Perforation:** Based on the mechanism of action, OFEV may increase the risk of gastrointestinal perforation. In IPF studies (Studies 1, 2, and 3), gastrointestinal perforation was reported in 0.3% of patients treated with OFEV, compared to 0 cases in the placebo-treated patients. In the SSc-ILD study (Study 4), no cases of gastrointestinal perforation were reported in patients treated with OFEV or in placebo-treated patients. In the postmarketing period, cases of gastrointestinal perforations have been reported, some of which were fatal. Use caution when treating patients who have had recent abdominal surgery, previous history of diverticular disease or receiving concomitant corticosteroids or NSAIDs. Discontinue therapy with OFEV in patients who develop gastrointestinal perforation. Only use OFEV in patients with known risk of gastrointestinal perforation if the anticipated benefit outweighs the potential risk.

6 ADVERSE REACTIONS: The following adverse reactions are discussed in greater detail in other sections of the labeling: Elevated Liver Enzymes and Drug-Induced Liver Injury *[see Warnings and Precautions]*; Gastrointestinal Disorders *[see Warnings and Precautions]*; Embryo-Fetal Toxicity *[see Warnings and Precautions]*; Arterial Thromboembolic Events *[see Warnings and Precautions]*; Risk of Bleeding *[see Warnings and Precautions]*; Gastrointestinal Perforation *[see Warnings and Precautions]*. **6.1 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. The safety of OFEV was evaluated in over 1000 IPF patients and over 280 patients with SSc-ILD. Over 200 IPF patients were exposed to OFEV for more than 2 years in clinical trials. Idiopathic Pulmonary Fibrosis: OFEV was studied in three randomized, double-blind, placebo-controlled, 52-week trials. In the phase 2 (Study 1) and phase 3 (Studies 2 and 3) trials, 723 patients with IPF received OFEV 150 mg twice daily and 508 patients received placebo. The median duration of exposure was 10 months for patients treated with OFEV and 11 months for patients treated with placebo. Subjects ranged in age from 42 to 89 years (median age of 67 years). Most patients were male (79%) and Caucasian (60%). The most frequent serious adverse reactions reported in patients treated with OFEV, more than placebo, were bronchitis (1.2% vs. 0.8%) and myocardial infarction (1.5% vs. 0.4%). The most common adverse events leading to death in patients treated with OFEV, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%). In the predefined category of major adverse cardiovascular events (MACE) including MI, fatal events were reported in 0.6% of OFEV-treated patients and 1.8% of placebo-treated patients. Adverse reactions leading to permanent dose reductions were reported in 16% of OFEV-treated patients and 1% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (11%). Adverse reactions leading to discontinuation were reported in 21% of OFEV-treated patients and 15% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (5%), nausea (2%), and decreased appetite (2%). The most common adverse

reactions with an incidence of greater than or equal to 5% and more frequent in the OFEV than placebo treatment group are listed in Table 1.

Table 1 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Studies 1, 2, and 3

Adverse Reaction	OFEV, 150 mg n=723	Placebo n=508
Gastrointestinal disorders		
Diarrhea	62%	18%
Nausea	24%	7%
Abdominal pain[a]	15%	6%
Vomiting	12%	3%
Hepatobiliary disorders		
Liver enzyme elevation[b]	14%	3%
Metabolism and nutrition disorders		
Decreased appetite	11%	5%
Nervous system disorders		
Headache	8%	5%
Investigations		
Weight decreased	10%	3%
Vascular disorders		
Hypertension[c]	5%	4%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain and abdominal tenderness.

[b] Includes gamma-glutamyltransferase increased, hepatic enzyme increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic function abnormal, liver function test abnormal, transaminase increased, blood alkaline phosphatase-increased, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and gamma-glutamyltransferase abnormal.

[c] Includes hypertension, blood pressure increased, hypertensive crisis, and hypertensive cardiomyopathy.

In addition, hypothyroidism was reported in patients treated with OFEV, more than placebo (1.1% vs. 0.6%).

Combination with Pirfenidone: Concomitant treatment with nintedanib and pirfenidone was investigated in an exploratory open-label, randomized (1:1) trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomized patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to Week 12. Gastrointestinal adverse events were in line with the established safety profile of each component and were experienced in 37 (70%) patients treated with pirfenidone added to nintedanib versus 27 (53%) patients treated with nintedanib alone. Diarrhea, nausea, vomiting, and abdominal pain (includes upper abdominal pain, abdominal discomfort, and abdominal pain) were the most frequent adverse events reported in 20 (38%) versus 16 (31%), in 22 (42%) versus 6 (12%), in 15 (28%) versus 6 (12%) patients, and in 15 (28%) versus 7 (14%) treated with pirfenidone added to nintedanib versus nintedanib alone, respectively. More subjects reported AST or ALT elevations (greater than or equal to 3x the upper limit of normal) when using pirfenidone in combination with nintedanib (n=3 (6%)) compared to nintedanib alone (n=0) [*see Warnings and Precautions*]. Systemic Sclerosis-Associated Interstitial Lung Disease: OFEV was studied in a phase 3, randomized, double-blind, placebo-controlled trial (Study 4) in which 576 patients with SSc-ILD received OFEV 150 mg twice daily (n=288) or placebo (n=288). Patients were to receive treatment for at least 52 weeks; individual patients were treated for up to 100 weeks. The median duration of exposure was 15 months for patients treated with OFEV and 16 months for patients treated with placebo. Subjects ranged in age from 20 to 79 years (median age of 55 years). Most patients were female (75%). Patients were mostly Caucasian (67%), Asian (25%), or Black (6%). At baseline, 49% of patients were on stable therapy with mycophenolate. The most frequent serious adverse events reported in patients treated with OFEV, more than placebo, were interstitial lung disease (2.4% nintedanib vs 1.7% placebo) and pneumonia (2.8% nintedanib vs 0.3% placebo). Within 52 weeks, 5 patients treated with OFEV (1.7%) and 4 patients treated with placebo (1.4%) died. There was no pattern among adverse events leading to death in either treatment arm. Adverse reactions leading to permanent dose reductions were reported in 34% of OFEV-treated patients and 4% of placebo-treated patients. The most frequent adverse reaction that led to permanent dose reduction in the patients treated with OFEV was diarrhea (22%). Adverse reactions leading to discontinuation were reported in 16% of OFEV-treated patients and 9% of placebo-treated patients. The most frequent adverse reactions that led to discontinuation in OFEV-treated patients were diarrhea (7%), nausea (2%), vomiting (1%), abdominal pain (1%), and interstitial lung disease (1%). The safety profile in patients with or without mycophenolate at baseline was comparable. The most common adverse reactions with an incidence of greater than or equal to 5% in OFEV-treated patients and more commonly than in placebo are listed in Table 2.

Table 2 Adverse Reactions Occurring in ≥5% of OFEV-treated Patients and More Commonly Than Placebo in Study 4

Adverse Reaction	OFEV, 150 mg n=288	Placebo n=288
Diarrhea	76%	32%
Nausea	32%	14%
Vomiting	25%	10%
Skin ulcer	18%	17%
Abdominal pain[a]	18%	11%
Liver enzyme elevation[b]	13%	3%
Weight decreased	12%	4%
Fatigue	11%	7%
Decreased appetite	9%	4%
Headache	9%	8%
Pyrexia	6%	5%
Back pain	6%	4%
Dizziness	6%	4%
Hypertension[c]	5%	2%

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, and esophageal pain.

[b] Includes alanine aminotransferase increased, gamma-glutamyltransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, blood alkaline phosphatase increased, transaminase increased, and hepatic function abnormal.

[c] Includes hypertension, blood pressure increased, and hypertensive crisis

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of OFEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during postapproval use of OFEV: drug-induced liver injury *[see Warnings and Precautions]*, non-serious and serious bleeding events, some of which were fatal *[see Warnings and Precautions]*, pancreatitis, thrombocytopenia, rash, pruritus.

7 DRUG INTERACTIONS: 7.1 P-glycoprotein (P-gp) and CYP3A4 Inhibitors and Inducers: Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with oral doses of a P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of P-gp and CYP3A4 inhibitors (e.g., erythromycin) with OFEV may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of OFEV. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with OFEV *[see Dosage and Administration]*. Coadministration with oral doses of a P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with OFEV should be avoided as these drugs may decrease exposure to nintedanib. **7.2 Anticoagulants:** Nintedanib is a VEGFR inhibitor and may increase the risk of bleeding. Monitor patients on full anticoagulation therapy closely for bleeding and adjust anticoagulation treatment as necessary *[see Warnings and Precautions]*. **7.3 Pirfenidone:** In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either agent. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone. **7.4 Bosentan:** Coadministration of nintedanib with bosentan did not alter the pharmacokinetics of nintedanib.

8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy: Risk Summary: Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman. There are no data on the use of OFEV during pregnancy. In animal studies of pregnant rats and rabbits treated during organogenesis, nintedanib caused embryo-fetal deaths and structural abnormalities at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2% to 4% and miscarriage in clinically recognized pregnancies is 15% to 20%. Data: *Animal Data:* In animal reproduction toxicity studies, nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability of rat pups during the first 4 post-natal days when dams were exposed to less than the MRHD (on an AUC basis at a maternal oral dose of 10 mg/kg/day). **8.2 Lactation:** Risk Summary: There is no information on the presence of nintedanib in human milk, the effects on the breast-fed infant or the effects on milk production. Nintedanib and/or its metabolites are present in the milk of lactating rats *[see Data]*. Because of the potential for serious adverse reactions in nursing infants from OFEV, advise women that breastfeeding is not recommended during treatment with OFEV. Data: Milk and plasma of lactating rats have similar concentrations of nintedanib and its metabolites. **8.3 Females and Males of Reproductive Potential:** Based on findings from animal studies and its mechanism of action, OFEV can cause fetal harm when administered to a pregnant woman and may reduce fertility in females of reproductive potential *[see Use in Specific Populations]*. Counsel patients on pregnancy prevention and planning. Pregnancy Testing: Verify the pregnancy status of females of reproductive potential prior to treatment with OFEV and during treatment as appropriate. *[see Dosage and Administration, Warnings and Precautions and Use in Specific Populations]*. Contraception: OFEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. It is currently unknown whether nintedanib may reduce the effectiveness of hormonal contraceptives, therefore advise women using hormonal contraceptives to add a barrier method. Infertility: Based on animal data, OFEV may reduce fertility in females of reproductive potential. **8.4 Pediatric Use:** Safety and effectiveness in pediatric patients have not been established. **8.5 Geriatric Use:** Of the total number of subjects in phase 2 and 3 clinical studies of OFEV in IPF, 60.8% were 65 and over, while 16.3% were 75 and over. In SSc-ILD, 21.4% were 65 and over, while 1.9% were 75 and older. In phase 3 studies, no overall differences in effectiveness were observed between subjects who were 65 and over and younger subjects; no overall differences in safety were observed between subjects who were 65 and over or 75 and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Hepatic Impairment:** Nintedanib is predominantly eliminated via biliary/fecal excretion (greater than 90%). In a PK study performed in patients with hepatic impairment (Child Pugh A, Child Pugh B), exposure to nintedanib was increased. In patients with mild hepatic impairment (Child Pugh A), the recommended dosage of OFEV is 100 mg twice daily *[see Dosage and Administration]*. Monitor for adverse reactions and consider treatment interruption, or discontinuation for management of adverse reactions in these patients *[see Dosage and Administration]*. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with OFEV

is not recommended *[see Warnings and Precautions]*.
8.7 Renal Impairment: Based on a single-dose study, less than 1% of the total dose of nintedanib is excreted via the kidney. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (less than 30 mL/min CrCl) and end-stage renal disease.
8.8 Smokers: Smoking was associated with decreased exposure to OFEV, which may alter the efficacy profile of OFEV. Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV.

10 OVERDOSAGE: In IPF trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of OFEV. Both patients recovered. In case of overdose, interrupt treatment and initiate general supportive measures as appropriate.

17 PATIENT COUNSELING INFORMATION: *Advise the patient to read the FDA-approved patient labeling (Patient Information).* Elevated Liver Enzymes and Drug-Induced Liver Injury: Advise patients that they will need to undergo liver function testing periodically. Advise patients to immediately report any symptoms of a liver problem (e.g., skin or the whites of eyes turn yellow, urine turns dark or brown (tea colored), pain on the right side of stomach, bleed or bruise more easily than normal, lethargy, loss of appetite) *[see Warnings and Precautions]*. Gastrointestinal Disorders: Inform patients that gastrointestinal disorders such as diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal events occurring in patients who received OFEV. Advise patients that their healthcare provider may recommend hydration, antidiarrheal medications (e.g., loperamide), or anti-emetic medications to treat these side effects. Temporary dosage reductions or discontinuations may be required. Instruct patients to contact their healthcare provider at the first signs of diarrhea or for any severe or persistent diarrhea, nausea, or vomiting *[see Warnings and Precautions and Adverse Reactions]*. Embryo-Fetal Toxicity: Counsel patients on pregnancy prevention and planning. Advise females of reproductive potential of the potential risk to a fetus and to avoid becoming pregnant while receiving treatment with OFEV. Advise females of reproductive potential to use highly effective contraception during treatment, and for at least 3 months after taking the last dose of OFEV. Advise women using hormonal contraceptives to add a barrier method. Advise female patients to notify their doctor if they become pregnant or suspect they are pregnant during therapy with OFEV *[see Warnings and Precautions and Use in Specific Populations]*. Arterial Thromboembolic Events: Advise patients about the signs and symptoms of acute myocardial ischemia and other arterial thromboembolic events and the urgency to seek immediate medical care for these conditions *[see Warnings and Precautions]*. Risk of Bleeding: Bleeding events have been reported. Advise patients to report unusual bleeding *[see Warnings and Precautions]*. Gastrointestinal Perforation: Serious gastrointestinal perforation events have been reported. Advise patients to report signs and symptoms of gastrointestinal perforation *[see Warnings and Precautions]*. Lactation: Advise patients that breastfeeding is not recommended while taking OFEV *[see Use in Specific Populations]*. Smokers: Encourage patients to stop smoking prior to treatment with OFEV and to avoid smoking when using OFEV. Administration: Instruct patients to swallow OFEV capsules whole with liquid and not to chew or crush the capsules due to the bitter taste. Advise patients to not make up for a missed dose *[see Dosage and Administration]*.

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RARE RHEUMATOLOGIC DISEASES

SPECIAL REPORT

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Rare rheumatologic disease registries expand and produce results

Registries now cover many rare rheumatologic diseases in numbers that give greater analytic power and generate more insights.

By Mitchel L. Zoler

Registries for rare rheumatologic diseases have now collected data from, in some instances, thousands of patients, enough to let researchers make better sense of disorders that were once much less comprehensible when they had just a few dozen cases to study.

"Registries have been vital for progress," summed up Lisa G. Rider, MD, a pediatric rheumatologist and deputy chief of the Environmental Autoimmunity Group, Clinical Research Branch, of the National Institute of Environmental Health Sciences. She linked the rise of rheumatology registries over roughly the past 3 decades to recognition by researchers that single-center case series were too limited in scope to allow for broadly meaningful conclusions. By the early 1990s, rheumatologists began to "appreciate the value of studying larger numbers of patients with rare diseases. It became necessary to develop registries and collaborate more," she said in an interview.

Registries now proliferate, and have contributed to important advances in understanding myositis, scleroderma, autoinflammatory diseases, juvenile idiopathic arthritis (JIA), and other uncommon rheumatologic disorders. Dr. Rider, who has given special attention to registries with myositis patients, tallied for a talk she gave late last year more than 65 registries just for this group of diseases, with more than 25,000 patients collectively enrolled. According to Dr. Rider, the largest myositis registry is EuroMyositis. It now includes more than 5,000 patients and more than 24 worldwide sites actively recruiting patients, said Ingrid Lundberg, MD, professor of rheumatology at the Karolinska Institute in Stockholm and a member of the EuroMyositis steering committee.

Other key registries include the European Scleroderma Trials and Research (EUSTAR) group, a registry of more than 16,000 patients from 232 centers around the world; the North American Scleroderma Family Registry & DNA Repository, which began in 2000 and has about 3,500 enrolled scleroderma patients, and while not now actively entering new patients, it remains a research resource; the EuroFever Registry for autoinflammatory diseases; and the Childhood Arthritis and Rheumatology Research Alliance (CARRA), which ran a successful but eventually discontinued registry during 2010-2014 (now called the CARRA Legacy Registry), and then started a second Registry in 2015 with more comprehensive and hence more usable data collection that began by focusing on JIA and has since expanded to included pediatric patients with systemic lupus erythematosus (SLE), juvenile dermatomyositis, and, starting soon, scleroderma (and tentatively autoinflammatory diseases after that). By August 2019, the new CARRA Registry had enrolled more than 9,000 patients and is now active at about 70 sites worldwide, said Yukiko Kimura, MD, professor of pediatrics at Hackensack (N.J.) Meridian School of Medicine at Seton Hall, chief

Dr. Lisa G. Rider

Dr. Yukiko Kimura

Dr. Rider has received research funding from Bristol-Myers Squibb, research support from Hope and Lilly, intramural research support from NIEHS, and has served as an unpaid adviser to ReveraGen. Dr. Kimura has received salary support from CARRA, and CARRA has received grant support from Genentech. Dr. Mayes had no commercial disclosures. Dr. Hoffmann-Vold has received funding from, has consulted for, or both from Actelion and Boehringer Ingelheim.

of pediatric rheumatology at Hackensack University Medical Center, and a coprincipal investigator of the CARRA Registry.

Myositis registries

The myositis registries, such as EuroMyositis, and the North America-based MYOVISION Registry, typify how registries have transformed understanding of several rheumatologic disorders. "The rapid advance of information on disease phenotypes, autoantibodies, prognosis, genetics, and pathogenesis could not have been done without the registries," Dr. Rider said. She cited the characterization of the clinical spectrum of myositis derived from data collected from more than 3,000 patients with idiopathic inflammatory myopathy in the EuroMyositis Registry.[1] Another example was the 2017 classification criteria for adult and juvenile idiopathic inflammatory myopathies, which relied on data from the EuroMyositis Registry, the U.K. juvenile dermatomyositis national registry, as well as other myositis registries for criteria validation.[2]

Dr. Rider highlighted the importance of standardized data collection and definitions for making large-scale registries feasible, such as the consensus agreement on the core dataset elements for defining juvenile dermatomyositis.[3] But other aspects of disease definition continue to lack consensus agreement, such as diversity in myositis autoantibody assays, she noted. Other challenges facing registries are increasing regulatory restrictions on data sharing, and funding that can be nonsustaining. One reason why Europe is home to several robust rare-disease registries is that they received levels of European Union funding that surpassed the support that some U.S.-based registries have received, Dr. Rider observed.

Despite these and other challenges, rheumatology registries seem on track for further expansion of both patient numbers and the breadth of captured data. "I foresee registries getting larger and being able to do more, using more sophisticated patient-reported outcomes, collecting real-world data on medication usage, and having longer and more robust data collection with mobile-device health apps and not just using what's collected in the clinic," Dr. Rider predicted.

The CARRA Registry

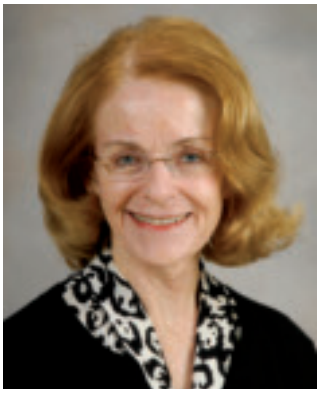
One of the most successful and rapidly expanding registries began in 2015 by CARRA, which has grown "beyond our expectations," reaching 9,000 patients after 4 years, by mid-2019, said Dr. Kimura. Despite an original goal enrollment of 10,000 patients, the steering committee now plans to continue adding patients beyond that "so that we can capture usage of new medications as they come on the market, and understand outcomes in more recently diagnosed patients," she said in an interview. Another goal is to follow enrolled patients for at least 10 years, as they become adults.

The current CARRA Registry represents a reboot, replacing a database now called the Legacy Registry that the group ran during 2010-2014 but which had inadequate data collection because of limited funding.[4] CARRA created its current registry to meet Food and Drug Administration requirements for pharmacosurveillance and postmarketing safety studies, Dr. Kimura explained. By March 2019, more than 90% of patients in the new registry had JIA, just over 5% had SLE, and about 1% had juvenile dermatomyositis.

Since 2015, data collected in the new CARRA Registry has resulted in more than 30 abstracts, she said. One notable study based on CARRA Registry data looked at factors related to successful discontinuation of disease-modifying treatment in more than 1,000 patients with well-controlled JIA who are enrolled in the registry. The results showed that only 15% of these patients could stay off treatment for at least a year, the researchers reported at the American College of Rheumatolo-

TABLE 1. A sampling of rheumatology registries

Registry	Disease	Approximate size	Year started	Enrollment ongoing?
EuroMyositis	any adult or pediatric myositis	>5,000 patients; >24 centers	2010	yes
EUSTAR	systemic sclerosis	>16,000 patients; 232 centers	2004	yes
Scleroderma Family Registry & DNA Repository	scleroderma	nearly 3,500 patients	2000	no
CARRA	juvenile idiopathic arthritis, SLE, etc.	>9,000 patients; >70 centers	2015	yes
EuroFever	any adult or pediatric autoinflammatory disease	1,880 patients; 67 centers	2010	no



Dr. Maureen D. Mayes

Dr. Anna-Maria Hoffmann-Vold

gy's 2017 annual meeting.[5] These findings "remind us that, even though we have excellent treatments for arthritis, they are not curative," Dr. Kimura said. The same researchers are in the process of repeating their study with more data and a more sophisticated analytic method to try to identify factors that link with a successful halt to medication, she added.

Another notable research effort now in progress using CARRA Registry data involves testing the performance of the several Consensus Treatment Plans that CARRA published for eight different pediatric rheumatologic diseases. The studies are assessing the Plans' performance in both routine practice and as a consistent platform for further study of optimal treatment approaches.[6]

Scleroderma registries

The Scleroderma Family Registry & DNA Repository (SFRDR) reached an enrollment of nearly 3,500 adult patients with scleroderma from centers in North America but has not enrolled additional patients recently because of inadequate funding, said Maureen D. Mayes, MD, professor of medicine at the University of Texas Health Science Center at Houston and principal investigator for the project. Several recent reports that used data from the SFRDR have focused on identifying genetic variants linked with increased risk for scleroderma, she noted, part of the study's ongoing effort to better understand the role of genetic variants in scleroderma pathogenesis.

One recent study identified five new genetic loci linked with several systemic, seropositive rheumatic diseases, including scleroderma and also SLE, rheumatoid arthritis, and idiopathic inflammatory myopathies. The loci all had some involvement in immune function.[7] Another study Dr. Mayes highlighted used data from the SFRDR and other sources with whole-exome sequencing to identify rare variants and gene networks that link with increased scleroderma susceptibility among African Americans, the largest study published so far to examine genetic correlates of systemic sclerosis in this population.[8]

An even larger scleroderma database is the EUSTAR Registry, begun in 2004 and now including more than 16,000 patients and continuing to actively enroll new patients and participating centers as a project of the World Scleroderma Foundation, said Anna-Maria Hoffmann-Vold, MD, director of scleroderma research at Oslo University Hospital and EUSTAR's secretary. Although EUSTAR's governing board has been satisfied with recent growth, members are working on new strategies to increase awareness of the Registry and its database, she said in an interview.

Recent, notable research that relied on data from the EUSTAR Registry includes a report that identified predictors of worsening diffuse systemic sclerosis in 1,451 patients in the database.[9] Another report Dr. Hoffmann-Vold highlighted prospectively examined the efficacy and safety of rituximab in 254 patients with systemic sclerosis in the EUSTAR database who received the drug. The observational results showed a "good safety profile," as well as significant improvement in skin fibrosis but not lung fibrosis.[10]

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HSCT leads cell- and gene-based therapies for rheumatic disease

By Will Pass

Over the past 3 decades, cell- and gene-based therapies have slowly made the transition from bench to bedside in several medical fields. In oncology, chimeric antigen receptor (CAR) T-cell therapy has become standard of care for some B-cell malignancies, while in hematology, gene vector therapy for hemophilia B may soon be a clinical reality. Using similar techniques in rheumatology, however, may be more elusive.

In contrast with B-cell malignancies, which have relatively well-understood cellular disease mechanisms, or hemophilia B, which is a monogenic condition, rheumatic disease tends to have highly complex pathophysiology, a low level of genetic concordance, and an array of poorly defined disease subtypes. Still, investigators are working on unique cell- and gene-based therapies for rheumatic disease, from laboratory studies focusing on the roles of individual immune cells to the clinic floor, where hematopoietic stem cell transplantation (HSCT) is now a standard of care for select patients with severe systemic sclerosis.

Foundational studies ongoing

At Northwestern University in Chicago, Deborah Winter, PhD, conducts functional genomic studies investigating the role of macrophages in rheumatic disease. In an interview, Dr. Winter described how rheumatology may be a fundamentally challenging field to employ cell- and gene-based therapies.

"Lupus, rheumatoid arthritis, systemic sclerosis, vasculitis, and others – they're all multifactorial … they're such complicated diseases," Dr. Winter said.

Because of this, Dr. Winter addressed the importance of foundational studies investigating rheumatic disease subtypes.

"To understand the heterogeneity across [rheumatic] disease is almost more important than developing treatments," Dr. Winter noted. "Even if we had the treatments, we wouldn't necessarily know who to treat with them. And even with the treatments we have today, we're not necessarily using them in the best ways."

For Dr. Winter, the way forward involves a closer look at disease mechanisms, cell by cell.

"Researchers have to focus on a particular cell type, so that you know that the genes being expressed are actually interacting with each other in the cell. Otherwise, using whole tissue or whole blood, trying to understand how the behavior emerges from the gene regulatory networks is totally impractical."

Dr. Deborah Winter

According to a recent review by David T. Ewart, MD, of the University of Minnesota, Minneapolis, and colleagues, despite the challenges, gene editing still holds promise in rheumatology.[1]

"There are several apparent niches for gene editing in the treatment of inflammatory diseases, including correction of monogenic autoinflammatory syndromes, CAR T-cell therapy for autoantigen-specific targeting of pathologic B-cell clones, modification of iPSCs [induced pluripotent stem cells] for controlled cytokine delivery and tissue regeneration, and Treg [regulatory T cells]-based therapies," Dr. Ewart and colleagues wrote.

According to the investigators, one gene editing technique is leading the field: clustered regularly interspaced short palindromic repeats, or CRISPR technology, using CRISPR-associated protein 9 (Cas9).

"CRISPR/Cas9 is versatile, efficient, simple to design and use, increasingly specific and is rapidly supplanting other modalities of gene editing," the investigators wrote, noting that the technology enables simultaneous targeting of multiple genes.

For now, precision gene editing in rheumatology remains in the realm of animal studies, xenograft models, and in vitro analysis.

Dr. Winter and Dr. Sullivan reported no relevant disclosures. Dr. van Laar reported a relationship with Trajectum Pharma.


Dr. Keith M. Sullivan


Dr. Jacob M. van Laar

HSCT becomes standard of care

While personalized gene editing remains on the horizon, cell-based therapy is a clinical reality, led by autologous HSCT, which is a new standard of care for select patients with early, severe systemic sclerosis, according to a 2018 position statement from the American Society for Blood and Marrow Transplantation.[2]

This consensus was reached on the basis of three randomized clinical trials published between 2011 and 2018 (ASSIST,[3] ASTIS,[4] and SCOT[5]). With up to 11 years of follow-up, the latest SCOT data[6] showed an 88% survival rate associated with HSCT, compared with 53% among those treated with cyclophosphamide (*P = .01).*

Keith M. Sullivan, MD, of Duke University Medical Center in Durham, N.C., was the lead author of both the SCOT trial and the ASBMT position statement. In an interview, Dr. Sullivan put the SCOT findings in perspective, highlighting durability of response.

"In publications for other autoimmune disease … when patients are started on DMARDs [disease-modifying antirheumatic drugs] and then the DMARDs are stopped, more than three-quarters of the patients will have the disease come back within a year," Dr. Sullivan said. "So when I'm talking about follow-up in the SCOT trial, with the transplant patients out to 11 years, they're off DMARDs for 6-11 years. That is extremely durable and extremely encouraging."

Responding to possible concerns about the risks of autologous HSCT, Dr. Sullivan suggested that hesitant clinicians reassess their conclusions. "I think physicians' fears need to be recalibrated in relationship to what the data actually show," Dr. Sullivan said. He noted an approximate 6% mortality associated with HSCT in the SCOT trial and the ASSIST trial, and pointed out that in the SCOT trial, no deaths occurred in the first year following transplant, and after the sixth year, no subsequent deaths occurred in the transplant arm, compared with four deaths in the cyclophosphamide arm.

Building upon these clinical findings, a series of SCOT companion studies have been implemented to uncover mechanistic processes and biomarkers related to autologous HSCT. These kinds of studies are essential to progress in the field, Dr. Sullivan noted.

"We had 10 abstracts at the last ACR meeting based on SCOT material," Dr. Sullivan said, "and we have two of those studies showing actually the genomic signatures of scleroderma resolve and go back to normal after stem cell transplantation and not change after [cyclophosphamide]. So this is a whole platform of scientific studies asking this: OK, it works, but why does it work?"

Jacob M. van Laar, MD, PhD, lead author of the ASTIS trial, agreed with Dr. Sullivan that companion studies are essential, as they have the potential to optimize treatment decisions. One such analysis shows normalization of genomic signature after HSCT.[7]

"Based on clinical data alone, we will not come to a final algorithm which will help us in the future," Dr. van Laar said. "So I really hope that we can marry data from these biomarker studies to clinical studies and hopefully this will add to the knowledge that is necessary for clinical decision making."

Selecting patients for HSCT

Currently, when selecting patients with systemic sclerosis for HSCT, both Dr. Sullivan and Dr. van Laar rely upon the eligibility criteria used in their respective clinical trials, supplemented with some insights learned along the way; for instance, they both noted that pulmonary function can be a key determinant of therapeutic outcome.

"It doesn't make any sense to refer somebody for transplantation when their pulmonary function is so severe that they're on oxygen," Dr. Sullivan said. "They won't have a safe transplant. So get serial pulmonary function tests. If they continue to fall, that's a certain time for referral urgently for transplant."

Dr. van Laar supported the importance of pulmonary health, noting that smokers tend to have worse outcomes with HSCT than do nonsmokers.

While international guidelines for patient selection remain elusive, both experts emphasized that patients with systemic sclerosis need to be made aware of HSCT and participate in shared decision making.

"I care deeply if a patient is never considered for referral for consultation to a transplant center, where at least they can make a decision" Dr. Sullivan said. "It's their shared decision after they have that knowledge, and then they say yes or no."

To help improve treatment timing, Dr. van Laar and his colleagues are planning a multicenter, multinational clinical randomized trial, which has received funding but remains unnamed.

Dr. van Laar described the key question that the trial will address: "Should HSCT be used as a kind of up-front, intensive immunosuppressive treatment for selected systemic

sclerosis patients with a poor prognosis, or should it be used as a rescue therapy in those patients who've failed conventional immunosuppression?"

Looking to the future

Beyond systemic sclerosis, Dr. van Laar noted that investigators have considered HSCT for systemic lupus erythematosus (SLE), but he believed this is a passing trend, with research gravitating toward biologic therapies.

When asked about other cell-based therapies for rheumatic disease, including mesenchymal stem cells, regulatory T cells, and tolerogenic dendritic cells, Dr. Sullivan and Dr. van Laar expressed similar opinions to those prevalent in the field of gene editing: What's coming is promising, but it's going to take time, and people need to maintain realistic expectations.

Dr. van Laar predicted that it might be a bumpy road to success, too, citing CAR T-cell therapy in oncology as an example.

"[CAR T-cell therapy] is a field that had ups and downs for tens of years before it finally had a breakthrough and led to use in the clinic," Dr. van Laar said. "I anticipate we will go the same way – that in 5-10 years' time, maybe tolerizing dendritic cells or maybe regulatory T cells are part of the routine clinical armamentarium."

For now, Dr. van Laar said, "Watch this space."

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Tackling the challenges of pediatric localized scleroderma

By Bruce Jancin

MAUI, HAWAII–One of the most important steps to take when a child has received a biopsy-confirmed diagnosis of localized scleroderma is to sit down with the family and explain the rationale for the aggressive therapies to come, Anne M. Stevens, MD, PhD, said at the 2019 Rheumatology Winter Clinical Symposium.

It can be a tough sell at first, especially when a child has only a small red streak on the nose and perhaps a subtle linear lesion on the forehead or scalp. But the family has to come to understand that this is a serious, chronic, progressive fibrotic disease.

"Talk about what a big impact this disease can have on growth of a limb and the normal life of a child because of the cosmetic appearance. Explain that the length of treatment course is based on the long-term outcomes and quality of life. This discussion is usually sufficient" to convince people to give their children "these pretty serious medications," said Dr. Stevens, professor of pediatrics and head of the division of pediatric rheumatology at the University of Washington, Seattle.

"The treatment goal is to control inflammation and prevent damage in these patients, who we like to catch very early, when it's a subtle lesion," she added.

The biggest problem

The biggest contributors to poor quality of life in patients with juvenile localized scleroderma are the extracutaneous manifestations, which occur in up to 50% of cases. Joint pain occurs in roughly 20% of patients, joint contractures due to fibrosis of skin and/or tendons in 30%, and myalgia with or without myositis in 15%. Muscle atrophy due to the deep component of the scleroderma can occur. Moreover, growth problems – especially leg or arm length discrepancies – happen in about 20% of patients in prospective studies. These growth problems may not be obvious until a child enters a growth spurt, at which point there is a limited ability to achieve improvement. That's why Dr. Stevens recommends that every child with localized scleroderma should get a full joint exam at every visit, with measurement and photos of lesions and recording of all erythematous, violaceous, and waxy-hued areas. And if there are lesions on the head, annual eye exams are warranted.

The prevalence of juvenile localized scleroderma in the United States is about 3 per 100,000, with a mean age of onset of 8.2 years. That makes it 100-fold more common than pediatric systemic sclerosis.

The treatment ladder

There are no Food and Drug Administration–approved medications for localized scleroderma in children. It's all off label. That being said, there is strong consensus among members of the Childhood Arthritis and Rheumatology Research Alliance that the first-line therapy is methotrexate at 15 mg/m^2 or a maximum of 20 mg/week plus intravenous corticosteroids weaned over the course of 3-6 months. This is the treatment regimen with the best supporting evidence of safety and efficacy, including a single Italian randomized, double-blind, placebo-controlled clinical trial[1] and an accompanying long-term, open-label follow-up study.[2]

Bruce Jancin/MDedge News

Dr. Anne M. Stevens

All of the other treatments she uses for juvenile localized scleroderma—mycophenolate mofetil (CellCept), abatacept (Orencia), tocilizumab (Actemra), and occasionally others—are backed only by a smattering of small case series. However, given the serious potential trajectory of this disease, that modest evi-

Dr. Stevens reported receiving research funding from Kineta and Seattle Genetics.

dence base has been sufficient for her to receive insurance coverage approval of these agents.

In the randomized trial of first-line methotrexate, 48 of 65 patients treated with methotrexate plus steroid (74%) were responders. And among those 48 responders, 35 (73%) maintained a clinical remission for a mean of 25 months off-drug, while another 13 (27%) were in clinical remission on methotrexate. Twenty-eight patients developed side effects that were generally mild; no one required treatment discontinuation. At the 5-year mark, after an average of an initial 2 years on methotrexate, half of the patients were in a sustained clinical remission, which Dr. Stevens deemed "pretty good" considering the well established and manageable safety profile of the drug.

If a patient fails to respond to methotrexate plus corticosteroids within a few months or later experiences disease progression, Dr. Stevens' second-line therapy is mycophenolate mofetil in conjunction with corticosteroids. Its use in arresting juvenile localized scleroderma is supported by two favorable published case series, the largest of which includes 10 patients.[3]

Dr. Stevens' third-line therapy is intravenous abatacept at 10 mg/kg monthly along with intravenous methylprednisolone at 500 mg/week. There are five published case series, the most recent and largest of which included 13 adult patients, 2 of whom had en coup de sabre lesions.[4] The biologic also shows promise in patients with advanced severe disease with deep tissue involvement.[5] And abatacept has a plausible mechanism of action in localized scleroderma: French investigators have shown it induces regression of skin fibrosis in a mouse model of the disease.[6]

Her fourth-line strategy is the anti-interleukin-6 agent tocilizumab, again in conjunction with corticosteroids. In a translational study, tocilizumab has been shown to normalize dermal fibroblasts and collagen in patients with systemic sclerosis.[7] And there have been two promising small retrospective case series as well. A more definitive clinical trial is planned.

Dr. Stevens said that when starting a biologic agent in a child with localized scleroderma, she routinely adds methotrexate until the disease is under control.

Drugs supported by case reports and worth considering on an individual basis as a last resort are hydroxychloroquine, azathioprine, cyclosporine, and imatinib mesylate (Gleevec).

For mild, superficial lesions that don't cross joints, ultraviolet light A phototherapy is a therapeutic option. It displayed significant benefit in a systematic review and meta-analysis of 19 studies comparing it to methotrexate, although the results with methotrexate were deemed superior.[8]

The pros and cons of getting a baseline brain MRI

Children with localized scleroderma have increased rates of severe headache, peripheral neuropathy, complex partial seizures, and stroke. So it had been Dr. Stevens' routine practice to obtain an initial brain MRI at the time of diagnosis. Of late, though, she has reconsidered that practice.

"The problem is that some patients with abnormal MRI lesions have no CNS disease at all, and there are also a fair number of patients with a normal MRI who have CNS symptoms. So in our practice we're pulling back on doing screening MRIs because we don't know what to do with the findings, and it just makes everybody worried," she said.

However, if a child with localized scleroderma develops headaches, seizures, neuropathies, or other CNS symptoms, then by all means get an MRI, and if it shows findings such as brain atrophy, white matter lesions, calcifications, or leptomeningeal enhancement, consider treatment, she added.

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Pain overtakes her every night.
She cannot run, she cannot fight.
She suffers as dawn ends the night.

nr-axSpA (nonradiographic axial spondyloarthritis): a painful reality

nr-axSpA lurks within the disease spectrum of axSpA. Despite no visible damage on x-ray, it still has a comparable symptom burden to AS.[1,2]

nr-axSpA affects young people (≤45) who present with chronic inflammatory back pain that improves with movement.[3] Surprisingly, up to two-thirds of patients are women.[4]

Are your patients experiencing symptoms in the night? Apply your clinical judgment to identify nr-axSpA in these patients, based on objective signs of inflammation, positive genetic testing, and at least 2 SpA features.[1,5*†]

Detect **nr-axSpA** and know that ***you*** can find this foe.

*Objective signs of inflammation include but are not limited to elevated CRP (with chronic back pain), enthesitis, dactylitis, and sacroiliitis on MRI. Genetic testing refers to HLA-B27 positivity.[5]

†SpA features include inflammatory back pain, arthritis, enthesitis (heel), uveitis, dactylitis, psoriasis, Crohn's disease/UC, good response to NSAIDs, family history of SpA, HLA-B27, and elevated CRP.[1]

AS=ankylosing spondylitis; axSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA=human leukocyte antigen; MRI=magnetic resonance imaging; NSAIDs=nonsteroidal anti-inflammatory drugs; SpA=spondyloarthritis; UC=ulcerative colitis.

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Polyarticular JIA research spurred by pediatric rheumatology group

The Childhood Arthritis and Rheumatology Research Alliance runs several studies aimed at a better understanding of polyarticular juvenile idiopathic arthritis.

By Mitchel L. Zoler

Many of the biggest studies underway in patients with polyarticular juvenile idiopathic arthritis not sponsored by a drug company have been organized by North America–based Childhood Arthritis and Rheumatology Research Alliance (CARRA), a network of roughly 600 pediatric rheumatologists, researchers, and other clinicians with an interest in pediatric rheumatologic diseases.

CARRA, which began in 2002 and now operates at 140 sites, is now running five studies examining key issues in the treatment of polyarticular juvenile idiopathic arthritis (pJIA) and other forms of JIA, as well as running a patient Registry that has enrolled more than 9,000 patients during 4 years in operation. All patients included in any of the CARRA JIA studies also are enrolled in the Registry.

Polyarticular JIA is not only the largest subgroup of patients within the universe of pediatric rheumatic diseases, but also among the sickest of JIA patients with disease that usually requires more aggressive treatment and has worse outcomes than patients with fewer involved joints, noted Yukiko Kimura, MD, former president of CARRA and a member of its steering committee, and Timothy Beukelman, MD, a pediatric rheumatologist who is scientific director for the CARRA Registry and a coinvestigator for several CARRA-organized studies. "For these reasons, understanding this group of diseases has become an important focus for the CARRA's JIA research committee," they said in a joint interview.

Among the several studies CARRA is running that include patients with pJIA, two standouts are STOP-JIA (Start Time Optimization of Biologics in Polyarticular JIA) and the linked study Precision Decisions. Both are aimed at addressing which drug class to use for initial treatment of patients newly diagnosed specifically with pJIA.

Dr. Yukiko Kimura

Dr. Timothy Beukelman

"This is an issue that is of critical importance," not only to patients, their families, clinicians, and researchers but also for insurance payers, Dr. Kimura and Dr. Beukelman said. "We currently don't know whether to start pJIA patients on methotrexate alone, and not start a biologic unless this doesn't work, or whether a biologic should start from the beginning, with or without methotrexate. We know that biologics work better [than methotrexate] for most patients, but is it necessary to start all patients on a biologic when a good percentage of patients will respond very well to a disease-modifying drug like methotrexate? Does it make sense to expose all pJIA patients to a biologic when it may not be needed?" The potential downside of holding off on a biologic is that in some patients this could miss a "window of opportunity" for a quicker and more effective response. That's why these questions require more evidence from studies like the STOP-JIA trial.

Recently published guidelines for treating JIA from the American College of Rheumatology and the Arthritis Founda-

Dr. Kimura receives salary support from CARRA, and CARRA receives support from Genentech. Dr. Beukelman has served as a consultant to Bristol-Myers Squibb, Novartis, Sobi, and UCB. Dr. Becker had no relevant disclosures.


Dr. Mara L. Becker

tion noted: "A topic of particular debate among the Voting Panel was the appropriateness of the use of biologics as initial therapy in children with polyarthritis, particularly for those with risk factors. Ultimately, non–biologic DMARD [disease-modifying antirheumatic drug] therapy was recommended, but it was noted that there may be some patients for whom initial biologic therapy is indicated. This remains an area of active research, and currently ongoing studies may better clarify which patients are most likely to benefit from initial biologic therapy."[1]

In the linked Precision Decisions study, researchers take blood specimens from patients enrolled in STOP-JIA and then attempt to find markers that identify patients who will get the most benefit from initial treatment with a biologic drug.

Another CARRA-organized study, PROMOTE (Identifying Pharmacogenetic Predictors of Methotrexate Response and Metabolite Biotransformation in JIA), is using a similar approach to try to identify pharmacogenetic predictors of response to methotrexate among patients with JIA, including pJIA but excluding patients with systemic JIA. The study includes patients receiving methotrexate orally or subcutaneously, and at any dosage.

"Essentially, all these studies are striving to identify factors that can help guide initial treatment of JIA," said Mara L. Becker, MD, coprimary investigator for PROMOTE and a pediatric rheumatologist at Duke University in Durham, N.C.

Two other CARRA-organized studies that are enrolling patients with pJIA as well as other forms of JIA are Recapture-JIA, and PEPR. Recapture-JIA is studying children with JIA who had been well controlled, taken off their treatment, and then flare. The study focuses on whether the flare can be controlled by restarting treatment and will try to find markers of patients who do or do not quickly return to having well-controlled disease. PEPR (Advancing the Science of Pediatric Patient Reported Outcomes for Children with Chronic Disease) seeks to validate patient-reported outcomes in a representative subgroup of patients enrolled in the CARRA Registry, which predominantly includes patients with JIA but also includes smaller numbers of pediatric patients with systemic lupus erythematosus, juvenile dermatomyositis, and soon other pediatric rheumatologic diseases.

This list of CARRA studies are "among the top [research] priorities" for the field, but of course many additional questions remain on how to optimize care for these patients, noted Dr. Kimura, professor of pediatrics at Hackensack (N.J.) Meridian School of Medicine at Seton Hall and chief of pediatric rheumatology at Hackensack University Medical Center, and Dr. Beukelman, a pediatric rheumatologist at the University of Alabama at Birmingham. For example, a very pressing issue is when is the best time to withdraw a medication that has worked successfully. "Many clinicians and parents are afraid to stop

TABLE 1. CARRA-organized polyarticular JIA trials

Name of trial	Types of patients	Number of patients & sites	Primary objective
STOP-JIA	exclusively patients with polyarticular JIA	401 patients at 53 sites	To determine which patients need a biologic drug as initial treatment.
Precision Decisions	polyarticular JIA (STOP-JIA subgroup)	48 of the STOP-JIA sites	To identify blood markers that flag need for early biologic treatment.
PROMOTE	all forms of JIA except systemic	n/a	To identify pharmacogenetic predictors of response to methotrexate.
Recapture-JIA	all forms of JIA	150 patients	To evaluate the efficacy of retreatment when patients flare after drug withdrawal.
PEPR	multiple pediatric rheumatologic diseases	451 patients at seven sites	To validate patient-reported outcome measures for pediatric rheumatologic diseases.

a drug that is working well with no disease activity because they have no way to know whether the disease will then flare. CARRA has a working group dedicated to answering this question," they said. "Recapture-JIA addresses one aspect of this question, but other studies are planned to investigate the best way to withdraw medications once remission occurs, and whether the method of drug withdrawal has an impact on flare."

Another current trial that CARRA is not directly involved with, Limit-JIA (Preventing Extension of Oligoarticular Juvenile Idiopathic Arthritis JIA), is examining strategies to prevent patients with oligoarticular JIA from developing additional joint involvement, uveitis, or both. Future trials also need to explore novel treatment options for patients who do not respond to existing medications, particularly many of the new drugs that have undergone testing in adults with rheumatologic diseases but not in children and adolescents. Dr. Kimura and Dr. Beukelman, and several other researchers as well as representatives from industry, rheumatologic disease organizations, and regulatory agencies recently published suggested new approaches for speeding the process of making new agents available for JIA patients.[2]

Another key tool for future progress in managing pJIA, other forms of JIA, and other pediatric rheumatologic diseases is the CARRA Registry, which was relaunched in 2015 to better reflect the data needs of postmarketing studies.

"The CARRA Registry is the largest prospectively enrolling registry of JIA patients. Drug companies understand that they can collaborate with CARRA and use the registry to fulfill their postmarketing requirements," said Dr. Kimura and Dr. Beukelman. "We are continually refining the Registry to meet the needs of investigators, clinicians, and patients and their families. We have learned how to better enroll and retain patients in the registry, improved the feasibility of sites to participate, and we have enhanced the types of data that the registry collects."

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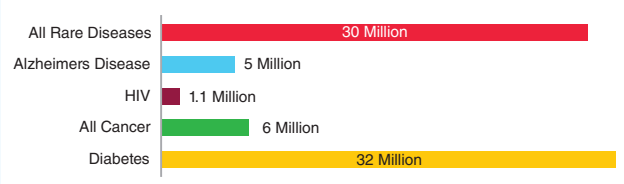
Rare diseases aren't as rare as you might think: look to the NIH's many resources for help


By Tiina K. Urv, PhD, and
Anne R. Pariser, MD

Rare diseases aren't rare. That statement might sound contradictory: After all, a rare disease is defined (in the United States) as a disease or condition of fewer than 200,000 affected persons living in the United States. Collectively, however, there are approximately 7,000 different rare diseases, with about 250 newly identified conditions added to the list each year. That equates to approximately 30 million Americans who are affected by a rare disease—more than the number of people who have cancer, human immunodeficiency virus infection, and Alzheimer's disease combined, and nearly as many as the number who have diabetes (Figure 1).

More than one half of the 30 million people affected by a rare disease in the United States are children. Most rare diseases are serious and can involve chronic illness, disability, and, often, premature death. Rare diseases are complex, and treatments exist for fewer than 5% of these conditions. It is important, therefore, to recognize that rare diseases are a significant public health issue. And since 350 million people are affected by rare diseases worldwide, it is not just a national problem, but a global problem.

FIGURE 1: Estimated prevalence of rare and other selected diseases



One of the greatest challenges facing people who have a rare disease is getting an accurate and timely diagnosis. The average time from onset of symptoms to diagnosis is 4.8 years (range, 0-20 years), during which time these people visit approximately 7 physicians, on average.[1] It is understandable why this process is often referred to as the diagnostic odyssey.

Since 1 in 10 Americans is affected with a rare disease, it is highly likely that during the course of any given day, a physician will encounter a patient with a rare disease in the examining room. This situation raises a question: How could a single physician be expected to have knowledge of more than 7,000 disorders that he has never encountered? During training, medical students have historically been taught that when you are working up a patient to make a diagnosis and you hear hoofbeats (i.e., see symptoms), you should look for horses, not for zebras—meaning that a common diagnosis is much more likely than an unusual one.

Many providers and researchers in the rare disease community have adopted the zebra as their mascot: They are the uncommon cause of hoofbeats in the medical field. Physicians, in this age of rapidly advancing science, might find themselves contending with not 1, but a herd of zebras, and it can be challenging to know where to turn for reliable information about rare diseases.

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This article reflects the views of the authors and should not be construed to represent the views or policies of NCATS or NIH.

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One good place to turn

The National Institutes of Health (NIH) (www.nih.gov), part of the US Department of Health and Human Services, is the nation's medical research agency. Among many other services, the NIH conducts and supports research related to rare diseases—from the most basic bench research to translational, clinical, and broad overall public health research.

The NIH comprises 27 institutes and centers (https://www.nih.gov/about-nih/what-we-do/nih-almanac/nih-organization), many of which conduct rare disease research. It can be daunting to know where within such a large institution to find information related to rare diseases. The answer? Within the National Center for Advancing Translational Science (NCATS) (https://ncats.nih.gov) of the NIH resides the Office of Rare Diseases Research (ORDR) (https://ncats.nih.gov/about/center/org/ordr).

> Since 1 in 10 Americans is affected by a rare disease, it is highly likely that during the course of any given day, a physician will encounter a patient with a rare disease in the examining room.

The ORDR was established at the NIH in 1985 (originally as the Office of Rare Diseases). The ORDR supports programs that help accelerate scientific discovery and offers patients and their health care providers information on identifying, diagnosing, treating, and living with a rare disease. The office does so by facilitating coordination among multiple stakeholders in the rare disease community, including scientists, clinicians, patients, and patient groups.

In 2002, Congress and President George W. Bush further established the ORDR and its responsibilities in a statute by enacting the Rare Diseases Act of 2002. The ORDR has established numerous resources for researchers, patients, and clinicians, which we catalogue and describe in this article.

NCATS ORDR programs for rare diseases

Genetic and Rare Diseases Information Center (GARD)

https://rarediseases.info.nih.gov

GARD is a collaboration of the National Human Genome Research Institute and NCATS/ORDR to provide comprehensive information about rare and genetic disease to patients, their families, health-care providers, researchers, and the public. Use of the GARD website and Contact Center is broad and has continued to grow (Figure 2).

The GARD website and database provide comprehensive, reliable, plain-language information on rare or genetic diseases that is freely accessible to the public and available in English and Spanish. Videos, brochures, publications, and links to disease-related organizations are also available. A contact center staffed by information specialists with expertise in genetic counseling provides free, individualized responses by telephone or email to support patients with a rare disease.

Rare Diseases Clinical Research Network (RDCRN)

https://www.rarediseasesnetwork.org

The RDCRN was established by the Rare Diseases Act of 2002 as the Rare Diseases Clinical Research Centers of Excellence. The RDCRN comprises a number of consortia, each studying at least 3 disorders and partnering closely with patient advocacy groups and NIH program staff (Table 1). The goal of the network, through its consortia, is to advance the diagnosis, management, and treatment of rare diseases. Each consortium promotes highly collaborative, multisite, patient-centric translational and clinical research. The individual consortia and the RDCRN are supported by a data management and coordinating center.

The network was first funded in 2003 and has been funded continuously since that time, with a recompetition every 5 years. To date, the program has successfully supported 31 individual consortia that have conducted research on 238 disorders, involving more than 40,000 participants, all leading to a greater understanding of rare diseases.

The aims of the upcoming program are to specifically address, through clinical research, 5 challenges to bringing effective treatment to more people living with rare diseases.

FIGURE 2: Genetic and Rare Diseases Information Center (GARD) utilization in recent years

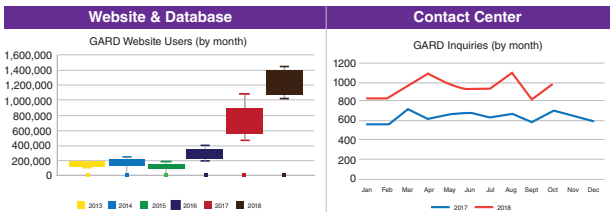

TABLE 1. Rare Diseases Clinical Research Network Consortia

Advancing Research and Treatment for Frontotemporal Lobar Degeneration Consortium (ARTFL) https://rdcrn.org/artfl	Lysosomal Disease Network (LDN) https://rdcrn.org/ldn
Autonomic Disorders Consortium (ADC) https://rdcrn.org/adc	NEPTUNE: Nephrotic Syndrome Study Network https://rdcrn.org/neptune
Brain Vascular Malformation Consortium (BVMC) https://rdcrn.org/bvmc	North American Mitochondrial Disease Consortium (NAMDC) https://rdcrn.org/namdc
Brittle Bone Disorders (BBD) https://rdcrn.org/bbd	Porphyrias Consortium (PC) https://rdcrn.org/porphyrias
Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) https://rdcrn.org/cegir	Primary Immune Deficiency Treatment Consortium (PIDTC) https://rdcrn.org/pidtc
CReATe: Clinical Research in ALS and Related Disorders for Therapeutic Development Consortium https://rdcrn.org/create	Rare Kidney Stone Consortium (RKSC) https://rdcrn.org/rksc
Developmental Synaptopathies Consortium (DSC) https://rdcrn.org/dsc	Rare Lung Diseases Consortium (RLDC) https://rdcrn.org/rld
Dystonia Coalition https://rdcrn.org/dystonia	Rett Syndrome, MECP2 Duplication, & Rett-Related Disorders Consortium (RTT) https://rdcrn.org/rett
Genetic Disorders of Mucociliary Clearance Consortium (GDMCC) https://rdcrn.org/gdmcc	STAIR: Sterol and Isoprenoid Research Consortium https://rdcrn.org/stair
Inherited Neuropathies Consortium (INC) https://rdcrn.org/inc	Urea Cycle Disorders Consortium (UCDC) https://rdcrn.org/ucdc
	Vasculitis Clinical Research Consortium (VCRC) https://rdcrn.org/vcrc

Making a diagnosis can be challenging. Many patients experience a diagnostic odyssey of many months, even years, because of limited knowledge of the range of disease manifestations and of genotype–phenotype studies.

Often, there are no high-quality natural history data sets documenting how a disease affects patients' functioning and how it progresses over time.

Often, there are no adequate clinical or biological markers to support the clinical development of new therapeutics

The number of patients and clinicians caring for them is relatively small, leading to challenges in the design and implementation of clinical trials.

Resources for developing therapeutics are limited, making it critical to find frameworks for leveraging partnerships among patient groups, industry, academic investigators, and federal funding agencies. In addition, the global burden associated with rare diseases necessitates international coordination and collaboration.

The RDCRN is a partnership of multiple NIH Institutes and Centers, including NCATS; the National Cancer Institute; the National Heart, Lung, and Blood Institute; the National Institute of Allergy and Infectious Diseases; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the National Institute of Dental and Craniofacial Research; the National Institute of Diabetes and Digestive and Kidney Diseases; and the National Institute of Neurological Disorders and Stroke.

An important component of the RDCRN is the Coalition of Patient Advocacy Groups (CPAG). This collective representation of patient groups is affiliated with the consortia within the RDCRN. The mission of CPAG is to promote collaboration between rare disease advocacy organizations and

the RDCRN to facilitate better access to and earlier benefit from research conducted on rare diseases. As the patient advocacy arm of the RDCRN, CPAG members use their position to advance rare disease research and improve patient outcomes through the network. There are 151 active member patient organizations participating in the CPAG.

NCATS toolkit for patient-focused therapy development

https://rarediseases.info.nih.gov/toolkit

The toolkit was developed by ORDR in collaboration with patient groups and is intended to provide patient groups with the tools needed to help advance their research agenda. It provides a single site that draws accessible, practical, action-centered information from many groups across the Internet. The goal of the program is to ensure that patients are engaged as essential partners from beginning to end of research and development. This is a living site to which tools are continually being added for and by patient groups in concert with their academic, government, industry, and advocacy partners. An example of a tool within the kit is a description of how a new therapy for a disorder is developed (https://rarediseases.info.nih.gov/toolkit/getting-started).

Rare Diseases Registry Program (RaDaR)

https://rarediseases.info.nih.gov/radar

The Rare Diseases Registry Program (RaDaR) is a component of the toolkit that is under development and expected to be released in 2019. This program is not a registry, but a tool to develop a registry. Registries and natural history studies are the foundations of any drug development program, especially for rare diseases. They provide information about the rare disease, establish a link to patients, aid in the identification and development of outcome measures, contribute to the interpretability of clinical studies, and serve as a comparator group in trials. Information collected in a registry has to meet specific needs to be used in research.

The intent of RaDaR is to be a "registry in a box." It will connect researchers and patient groups to tools with training and instruction on key decisions, tasks, and challenges needed for creating and managing a registry. When complete, RaDaR will provide step-by-step directions for creating high-quality registries to support clinical trials and therapy development. It will provide templates and tools to incorporate best practices and standards for registries, along with strategies for maintaining, promoting, using, and expanding registries.

NIH resources beyond the ORDR

The Undiagnosed Diseases Network

https://undiagnosed.hms.harvard.edu

The Undiagnosed Diseases Network (UDN) was established to meet the needs of the hundreds of men, women, and children who face uncertainty when their providers are unable to discover the cause of their symptoms. The UDN provides information for patients and families affected by mysterious conditions and helps them learn more about common diseases. The goals of the network are the following:

- **improve the level of diagnosis and care** for patients with undiagnosed diseases, through development of common protocols designed by a large community of investigators.
- **facilitate research into the etiology of undiagnosed diseases** by collecting and sharing standardized, high-quality clinical and laboratory data, including genotyping, phenotyping, and documentation of environmental exposures.
- **create an integrated and collaborative community** across multiple clinical sites and among laboratory and clinical investigators prepared to investigate the pathophysiology of these new and rare diseases.

The program consists of clinical sites across the United States (Table 2) and supporting cores related to DNA sequencing, metabolomics, and model organisms. Because of the complex nature of the human body and the diseases being investigated, the UDN cannot accept all applicants into the study. However, all applications receive full review. To date, 2,939 applications have been submitted; 1,215 have been accepted into the program; 952 participants have been evaluated; and 249 have been given a diagnosis.

This program is funded by the NIH Common Fund (https://commonfund.nih.gov). Physicians and patients can refer themselves; however, a study recommendation letter is needed from a licensed primary health care provider. To be eligible for the UDN program, a participant must:

- have a condition that remains undiagnosed despite thorough evaluation by a provider
- have at least 1 objective finding
- agree to the storage and sharing of information and biomaterials in an identified fashion amongst the UDN centers, and in a deidentified fashion to research sites beyond the network (https://undiagnosed.hms.harvard.edu/apply).

Educational materials about genetics and genomics

https://www.genome.gov/education

Approximately 80% of rare diseases adhere to Mendelian laws of inheritance, and genomic science and technology are fast-moving. To continually educate the public and health-care professionals, the National Human Genome Research Institute has developed extensive materials and online genetic education resources, as well as online courses related to genomics and genetics.

TABLE 2. Clinical sites of the Undiagnosed Diseases Network (UDN)

Bethesda, Maryland (National Institutes of Health)
Boston, Massachusetts (Brigham and Women's Hospital, Boston Children's Hospital, and Massachusetts General Hospital)
Durham, North Carolina (Duke University and Columbia University)
Houston, Texas (Baylor College of Medicine)
Los Angeles, California (University of California, Los Angeles)
Miami, Florida (University of Miami School of Medicine)
Nashville, Tennessee (Vanderbilt University Medical Center)
Philadelphia, Pennsylvania (Children's Hospital of Philadelphia and University of Pennsylvania)
Salt Lake City, Utah (University of Utah)
Seattle, Washington (University of Washington School of Medicine and Seattle Children's Hospital)
Stanford, California (Stanford Medicine)
St. Louis, Missouri (Washington University in St. Louis)

Clinicaltrials.gov

https://clinicaltrials.gov/ct2/home

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world. This web-based resource, provided by the National Library of Medicine, provides patients and their family members, health care professionals, researchers, and the public witheasy access to information on clinical trials on a range of diseases and conditions. The site allows users to find and view clinical studies, learn more about clinical research, manage study records, and use site tools and data.

Research Portfolio Online Reporting Tools (RePORT)

https://report.nih.gov/index.aspx

The Research Portfolio Online Reporting Tool provides a central point of access to reports, data, and analyses of NIH research activities, including expenditures and results of NIH-supported research. A tool that is exceptionally valuable in finding information about specific rare diseases is the NIH RePORTER tool (https://projectreporter.nih.gov/reporter.cfm), which allows members of the public to search for research related to any disease or disorder. Using a simple, web-based query, information regarding ongoing research projects, publications, patents, and clinical studies can be accessed, along with data visualization and the NIH institute that is funding the research.

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NORD offers resources to benefit health care providers, patients, and caregivers

By Mary Dunkle

The National Organization for Rare Disorders (NORD) (https://rarediseases.org) has been providing resources for health care providers since 1983. As the primary nonprofit organization representing patients and families affected by rare diseases in the United States, NORD considers support for health care providers to be an essential part of its mission.

An informed and supported medical care team is one of the most important assets that patients and caregivers coping with a rare disease can have. As a result, NORD sees outreach to health care providers as one of the foundations of its services for patients and caregivers.

NORD resources for health care providers can be found within each of the 4 pillars of NORD programs and services: education, advocacy, patient and family services, and research.

1. Education

NORD's Rare Disease Database (https://rarediseases.org/for-patients-and-families/information-resources/rare-disease-information/) is a unique and widely cited resource that encompasses expert-reviewed, disease-specific reports providing overviews of approximately 1,200 rare diseases.[1] These reports include general descriptions, synonyms and subdivisions, signs and symptoms, causes, affected populations, related disorders, standard therapies, investigational therapies, resources (including disease-specific patient organizations), and references.

Of the approximately 1 million visits to NORD's website each month, 85% first go to the Rare Disease Database. Medical experts assist NORD in developing the reports and serve as reviewers to ensure accuracy. In many cases, the reviewers are the physicians for whom the diseases are named, or who serve as the world's leading experts on their topic. These medical experts volunteer their time and support because of the value of the database in educating other providers and students, as well as affected patients and caregivers.

NORD recently obtained permission from the National Institutes of Health (NIH) to display information from the NIH **Genetic and Rare Diseases Information Center (GARD)** (https://rarediseases.info.nih.gov/) alongside NORD's disease information on the NORD website. These combined resources cover all 7,000-plus known rare diseases.

In addition to the database of disease reports, NORD maintains a database of more than **1,000 patient organizations** (https://rarediseases.org/for-patients-and-families/connect-others/find-patient-organization/) that provide services for people affected by rare diseases. This database can be searched by disease or organization name. Many patient organizations in this database provide services helpful to providers, including information about genetic testing, centers of excellence, and consultation and telemedicine services.

NORD's **Rare Disease Video Library** (https://rarediseases.org/video-topic/medical-education/) includes short (approximately 4-minute) animated videos that provide overviews of rare diseases. These videos cover information similar to what is in the Rare Disease Database reports, but in an engaging format for providers as well as students, patients and caregivers. Categories include advocacy, medical education, patient and caregiver resources, and research and science. The videos are available on the NORD website.

The monthly **NORD eNews** digital newsletter reaches a broad audience, including many health care providers. It covers upcoming conferences and events, funding opportunities, advocacy initiatives, news from NIH and the Food and Drug Administration (FDA), including recently approved drugs for rare disorders, and other topics of interest to providers caring for patients who have rare diseases.

In 2019, NORD launched a **Continuing Medical Education (CME) program** that includes a mix of live events and online access-on-demand resources. NORD hosted its

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first CME event in 2017 and has been building on that experience to develop an expanded program to meet the needs of community physicians, RNs, PAs, and others serving as members of the health care team for patients affected by rare diseases.

The annual **NORD Rare Diseases and Orphan Products Breakthrough Summit** (www.nordsummit.org/) takes place each October in Washington, DC, and addresses cutting-edge topics related to rare diseases. The 2018 Summit was the largest to date, with more than 800 participants, including NIH and FDA staff, clinicians, researchers, patient organization leaders, and industry representatives. With a mix of general and breakout sessions, topics in 2019 include drug pricing, gene therapy, social determinants of health, and patient registries.

NORD also hosts conferences for patients, caregivers, students, and providers at locations around the United States. The 2020 Living Rare, Living Stronger Forum will be health in Cleveland, Ohio in May 2020.

NORD provides **educational resources for patients and caregivers** about current topics related to rare diseases that can be helpful to members of the care team. NORD hosts a webinar series for patients and caregivers on topics such as "Genetic Testing 101" and "How to Make Your Insurance Work for You." Some of NORD's webinars are also geared to providers, such as a recent session on "Emergency Protocols" and guidelines for responding to patients with rare diseases in emergency situations. Other recent topics include generic drugs and biosimilars; specialty pharmacies; self-advocacy/care coordination; and gene therapy.

In its **Patient/Caregiver Resource Center**, (https://rarediseases.org/for-patients-and-families/information-resources/patient-and-caregiver-resource-center/) NORD provides links to videos and free downloadable resources. A recently created video, "Patient/Caregiver Questions About Gene Therapy," has been widely viewed and circulated among patients, caregivers, and providers. Another video provides an overview of resources for patients whose rare disease is newly diagnosed.

For **Rare Disease Day** (www.rarediseaseday.us), observed globally on the last day of February each year, NORD provides special resources and news about events of interest to providers, patients, and caregivers.

2. Advocacy

Through its office in Washington, DC, and a network of state and local volunteers known as the **Rare Action Network®** (https://rareaction.org/), NORD leads advocacy on state and federal public policy issues that affect the rare disease community. These initiatives include advocating for:

- funding for medical research
- patient access to affordable health insurance
- coverage for medical foods and newborn screening
- patient protections around the use of step therapy and related practices.

Over the years, NORD has played a major role in advocacy to encourage development of diagnostics and treatments for people with rare diseases, to end discrimination against those with pre-existing medical conditions, and to support expanded funding for rare disease research at the NIH.

3. Patient and family services

Since 1987, NORD has provided assistance programs (https://rarediseases.org/for-patients-and-families/help-access-medications/patient-assistance-programs-2/) to help patients obtain life-saving and life-sustaining medical and other resources that they could not otherwise afford. These programs provide medication, financial assistance with insurance premiums and co-pays, diagnostic testing assistance, and travel assistance for clinical trials or consultation with disease specialists.

NORD's **Patient Services** staff provides white-glove service to patients and caregivers, working closely with physicians and physicians' office staff to ensure that patients have access to the medical care their providers believe is best for them.

NORD's Rare Disease Video Library, mentioned above, also includes patient and caregiver resources, including videos on pediatric movement disorders, gene therapy, newly diagnosed patients, and rare disease facts.

4. Research

NORD and Critical Path Institute launched the Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP) through funding from the FDA. The Platform is an integrated database and analytics hub that is designed to be used in building novel tools to accelerate drug development across rare diseases by pulling in patient-level data from diverse sources, including clinical trials, longitudinal observational studies, patient registries and real-world data (eg, electronic health records) across a multitude of rare diseases.

This year marks the 30th anniversary of NORD's **Research Grants Program** (https://rarediseases.org/for-clinicians-and-researchers/research-opportunities/research-grant-program/), which provides grants—typically $30,000 to $50,000, sometimes greater—for the study of rare diseases. The intent is to advance understanding of specific rare diseases and provide funding for studies that might lead to new diagnostic tools or treatments for patients.

In at least 2 cases, research that was initially funded by a NORD seed grant led to a product approved by the FDA:

• The so-called titanium rib, approved in 2004 through FDA's Humanitarian Use Device pathway, was developed by researchers at Santa Rosa Children's Hospital, San Antonio, Texas, for children affected with any of several rare disorders resulting in thoracic insufficiency syndrome (https://news.uthscsa.edu/titanium-rib-becomes-1st-new-fda-approved-spine-deformity-treatment-in-40-years/). This medical device has been credited with saving the lives of hundreds of children over the years.

• A drug for neurogenic orthostatic hypotension, approved by FDA in 2014, resulted from research that began with a grant from the NORD Research Grants Program (https://www.drugs.com/history/northera.html).

As the primary nonprofit organization representing patients and families affected by rare diseases in the United States, NORD considers support for health care providers to be an essential part of its mission.

NORD grants are competitive and international. The intent is to support the most promising research that has the greatest likelihood of improving the lives of patients. Each year, funding opportunities are posted on the NORD website, usually in late winter or early spring.

Letters of intent and final proposals are reviewed by the NORD Medical Advisory Committee, whose members are rare disease experts at teaching hospitals and medical schools across the United States. Members of this committee volunteer their time to make it possible for NORD to offer this program.

Grants are funded by donations from patients, family and friends of patients, patient organizations, foundations, and other sources. Anyone can make a donation to NORD for this purpose, and if no fund exists for a specific disease, a new one can be started. Typically, NORD has active funds for more than 200 rare diseases. When a fund reaches the required minimal amount, a Request for Proposals (https://rarediseases.org/for-clinicians-and-researchers/research-opportunities/requests-proposals/) will be generated.

Program guidelines and policies are available on the NORD website. When new requests for proposals are posted, NORD advertises them through its eNews, on its website, and through disease-specific patient organizations. The intent is to cast the broadest possible net to get the best possible proposals.

In recent years, NORD has also launched a **platform for patient registries and natural history studies** to advance understanding of rare diseases and support research. NORD works with disease-specific patient organizations to develop global registries that are tailored to the needs of each patient community.

NORD is currently hosting or developing 29 registries, working with organizations such as the Foundation for Prader-Willi Research, the OMSLife (Opsoclonus Myoclonus Syndrome) Foundation, the Fibrous Dysplasia Foundation, and the Platelet Disorder Support Association. These organizations are encouraged to interact with medical researchers and look for opportunities to collaborate for the benefit of the patient community.

Resources of NORD member organizations

In addition to NORD's own resources, those developed by its **nearly 300 member organizations** (https://rarediseases.org/for-patient-organizations/membership-profiles/member-list/) are also often featured on the NORD website or through its communications media.

For example, **CureSMA**, which represents families affected by spinal muscular atrophy (SMA), recently launched a new **SMArt Moves** microsite (http://events.curesma.org/site/PageNavigator/SmartMoves/SmartMoves.html) and campaign to help parents and providers recognize early signs and symptoms of SMA. Early identification of infants affected by SMA is extremely important because treatment is available that, begun early, can greatly improve quality of life and, for some patients, slow the advance of this progressive condition.

NORD helps its member organizations promote awareness of these types of resources to educate patients and providers about specific rare diseases.

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Efforts toward producing CNO/CRMO classification criteria show first results

By Jeff Evans

MADRID–Surveys and consensus techniques have been instrumental in identifying much needed candidate criteria toward the classification of chronic nonbacterial osteomyelitis (CNO), according to recent findings from international surveys of pediatric rheumatologists that were presented at the European Congress of Rheumatology.

Melissa Oliver, MD, a pediatric rheumatologist at Riley Hospital for Children, Indianapolis, and colleagues recently undertook the multiphase study[1] as part of an international collaborative effort led by the Childhood Arthritis and Rheumatology Research Alliance to establish consensus-based diagnostic and classification criteria for CNO, an autoinflammatory bone disease of unknown cause that primarily affects children and adolescents. CNO is also known as chronic recurrent multifocal osteomyelitis (CRMO). If this disease is not diagnosed and treated appropriately in a timely fashion, damage and long-term disability are possible. In the absence of widely accepted, consensus-driven criteria, treatment is based largely on expert opinion, Dr. Oliver explained in an interview.

"There is an urgent need for a new and more robust set of classification criteria for CRMO, based on large expert consensus and the analysis of a large sample of patients and controls," she said.

There are two proposed diagnostic criteria, the 2007 classification of nonbacterial osteitis[2] and the 2016 Bristol diagnostic criteria for CRMO,[3] but both are derived from single-center cohort studies and have not been validated, Dr. Oliver explained.

The list of candidate items that have come out of the study is moving clinicians a step closer toward the design of a practical patient data collection form that appropriately weighs each item included in the classification criteria.

The study employed anonymous survey and nominal group techniques with the goal of developing a set of classification criteria sensitive and specific enough to identify CRMO/CNO patients. In phase 1, a Delphi survey was administered among international rheumatologists to generate candidate criteria items. Phase 2 sought to reduce candidate criteria items through consensus processes via input from physicians managing CNO and patients or caregivers of children with CNO.


Dr. Melissa Oliver

Altogether, 259 of 865 pediatric rheumatologists (30%) completed an online questionnaire addressing features key to the classification of CNO, including 77 who practice in Europe (30%), 132 in North America (51%), and 50 on other continents (19%). Of these, 138 (53%) had greater than 10 years of clinical practice experience, and 108 (42%) had managed more than 10 CNO patients.

Initially, Dr. Oliver and colleagues identified 33 candidate criteria items that fell into six domains: clinical presentation, physical exam, laboratory findings, imaging findings, bone biopsy, and treatment response. The top eight weighted items that increased the likelihood of CNO/CRMO were exclusion of malignancy by bone biopsy; multifocal bone lesions; presence of bone pain, swelling, and/or warmth; signs of fibrosis and/or inflammation on bone biopsy; typical location of CNO/CRMO lesion, such as the clavicle, metaphysis of long bones, the mandible, and vertebrae; presence of CNO/CRMO–related comor-

Dr. Oliver had no disclosures to report, but several coauthors reported financial ties to industry.

Access a video interview with Dr. Oliver at: https://www.mdedge.com/rheumatology/article/203338/pediatrics/efforts-toward-producing-cno/crmo-classification-criteria.

bidities; normal C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR); and typical MRI findings of CNO/CRMO.

By phase 2, candidate items, which were presented to 39 rheumatologists and 7 parents, were refined or eliminated using item-reduction techniques. A second survey was issued to 77 of 82 members of a work group so that the remaining items could be ranked by their power of distinguishing CNO from conditions that merely mimicked the disease. The greatest mean discriminatory scores were identified with multifocal lesions (ruling out malignancy and infection) and typical location on imaging. Normal C-reactive protein and/or an erythrocyte sedimentation rate more than three times the upper limit of normal had the greatest negative mean discriminatory scores.

The next steps will be to form an expert panel who will use 1000minds software to determine the final criteria and identify a threshold for disease. The investigators hope to build a large multinational case repository of at least 500 patients with CNO/CRMO and 500 patients with mimicking conditions from which to derive a development cohort and an external validation cohort. So far, 10 sites, including 4 in Europe, have obtained approval from an institutional review board. The group has also submitted a proposal for classification criteria to the American College of Rheumatology and the European League Against Rheumatism, Dr. Oliver said.

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EULAR overhauls large-vessel vasculitis management recommendations

By Sara Freeman

MADRID – Ten years after they were last published, an expert task force of the European League Against Rheumatism has revamped guidance on how to manage patients with large-vessel vasculitis.

The "substantial revision" of the 2009 recommendations[1] was based on two new systematic literature reviews, focusing on general management and treatments, respectively.

Sara Freeman/MDedge News

Dr. Bernhard Hellmich

These were performed "without limits," task force member Bernhard Hellmich, MD, said at the European Congress of Rheumatology.

The reason for starting from scratch was the amount of "high-impact" data that have been published in the intervening years, including the results of several randomized clinical trials, and also the fact that EULAR had released guidance on imaging in large-vessel vasculitis (LVV) in 2018.[2]

The recommendations, which are published in Annals of the Rheumatic Diseases,[3] now include three overarching principles, said Dr. Hellmich, who is the chief physician of the Clinic for Internal Medicine, Rheumatology and Immunology at Medius Kliniken in Kirchheim unter Teck, Germany.

The first overarching principle says that patients with LVV "should be offered best care which must be based on a shared decision between the patient and the rheumatologist, considering, of course, efficacy, safety, and costs," Dr. Hellmich stated.

"Second, patients should have access to education focusing on the impact of LVV, its key warning symptoms, and its treatment, including treatment-related complications," he added.

"Third, patients with large-vessel vasculitis should be screened for treatment-related comorbidities and also cardiovascular comorbidities, and we recommend prophylaxis and lifestyle advice to reduce cardiovascular risks and treatment-related complications."

Another key change is that there are 10 rather than 15 recommendations. These include new recommendations on early diagnosis, management, and the treatment of relapse.

The first two recommendations highlight the need for specialist referral and multidisciplinary management of giant cell arteritis (GCA) and Takayasu arteritis (TAK).

Recommendation 3 offers advice on confirming a diagnosis of LVV by imaging or histology. "If you decide to do it by imaging, you should follow the EULAR recommendations on imaging, that say that ultrasound or MRI should be used for temporal or other cranial arteries, or ultrasound, PET-CT, or MRI for the aorta and extracranial arteries," Dr. Hellmich said. "It's important to confirm the diagnosis," he added, cautioning that the speed was important in testing as these imaging tests lose their sensitivity the longer patients have been treated with glucocorticoids or other drugs.

Dr. Hellmich disclosed receiving honoraria for lectures and advisory services from multiple pharmaceutical companies, including AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Chugai, Merck Sharpe & Dohme, Pfizer, Novartis, and Roche.

Recommendation 4 covers the use of high-dose glucocorticoid therapy when there is active disease. This recommendation also includes advice on how to taper glucocorticoid doses: first to a target dose of 15-20 mg/day within 2-3 months and then how to get the dose down within the year to 5 mg/day or less for GCA and to 10 mg/day or less for TAK.

There has been major revision of the recommendation for adjunctive therapy, Dr. Hellmich observed, with recommendation 5 advising the use of tocilizumab in selected patients with GCA—those with refractory or relapsing disease or who have an increased risk of glucocorticoid-induced adverse effects or complications; methotrexate may be used as an alternative.

Recommendation 6 states that all patients with TAK should be given nonbiologic disease-modifying agents in combination with glucocorticoids. In patients where this treatment fails, tocilizumab and tumor necrosis factor (TNF) inhibitors may be considered.

Recommendation 7 addresses advice on treatment of major and minor relapses. "In case of a major relapse, which we defined as signs or symptoms of ischemia or progressive vascular inflammation, we recommend a reinstitution or dose escalation of steroid therapy, as recommended for new-onset disease," Dr. Hellmich said. For minor relapses, the task force advised increasing glucocorticoid doses to the last effective dose and considering a change to adjunctive therapy.

Guidance on the use of antiplatelet agents has undergone major revision. Recommendation 8 states that antiplatelet agents should not be used routinely unless there is another reason to do so, such as in patients with cardiovascular disease or vascular ischemic complications. "This is a change from the 2009 recommendations where the use of aspirin was recommended for all GCA patients, but that recommendation in the past was based on one observational study, and the studies later on did not confirm this observation," Dr. Hellmich said.

The ninth recommendation concerns surgery. "Elective endovascular interventions or reconstructive surgery should be performed in phases of stable remission. However, arterial vessel dissection or critical vascular ischemia requires urgent referral to a vascular team for urgent work-up."

The last and tenth recommendation notes that regular follow-up and monitoring of disease activity in patients with LVV is needed, and that this should be mainly based on patients' symptoms, clinical findings, erythrocyte sedimentation rate, and C-reactive protein levels. Dr. Hellmich again said to refer to the separate EULAR imaging guidelines as there was "insufficient evidence to recommend the routine use of imaging."

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Four distinct IgG4-related disease groups described in study

By Andrew D. Bowser

IgG4-related disease can be grouped into four distinct clusters based on the distribution of organs involved, according to researchers who analyzed a large, multicenter cohort of patients with this heterogeneous, autoimmune-mediated condition.

The four groups also varied by age, race, sex, time to diagnosis, and concentration of serum IgG4, according to the investigators, led by Zachary S. Wallace, MD, of the division of rheumatology, allergy, and immunology at Massachusetts General Hospital and Harvard Medical School, both in Boston.

Dr. Zachary S. Wallace

"These phenotypes may be used by clinicians to improve recognition of IgG4-related disease," Dr. Wallace and his coauthors wrote in a report on the study that appears in the Annals of the Rheumatic Diseases.[1]

First described in a Japanese population, IgG4-related disease has been subsequently seen in all racial and ethnic groups, according to the researchers. It is associated with organ failure and can affect nearly any organ or anatomic site, most notably the lungs, kidneys, lymph nodes, salivary glands, pancreatobiliary structures, and retroperitoneum.

In the present study, Dr. Wallace and his coinvestigators used a novel cluster analysis method, called latent class analysis, to categorize 765 cases of IgG4-related disease submitted by 52 investigators from 17 countries. The investigators included 493 of those cases in a primary study population, and the remaining 272 in a smaller cohort used to replicate the results.

In the larger, primary study cohort, about 65% of cases were male, 58% were non-Asian and 40% were white, and the mean age at diagnosis was 59.5 years. The replication cohort had similar characteristics, according to the investigators.

The clustering analysis revealed four distinct subgroups, characterized by pancreato-hepatobiliary, accounting for 31% of cases; retroperitoneal fibrosis and/or aortitis in 24%; disease generally limited to head and neck structures in 24%; and head and neck disease consistent with Mikulicz syndrome plus systemic involvement in 22%.

The highest IgG4 concentrations were seen in the group of patients with Mikulicz syndrome and systemic involvement, according to Dr. Wallace and his coauthors. The serum concentration was 1,170 mg/dL in that group, compared with 445 mg/dL in the group of patients with head and neck-limited disease, 316 mg/dL in the pancreato-hepatobiliary group, and just 178 mg/dL in the retroperitoneal fibrosis/aorta group.

Female and Asian patients were overrepresented in the group characterized by head and neck involvement, investigators also found. Moreover, that group had a significantly lower mean age at diagnosis than did the other groups.

Those variations suggested differences in genetic or environmental risk factors between clusters, according to the investigators.

"Given the similar distribution of subspecialists among investigators in this study practicing in Asian and non-Asian countries, the observed differences are unlikely to be the result of detection or selection biases," they said in their report.

The findings of this study help to inform subsequent investigations intended to evaluate those factors in more detail, they said.

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Dr. Wallace and his coauthors reported no conflicts of interest related to their work, which was previously presented at the American College of Rheumatology annual meeting.

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Madilyn (left) has been battling a rare breathing disorder since birth called Congenital Central Hypoventilation Syndrome (CCHS), or Ondine's Curse.

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