The Search is On
For Treatment Drugs and a Vaccine

Population Health  Telehealth, Opportunity Calling
Oncology  Treatment Amid COVID-19
Formulary/Pharmacy Development  Civica’s Martin VanTrieste
Technology  Pain Control Devices
As part of a combination regimen, **provide your members with the only FDA-approved treatment for refractory MAC lung disease**

**INDICATION**

LIMITED POPULATION: **ARIKAYCE** is indicated in adults, who have limited or no alternative treatment options, for the treatment of Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients.

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

**Limitation of Use:** ARIKAYCE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

**IMPORTANT SAFETY INFORMATION**

**WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS**

ARIKAYCE has been associated with an increased risk of respiratory adverse reactions, including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.

**Hypersensitivity Pneumonitis** has been reported with the use of ARIKAYCE in the clinical trials. Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis, interstitial lung disease, allergic reaction to ARIKAYCE) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (3.3%) compared to patients treated with a background regimen alone (0.3%). Most patients with hypersensitivity pneumonitis discontinued treatment with ARIKAYCE and received treatment with corticosteroids. If hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate.

**Hemoptysis** has been reported with the use of ARIKAYCE in the clinical trials. Hemoptysis was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (17.9%) compared to patients treated with a background regimen alone (12.5%). If hemoptysis occurs, manage patients as medically appropriate.

**Bronchospasm** has been reported with the use of ARIKAYCE in the clinical trials. Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (28.7%) compared to patients treated with a background regimen alone (10.7%). If bronchospasm occurs during the use of ARIKAYCE, treat patients as medically appropriate.

ARIKAYCE, through its proprietary liposomal technology **PULMOVANCE**, delivers inhaled liposomal amikacin directly to the lungs where the infection resides, and has been shown to penetrate biofilms and macrophages.

ARIKAYCE and the Lamira™ Nebulizer System were approved as a drug-device combination and are both processed under pharmacy benefits.

– The Lamira Nebulizer System is shipped to patients concurrently with their first dose at no additional cost to the patient or health plan.

**In the United States, MAC is responsible for causing approximately 80% of pulmonary NTM infections.**

**An animal study analyzed the in vivo uptake of various formulations of amikacin, including ARIKAYCE, IV amikacin, and inhaled IV amikacin.** Five to eight times more amikacin was delivered to pulmonary macrophages treated with ARIKAYCE compared with inhaled IV amikacin. The clinical relevance of this is unknown.
A clinical trial investigated the safety and efficacy of ARIKAYCE + background regimen vs background regimen alone. Efficacy was assessed through a primary endpoint that was based on culture conversion (3 consecutive monthly MAC-negative sputum cultures) by Month 6. ARIKAYCE + background regimen achieved a 3-fold increase in the percentage of patients who experienced culture conversion by Month 6 (29.0% [65/224] vs 8.9% [10/112]) (P<0.0001) compared with the background regimen alone.

- The additional endpoints of 6-minute walk test distance and St George’s Respiratory Questionnaire did not demonstrate clinical benefit by Month 6.

Exacerbations of underlying pulmonary disease has been reported with the use of ARIKAYCE in the clinical trials. Exacerbations of underlying pulmonary disease (reported as chronic obstructive pulmonary disease [COPD], infective exacerbation of COPD, infective exacerbation of bronchiectasis) have been reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (14.8%) compared to patients treated with background regimen alone (9.8%). If exacerbations of underlying pulmonary disease occur during the use of ARIKAYCE, treat patients as medically appropriate.

Anaphylaxis and Hypersensitivity Reactions: Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. Signs and symptoms include acute onset of skin and mucosal tissue hypersensitivity reactions (hives, itching, flushing, swollen lips/tongue/uvala), respiratory difficulty (shortness of breath, wheezing, stridor, cough), gastrointestinal symptoms (nausea, vomiting, diarrhea, crampy abdominal pain), and cardiovascular signs and symptoms of anaphylaxis (tachycardia, low blood pressure, syncope, incontinence, dizziness). Before therapy with ARIKAYCE is instituted, evaluate for previous hypersensitivity reactions to aminoglycosides. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures.

Ototoxicity has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported with a higher frequency in patients treated with ARIKAYCE plus background regimen (17%) compared to patients treated with background regimen alone (9.8%). This was primarily driven by tinnitus (7.6% in ARIKAYCE plus background regimen vs 0.9% in the background regimen alone arm) and dizziness (6.3% in ARIKAYCE plus background regimen vs 2.7% in the background regimen alone arm). Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage patients as medically appropriate, including potentially discontinuing ARIKAYCE.

Nephrotoxicity was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than background regimen alone. Nephrotoxicity has been associated with the aminoglycosides. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE.

Neuromuscular Blockade: Patients with neuromuscular disorders were not enrolled in ARIKAYCE clinical trials. Patients with known or suspected neuromuscular disorders, such as myasthenia gravis, should be closely monitored since aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions.

Embryo-Fetal Toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero. Patients who use ARIKAYCE during pregnancy, or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus.

Contraindications: ARIKAYCE is contraindicated in patients with known hypersensitivity to any aminoglycoside.

Most Common Adverse Reactions: The most common adverse reactions in Trial 1 at an incidence ≥5% for patients using ARIKAYCE plus background regimen compared to patients treated with background regimen alone were dysphonia (47% vs 1%), cough (39% vs 17%), bronchospasm (29% vs 11%), hemoptysis (18% vs 13%), ototoxicity (17% vs 10%), upper airway irritation (17% vs 2%), musculoskeletal pain (17% vs 8%), fatigue and asthenia (16% vs 10%), exacerbation of underlying pulmonary disease (15% vs 10%), diaphrea (13% vs 5%), nausea (12% vs 4%), pneumonia (10% vs 8%), headache (10% vs 5%), pyrexia (7% vs 5%), vomiting (7% vs 4%), rash (6% vs 2%), decreased weight (6% vs 1%), chest discomfort (5% vs 3%).

Drug Interactions: Avoid concomitant use of ARIKAYCE with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity. Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue. Avoid concomitant use of ARIKAYCE with ethacrynic acid, furosemide, urea, or intravenous mannitol.

Overdosage: Adverse reactions specifically associated with overdose of ARIKAYCE have not been identified. Acute toxicity should be treated with immediate withdrawal of ARIKAYCE, and baseline tests of renal function should be undertaken. Hemodialysis may be helpful in removing amikacin from the body. In all cases of suspected overdose, physicians should contact the Regional Poison Control Center for information about effective treatment.


Please see the Brief Summary on the following pages.
ARIKAYCE® (amikacin liposome inhalation suspension)

**WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS**

ARIKAYCE has been associated with an increased risk of respiratory adverse reactions including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases (see Warnings and Precautions (5.1, 2.3, 5.3, 5.4)).

1 INDICATIONS AND USAGE

LIMITED POPULATION: ARIKAYCE® is indicated in adults, who have limited or no alternative treatment options, for the treatment of Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients. This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative sputum cultures) by Month 6. Clinical benefit has not yet been established (see Clinical Studies (14)). Continued approval for this indication may be contingent upon verification and demonstration of clinical benefit in confirmatory trials.

Ariminum Use: ARIKAYCE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions: ARIKAYCE is for oral inhalation use only. Administer by nebulization only with the Luminair Nebulizer System. Refer to the Instructions for Use for full administration information on use of ARIKAYCE with the Luminair Nebulizer System.

Instruct patients using a bronchodilator (‘reliever’) to first use the bronchodilator following the bronchodilator instruction before inhaled medication use information before using ARIKAYCE. Pre-treatment with short-acting beta-2 agonists should be considered for patients with known hyperreactive airway disease, chronic obstructive pulmonary disease, asthma, or bronchospasm (see Warnings and Precautions (5.3)).

2.2 Recommended Dosing: The recommended dosedage of ARIKAYCE in adults is once daily inhalation of the contents of one 580 mg/mL ARIKAYCE vial (590 mg of amikacin) using the Luminair Nebulizer System. Administer ARIKAYCE with the Luminair Nebulizer System only. ARIKAYCE should be at room temperature before use. Prior to opening, shake the ARIKAYCE vial well for at least 10 to 15 seconds until the contents appear uniform and well mixed. The ARIKAYCE vial is opened by flipping up the plastic top of the vial then pushing downward to loosen the metal ring. The metal ring and the rubber stopper should be removed carefully. The contents of the ARIKAYCE vial can then be poured into the medication reservoir of the nebulizer/absorber.

If a daily dose of ARIKAYCE is missed, administer the next dose the next day. DO NOT double the dose to make up for the missed dose.

4 CONTRAINDICATIONS

ARIKAYCE is contraindicated in patients with a known hypersensitivity to any aminoglycoside.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Pneumonitis: Hypersensitivity pneumonitis has been reported with the use of ARIKAYCE in the clinical trials. Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis interstitial lung disease, allergic reaction to ARIKAYCE) was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (3.1%) compared to patients treated with a background regimen alone (0.9%). Most patients with hypersensitivity pneumonitis discontinued treatment with ARIKAYCE and received treatment with corticosteroids (see Adverse Reactions (6.1)). If hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage the patient as medically appropriate.

5.2 Hemoptysis: Hemoptysis has been reported with the use of ARIKAYCE in the clinical trials. Hemoptysis was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (17.9%) compared to patients treated with a background regimen alone (12.5%) (see Adverse Reactions (6.1)). If hemoptysis occurs, manage the patients as medically appropriate.

5.3 Bronchospasm: Bronchospasm has been reported with the use of ARIKAYCE in the clinical trials. Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing) was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (28.7%) compared to patients treated with a background regimen alone (10.7%) (see Adverse Reactions (6.1)). If bronchospasm occurs during the use of ARIKAYCE treat the patients as medically appropriate.

5.4 Exacerbation of Underlying Pulmonary Disease: Exacerbations of underlying pulmonary disease has been reported with the use of ARIKAYCE in the clinical trials. Exacerbations of underlying pulmonary disease (reported as chronic obstructive pulmonary disease, intelective exacerbation of chronic obstructive pulmonary disease, intective exacerbation of bronchectasis) have been reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (14.8%) compared to patients treated with a background regimen alone (9.8%). (see Adverse Reactions (6.1)). If exacerbations of underlying pulmonary disease occurs during the use of ARIKAYCE treat the patients as medically appropriate.

5.5 Anaphylaxis and Hypersensitivity Reactions: Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. Signs and symptoms include angioedema, asthma, bronchospasm, cough, erythema multiforme, flushing, rash, respiratory distress (shortness of breath, wheezing, stridor, cough), gastrointestinal reactions (nausea, vomiting, diarrhea, crampy abdominal pain), and cardiovascular signs and symptoms of angina, hypertension, hypotension, palpitations, nervousness, syncope, tachycardia, vasodepression, which need immediate medical evaluation for potential hypersensitivity reactions to aminoglycosides. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures.

5.6 Ototoxicity: Ototoxicity has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (reported as deafness, hypoacusis, tinnitus, vertigo) was reported at a higher frequency in patients treated with ARIKAYCE plus a background regimen (17%) compared to patients treated with background regimen alone (6.8%). This was primarily driven by tinnitus (7% in ARIKAYCE plus background regimen vs 0% in the background regimen alone arm) and dizziness (0.3% in ARIKAYCE plus background regimen vs 2.7% in the background regimen alone arm) (see Adverse Reactions (6.1)). Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage the patient as medically appropriate, including potentially discontinuing ARIKAYCE.

5.7 Nephrotoxicity: Nephrotocicity was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than the background regimen alone (see Adverse Reactions (6.1)). Nephrotocicity has been associated with the aminoglycosides. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE.

5.8 Neuromuscular Blockade: Patients with neuromuscular disorders were not enrolled in ARIKAYCE clinical trials. Patients with known or suspected neuromuscular disorders, such as myasthenia gravis, should be closely monitored since aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuro muscular junctions.

5.9 Embryo-Fetal Toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in perinatal patients exposed in utero. Patients who use ARIKAYCE during pregnancy or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus (see Use in Specific Populations (8.1)).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in greater detail in other sections of the label:

• Hypersensitivity Pneumonitis [see Boxed Warning and Warnings and Precautions (5.1)].

• Hemoptysis [see Boxed Warning and Warnings and Precautions (5.2)].

• Bronchospasm [see Boxed Warning and Warnings and Precautions (5.3)].

• Exacerbation of Underlying Pulmonary Disease [see Boxed Warning and Warnings and Precautions (5.4)].

• Anaphylaxis and Hypersensitivity Reactions [see Warnings and Precautions (5.5)].

• Ototoxicity [see Warnings and Precautions (5.6)].

• Nephrotoxicity [see Warnings and Precautions (5.7)].

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.

6.2 Overall Adverse Reactions: ARIKAYCE was well tolerated in these clinical trials. Most adverse reactions were mild to moderate in intensity. The overall incidence of adverse reactions was similar between the ARIKAYCE plus background regimen arm and the placebo plus background regimen arm. In the three NTM studies, there was a higher incidence of premature discontinuation of ARIKAYCE. In Trial 1, 33.5% discontinued ARIKAYCE prematurely due to adverse reactions (17.4%) and withdrawal by subject (9.4%). In the comparator arm 8% of subjects discontinued their background regimen, with 0.9% due to adverse reactions and 5.4% due to withdrawal by subject. In Trial 2 the single-arm extension of Trial 1, 20.3% of patients starting on ARIKAYCE discontinued prematurely with 14.9% discontinuing due to adverse reactions. In Trial 3, all 9 (20.5%) premature discontinuations occurred in the ARIKAYCE plus background regimen-treated patients and there were no premature discontinuations in the placebo plus background regimen arm.

In the two randomized trials (Trial 1 and Trial 3), there were more serious adverse reactions (SARs) reported in the ARIKAYCE-treated arm as compared to the respective control arm. In Trial 1, 20.2% of patients treated with ARIKAYCE plus background regimen reported SARs as compared to 16.1% of patients treated with background regimen alone. In addition, in Trial 1 12 to 1 randomization, ARIKAYCE plus background regimen versus background regimen alone, there were 62 hospitalizations in 41 patients (18.4%) treated with ARIKAYCE plus background regimen compared to 23 hospitalizations in 15 patients (13.4%) treated with background regimen alone. The most common SARs and reasons for hospitalization in the ARIKAYCE plus background regimen arm were related to exacerbation of underlying pulmonary disease and lower respiratory tract infections, such as pneumonia.

In Trial 3, 18.2% of patients treated with ARIKAYCE plus background regimen reported SARs compared to 6.9% of patients treated with background regimen plus inhaled placebo.

7 Common Adverse Reactions

The incidence of adverse reactions in Trial 1 are displayed in Table 1. Only those adverse reactions with a rate of at least 5% in the ARIKAYCE plus background regimen group and greater than the background regimen alone group, are shown.

(continued on next page)
Animal reproductive toxicology studies have not been conducted with inhaled amikacin. Subcutaneous administration of amikacin to pregnant rats (up to 100 mg/kg/day) and mice (up to 400 mg/kg/day) during organogenesis was not associated with total malformations. Otopathy was not adequately evaluated in offspring in animal studies. The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
No animal reproductive toxicology studies have been conducted with ARIKAYCE or non-liposomal amikacin administered by inhalation.

Arikayce was subcutaneously administered to pregnant rats (Gestation Days 6-14) and mice (Gestation Days 7-13) at doses of 25, 100, or 400 mg/kg to assess developmental toxicity. These doses did not cause fetal visceral or skeletal malformations in mice. The high dose was excessively maternally toxic in rats (neurotoxicity and mortality were observed), precluding the evaluation of offspring at this dose. Fetal malformations were not observed at the low or mid dose in rats. Postnatal development of the rats and mice exposed to these doses of amikacin in utero did not differ significantly from control.

Otopathy was not adequately evaluated in offspring in animal development toxicology studies.

8.2 Lactation
Risk Summary
There is no information regarding the presence of ARIKAYCE in human milk, the effects on the breastfed infant, or the effects on milk production after the administration of ARIKAYCE. Given the low systemic exposure to amikacin following administration of ARIKAYCE, breast milk levels are not expected to be clinically meaningful.

8.5 Genicidal Use:
In the NTM clinical trials, of the total number of patients receiving ARIKAYCE, 196 (50.5%) were ≥65 years and 55 (14.2%) were ≥75 years. No overall differences in safety and effectiveness were observed between elderly subjects and younger subjects. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function (see Warnings and Precautions (8.7)).

8.6 Hepatic Impairment: ARIKAYCE has not been studied in patients with hepatic impairment. No dose adjustments based on hepatic impairment are required since amikacin is not hepatically metabolized (see Clinical Pharmacology (12.3)).

8.7 Renal Impairment: ARIKAYCE has not been studied in patients with renal impairment. Given the low systemic exposure to amikacin following administration of ARIKAYCE, clinically relevant accumulation of amikacin is unlikely to occur in patients with renal impairment. However, renal function should be monitored in patients with known or suspected renal impairment, including elderly patients with potential age-related decreases in renal function (see Warnings and Precautions (8.7), use in Specific Populations (8.5)).

10 OVERDOSAGE
Adverse reactions specifically associated with overdose of ARIKAYCE have not been identified. Acute toxicity should be treated with immediate withdrawal of ARIKAYCE, and baseline tests of renal function should be undertaken.

Hemodialysis may be helpful in removing amikacin from the body.

In all cases of suspected overdosage, physicians should contact the Regional Poison Control Center for information about effective treatment. In the case of any overdose, the possibility of drug interactions with alterations in drug disposition should be considered.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year inhalation carcinogenicity study, rats were exposed to ARIKAYCE for 15-25, 50-70, or 155-170 minutes per day for 96-104 weeks. These provided approximate inhalation doses of 5, 15, and 45 mg/kg/day. SQuaMous cell carcinoma was observed in the lungs of 1 of 120 rats administered the highest dose tested. Maximum serum AUC levels of amikacin in the rats at study were approximately 1.3, 2.8, and 6.7 mcg/mL at the low, mid, and high doses, respectively, compared with 23.5 mcg/mL at 5 mL/kg/day in humans. The squamous cell carcinomas may be the result of a high lung burden of particulates from ARIKAYCE in the rat lung. The relevance of the lung tumors findings with regards to humans receiving ARIKAYCE is unknown. No evidence of mutagenicity or genotoxicity was observed in a battery of in vitro and in vivo genotoxicity studies with a liposome-encapsulated amikacin formulation similar to ARIKAYCE (in vitro microbial mutagenesis test, in vivo mouse lymphoma mutation assay, in vivo micronucleus aberration test, and in vivo micronucleus study in rats).

No fertility studies were conducted with ARIKAYCE. Intraperitoneal administration of amikacin to male and female rats at doses up to 200 mg/kg/day prior to mating through Day 7 of pregnancy was not associated with impairment of fertility or adverse effects on early embryonic development.

13.2 Animal Toxicology and/or Pharmacology: To provide information about chronic dosing of ARIKAYCE to another animal species, a 9-month inhalation toxicity study was conducted in dogs. Foamy alveolar macrophages associated with clearance of the inhaled product were present at dose–related incidence and severity, but they were not associated with inflammation, tissue hyperplasia, or the presence of pneumoconiosis or neoplastic changes. Dogs were exposed to ARIKAYCE for up to 90 minutes per day, providing inhaled amikacin doses of approximately 5, 10, and 30 mg/kg/day.

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Table 1: Adverse Reactions in Patients who Achieved Sputum Culture Conversion 90 Days After Initiation of ARIKAYCE Therapy

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ARIKAYCE plus Background Regimen (n=223)</th>
<th>ARIKAYCE Alone (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough*</td>
<td>185 (41)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>67 (19)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Fatigue and asthenia</td>
<td>100 (36)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Oral fungal infection</td>
<td>9 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>58 (26)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25 (11)</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>10 (4)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>15 (7)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>15 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>16 (7)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

*Includes sputum culture conversion 90 days after ARIKAYCE treatment was initiated.

Table 2: Selected Adverse Reactions in <5% of ARIKAYCE-treated MAC Patients and More Frequent than Background Regimen Alone in Trial 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ARIKAYCE plus Background Regimen (n=223)</th>
<th>ARIKAYCE Alone (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphonia</td>
<td>10 (4.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Oral fungal infection</td>
<td>9 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8 (3.6)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis*</td>
<td>8 (3.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>7 (3.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>6 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6 (2.7)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Neuro muscular disorders</td>
<td>5 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>5 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumothorax*</td>
<td>5 (2.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Exercise tolerance decreased</td>
<td>11 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>3 (1.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Includes oral candidiasis and oral fungal infection.

7.1 Drugs with Neurotoxic, Nephrotoxic, or Otoxic Potential: Avoid concomitant use of ARIKAYCE with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity.

7.2 Ethylmethyl Acid, Furosemide, Urea, or Mannitol: Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue. Avoid concomitant use of ARIKAYCE with ethylmethyl acid, furosemide, urea, or intravenous mannitol.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no data on ARIKAYCE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Although systemic absorption of amikacin following oral inhalation is expected to be low (see Clinical Pharmacology (12.3)), systemic exposure to aminoglycoside antibacterial drugs, including ARIKAYCE, may be associated with total, irreversible bilateral congenital deafness when administered to pregnant women (see Warnings and Precautions (5.8)).

Advising pregnant women of the potential risk to a fetus.
A Silver Lining and Reasons To Be Hopeful

Over a million cases in the United States. About 60,000 deaths. The economy and much of life on hold.

The COVID-19 outbreak was still very much with us as I write this. And Managed Healthcare Executive® continues to report on how the disease is affecting American healthcare, in this, an unprecedented present but also with an eye toward an uncharted future.

In this issue we take a look at the terrible toll the disease has taken on the country’s nursing homes. An estimated 10,000 deaths have occurred in long-term care facilities, including staff and residents. As we report, nursing home officials say they need access to testing to detect cases and prevent serious illness and death. More needs to be done to blunt the effect of COVID-19 on one of our most vulnerable populations.

We also look at how COVID-19 is affecting cancer care. Patients, their families and their oncologists have had to balance the risk of delaying treatment and — depending on the treatment and the cancer — what may be a greater risk of infection. Oncology, never easy, got harder.

The use of telehealth has surged, partly because CMS loosened some needlessly restrictive rules. Our coverage focuses on the implications for population health. Sewing silver linings can be the smallest of consolations. But if the long-overdue incorporation of telehealth into American healthcare is a consequence of COVID-19, we can point to some good that has happened.

And speaking of good. There was, in fact, good news as April came to a close. As our cover stories on COVID-19 treatments and vaccines report, clinical trials of remdesivir, a treatment drug for the disease, are showing positive results. Anthony Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases, said the interim findings of remdesivir trial sponsored by his institute is a proof of concept that “a drug can block this virus.” Meanwhile, scores of vaccine candidates are under investigation. Decades of scientific achievements in recombinant DNA and other technologies are paying off. Some groups have come up with ingenious ways to test vaccines that may give us a safe and effective vaccine in record time.

There’s hope — and good reasons for it.

Mike Hennessy Sr.
Chairman and Founder
of MJH Life Sciences
### Mission

Managed Healthcare Executive® provides healthcare executives at health plans and provider organizations with analysis, insights, and strategies to pursue value-driven solutions.

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As a physician-led insurer, ISMIE understands the immense challenges healthcare professionals face every day – especially in recent weeks. Our Wellness Center includes a wealth of resources to help your physicians navigate personal and professional challenges, including private consultations. Visit it at ismie.com/wellness.

For other COVID-19 resources, visit ismie.com/covid-19.
At the March 16 daily press briefing by the White House Coronavirus Task Force, Anthony Fauci, M.D., seemed excited in his buttoned-down way. This was before Fauci, director of the National Institute of Allergy and Infectious Diseases, became a household name; before millions of Americans grew familiar with his gravelly, Brooklyn-accented voice and carefully qualified statements; and well before Brad Pitt played him on “Saturday Night Live.” Fauci told reporters and the TV audience that earlier that day, the first volunteer for a phase 1 trial of a candidate vaccine against COVID-19 had been injected. The volunteer was later identified as Jennifer Haller, an operations manager at a tech company in Seattle.

“You might recall when we first got started that I said it would be two to three months, and...
if we did that, that would be the fastest we had ever gone from obtaining the sequence (of a virus) to being to a phase 1 trial,” Fauci said, with President Donald Trump standing to his left at a pre-social-distancing distance. “This has now been 65 days, which I believe is the record.”

Now it seems like that record was for the first 100 meters of what may turn into a full, 26.2-mile marathon. Fauci has since said repeatedly in interviews that it will probably be a year or more before a COVID-19 vaccine is not only tested but also deemed both safe and effective. “It isn’t just the timetable. It has to be safe and it has to be effective,” Fauci said in an interview with a Canadian TV network.

As Fauci tapped the brakes, some vaccine developers raced ahead, raising hopes that more records would be set. At the end of April, CanSino Biologics, a Chinese company, said it was poised to start a phase 2 trial of its vaccine and would enroll 500 people in Wuhan, China, where the pandemic started. Vaccine developers at Oxford University in England were going at an unheard-of speed. They collapsed the normally sequenced phase 1 safety and phase 2 efficacy trials into a single trial designed to enroll more than 500 volunteers. And as we went to press, they were gearing up for a phase 2/3 trial that would include 5,000 volunteers.

An inviting target
By some accounts, there are 86 COVID-19 vaccine candidates; by others, 115. In those two tallies, and in every other reasonable count, the vast majority of the COVID-19 vaccine candidates are in a preclinical stage and not ready to be tested in people. “There will be fierce attrition,” wrote Derek Lowe in his widely read blog for Science Translational Medicine, “and only a few (low single digits) will make it deep into the process.” As COVID-19 vaccine kicked into gear, Regulatory Focus, the online publication of the Regulatory Affairs Professionals Society, started a helpful COVID-19 vaccine tracker to keep tabs on. At the end of April, the tracker listed one COVID-19 candidate, the bacillus Calmette-Guerin vaccine used primarily against tuberculosis, in as being in a phase 2/3 trials, six in phase 1, 10 in preclinical development, and 27 in a catchall “research in additional vaccine candidate” category.

In many ways, SARS-CoV-2, the virus that causes COVID-19, is an inviting target for a vaccine. Because of today’s powerful sequencing technology and prior experience with other coronaviruses, the RNA genome of the virus was sequenced quickly, giving researchers a handle on the virus’s reproduction and the encoding of its spherical outer shell, including those now-familiar spikes that give it the menacing look of the head of a medieval mace. For vaccine developers, those spikes, called S proteins, are something of a dream come true because they are the means by which the virus binds to and infects cells, and antibodies that home in on and stick to S proteins can block that process. Many of the current crop of vaccines are designed to deliver this S protein (or a fragment of it) to trigger an immune response and unleash antibodies that will fend off future infection by SARS-CoV-2.

Vaccine developers also seem to have a relatively stable target in SARS-CoV-2. Decades of research into vaccines for HIV and hepatitis C have come up empty-handed partly because those viruses are elusive shape-shifters.

Technologies abound
But perhaps the principal reason for the momentum behind COVID-19 vaccine development is the blossoming of recombinant DNA and other related technologies over the past few decades. Vaccine developers have at their disposal any number of techniques for tweaking genomic material so it produce antigens that will provoke an antibody response and another workshop full of choices for how to assemble the vehicle for delivering it. The abundance explains the large field of candidates at the starting line of COVID-19 vaccine development and the large number of private com-
panies involved, each betting that it has the smartest idea. By one count, private companies are developing three-quarters of the COVID-19 vaccine candidates, with academic, government and nonprofit organizations developing the remaining quarter.

The classic vaccine against viral diseases produces immunity using a live attenuated (or weakened) version of the virus. The smallpox, chickenpox, and measles, mumps and rubella vaccines — among the most effective available — use live attenuated vaccines. But with recombinant protein and genetic engineering tools, vaccine developers don’t need to use the whole virus. They can create vaccines that depend on crucial fragments of the antigen that provokes an antibody response; in the case of COVID-19, the go-to antigen is that spiky S protein.

In some cases, instead of employing a live attenuated virus, vaccine developers can patch together a facsimile of one, using the genomic material of re-engineered virus to express the parts of the antigen that trigger antibodies. Some current technologies, including some COVID-19 vaccine candidates, use DNA to get into cells and express the antibody-provoking antigens. Others hire RNA to do the job.

Problems and pitfalls
There might be some wind in the sails right now, but enthusiasm about a COVID-19 should be kept on a short leash. For one thing, there are no coronavirus vaccines on the market. A small number of vaccines against another coronavirus, SARS-CoV-1, made it into phase 1 trials but were abandoned when the 2003 SARS outbreak caused by that virus receded. The story is similar regarding a vaccine against the coronavirus that causes Middle East respiratory syndrome (MERS). The lack of a vaccine against other coronaviruses means aspects of testing and manufacturing a putative COVID-19 vaccine will be created more or less from scratch. Vaccines must be developed according to strict manufacturing. If one of the vaccine candidates that uses a new technology is deemed safe and effective, scaling up production will be uncharted territory.

Researchers don’t have an agree-upon animal model. Fauci has spoken about a mouse model, and the Oxford group’s vaccine has been tested in rhesus monkeys. If several different types of animals are used for vaccines in the preclinical phase, comparing results may be difficult.

Another challenge: identifying a vaccine that produces an enduring immune response. Coronavirus also cause the common cold, and the immune response to those viruses is fleeting, a concern despite the significant differences between the common cold coronaviruses and SARS-CoV-2. Also, to produce long-lasting immunity, a vaccine must produce an antibody response. A branch of the immune system called innate immunity doesn’t depend on antibodies or recognition of an antigen; it’s more of an all-purpose response to an invasive organism. A vaccine that stirs up a transitory innate response won’t afford the specific protection against SARS-CoV-2 that the world is hoping for.

Many vaccines require booster shots. In a perspective piece published in the April issue of the medical journal Immunity, Fatima Amanat and Florian Krammer of Icahn School of Medicine at Mount Sinai in New York City said that it is “highly likely” that more than one dose of a COVID-19 vaccine will be needed because the population is currently naive to SARS-CoV-2. Full protective immunity probably won’t kick in till one or two weeks after the second vaccination. Some people won’t come back for the second shot, so even if a vaccine is identified, real-world effectiveness may fall short. What’s more, Amanat and Krammer noted, the two-shot schedule lengthens any vaccine timeline by about a month because the initial injection and the booster shot usually have to be given several weeks a part.

Another possible complexity with COVID-19 vaccination is the need for an adjuvant, an additive that enhance the antibody response. Sometimes adjuvants make a vaccine safer by lowering the dose required to get the same, or an even stronger, antibody response. Several companies, including GlaxoSmithKline and Dynavax, have promised to make adjuvants available for use with COVID-19 vaccines developed by other entities.

So far, COVID-19 appears to be far more harmful for older people than younger people. CDC data show that the gradient for COVID-19
hospitalizations steepens with age; for example, the rate for people ages 85 and older is twice that of those 65 to 74. This is a problem for vaccine development, as Amanat and Krammer point out, because the immune system wanes with age and becomes less responsive to vaccines. A COVID-19 vaccine that doesn’t protect what appears to be one of the most vulnerable parts of the population would obviously be a rather flawed vaccine. Higher doses or different adjuvants might be needed for older people.

Another obstacle may be antibody-dependent enhancement, a risk Fauci has discussed in several interviews. Instead of blocking viral infection, the antibodies that a vaccine produces can latch onto the virus and abet rather than block infection. Antibody-dependent enhancement can also trigger an out-of-control immune response. Enhancement has been an issue with vaccines against dengue and respiratory syncytial virus, according to Fauci, and results from lab tests when the vaccines against SARS and MERS were in development suggested that enhancement might be a problem. The risk of a vaccine resulting in more COVID-19, not less, is one of the many reasons Fauci and others have stressed the need for careful evaluation of COVID-19 vaccines.

Christine Blank is a freelance writer based in Orlando, Florida. Peter Wehrwein is the senior editor of Managed Healthcare Executive.

A FEW OF THE TOP COVID-19 CANDIDATES

Here is a brief rundown of some of the vaccines in development:

**Bacillus Calmette-Guerin**
Some evidence suggests that bacillus Calmette-Guerin (BCG) vaccine against tuberculosis has an ancillary effect of protecting children and older people against the flu and respiratory diseases. Researchers in Australia and the Netherlands are conducting a phase 3 trial of the BCG vaccine among healthcare workers to see if it might have a protective effect against COVID-19.

**Moderna’s mRNA-1273**
This is the vaccine that Anthony Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases, mentioned at a White House Coronavirus Task Force press briefing on March 16. The initial phase 1 trial included 45 patients at Kaiser Permanente Washington Health Research Institute in Seattle and a second, larger phase 1 trial is being conducted at Emory University in Atlanta. Moderna is a Massachusetts-based biotech company and may receive close to $500 million from the Department of Health and Human Services to step up clinical work and manufacturing. Moderna’s vaccine uses messenger RNA to carry the genomic code that generates the SARS-CoV-2 S protein that induces an antibody response. This is a new vaccine technology, so it has the risks that attend to any medical intervention with no track record.

**CanSino Biologics’ Ad5-nCOV**
In an April 23 blog post, Lowe described the Chinese company’s Ad5-nCoV vaccine as the “most advanced candidate.” It uses the adenovirus to deliver DNA that encodes the SARS-CoV-2 S protein. Lowe reported that the company has a similar adenovirus vaccine against Ebola in phase 2 trials. The company announced in mid-April that it was starting a phase 2 trial that would enroll 500 volunteers in Wuhan.

**Oxford’s ChAdOx1 nCoV-19**
The University of Oxford’s vaccine is conceptually similar to that of CanSino. It also uses an adenovirus to deliver DNA that produces the antigen that fires up antibody production, but the Oxford group is using another adenovirus, one that infects chimpanzees. “Oxford is definitely taking a chance with their trial design, but then, everyone else is taking chances of one kind or another here,” Lowe wrote.

**Inovio’s INO-4800**
On April 28, Inovio, headquartered in suburban Philadelphia, announced that its phase 1 trial of 40 volunteers was fully enrolled. Inovio’s vaccine uses DNA plasmids — small circular strands of DNA — rather than RNA to deliver the genetic code that will lead to expression of the S protein and, the developers hope, a strong antibody response to SARS-CoV-2. Inovio used the same approach to develop a MERS vaccine that is in a phase 2a trial. The company also developed a new device for delivering its COVID-19 vaccine candidate into the skin.

Drugs In The Pipeline
There are a variety of medications being studied for the COVID-19, and the possible treatment landscape is rapidly evolving. There are no FDA-approved medications for the treatment of COVID-19. Currently, medical management consists of infection prevention and supportive care, which includes supplemental oxygen and mechanical ventilator support when indicated. Based on a search of ClinicalTrials.gov, there are at least 181 clinical trials being conducted as of April 14, 2020, both studies at the recruiting stage and those that have already begun. The scientific community is coming together to find safe and effective treatment options to combat COVID-19, which include existing and novel drugs.

**Remdesivir**

Remdesivir is an intravenous (IV) drug with broad antiviral activity (for example, SARS virus and Middle East respiratory syndrome) that has been used for the treatment of Ebola virus, and it works by inhibiting viral replication through premature termination of RNA transcription. Additionally, remdesivir appears to have a favorable safety profile based on its having been used to treat approximately 500 individuals, including healthy volunteers and those with acute Ebola virus infection. Remdesivir is being studied by Gilead Sciences for the treatment of COVID-19 and evidence suggests that it is currently one of the most promising investigational drugs.

On April 29, Anthony Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID), announced positive interim results of an NIAID-sponsored study of remdesivir. Fauci said the time to recovery was shorter for COVID-19 patients randomized to the remdesivir arm of the study than the patients in the placebo arm (11 days vs. 15 days) and that difference was statistically significant. However, on the same day, results published in *Lancet* from a randomized, placebo-controlled trial of remdesivir conducted in the Hubei province in China showed no association between treatment with the antiviral and a difference in time to recovery. Results of a cohort study were published in the *New England Journal of Medicine* on April 10, 2020, examining compassionate use of remdesivir in 61 patients hospitalized with COVID-19 with an oxygen saturation of 94% or less while breathing ambient air or who required oxygen support. Patients received a 10-day treatment of remdesivir 200 milligrams (mg) IV on day 1 followed by 100 mg for the remaining 9 days of therapy. Fifty-three patients had data analyzed (seven lacked posttreatment data, one had a dosing error) and clinical improvement was seen in 68% of patients. A total of 32 patients (60%) reported adverse events (AEs) during follow-up. The most common AEs were increased hepatic enzymes, diarrhea, rash, renal impairment and hypotension. Twelve patients (23%) experienced serious AEs, including multiple organ dysfunction syndrome, septic shock, acute kidney injury and hypotension, with most occurring in those receiving invasive ventilation. The results are promising, but more robust studies are needed to determine the safety and efficacy of remdesivir for patients with COVID-19. Study limitations included the drug not being randomized and lacking a control, missing data, and a short follow-up duration.

There are currently two phase 3 randomized clinical trials, known as the SIMPLE studies, for patients with COVID-19.
severe COVID-19 symptoms (NCT04292899) and for those with moderate symptoms (NCT04292730). Gilead released topline results from the SIMPLE trial studying patients with severe COVID-19, which demonstrated similar improvement with the five- and 10-day treatment regimens of remdesivir. Time to improvement for 50% of study participants was 10 days in the five-day treatment group, and more than half of patients in both groups were discharged from the hospital by 14 days. Results are expected by May 2020 for the study evaluating patients with moderate COVID-19. Since January 25, 2020, as part of individual compassionate use protocols, Gilead has been providing emergency access to remdesivir for over 1,800 qualifying patients with severe COVID-19 symptoms who are unable to enroll in ongoing clinical trials. The company is currently working on transitioning to expanded access of remdesivir for patients with severe symptoms and will collect and analyze treatment data.

HYDROXYCHLOROQUINE, CHLOROQUINE AND AZITHROMYCIN

The FDA recently issued an emergency use authorization (EUA) for the use of the antimalarial drugs chloroquine and hydroxychloroquine (Plaquenil) for the treatment of hospitalized adult and adolescent patients with COVID-19 who are unable to participate in a clinical trial and who weigh 50 kg or more. These medications have immunomodulatory activity that could contribute to an anti-inflammatory response, which is the theoretical mechanism of action for the proposed treatment of COVID-19. The dosage of hydroxychloroquine recommended by the EUA is 800 mg on the first day of treatment followed by 400 mg daily for four to seven days of total therapy, based on clinical evaluation. Chloroquine’s EUA recommends 1 g on day one followed by 500 mg daily for four to seven days of total treatment, based on clinical evaluation. However, there is controversy surrounding these drugs, as their safety and efficacy for the treatment of COVID-19 have not been established. Limited evidence suggests that these medications may have clinical benefits in patients with COVID-19.

Hydroxychloroquine with azithromycin was examined in observational and nonrandomized studies in France for the treatment of COVID-19, but data were limited as many individuals were considered to be low risk and only a small number of patients were included.

Azithromycin has immunomodulatory and anti-inflammatory properties, but there are currently insufficient data for its adjunctive use in the management of COVID-19. Both hydroxychloroquine and azithromycin are associated with QT prolongation, so patients with chronic medical conditions should be closely monitored to prevent drug-induced cardiac AEs. A jointly published guidance was released on April 8, 2020, by the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society regarding possible serious health risks associated with hydroxychloroquine and azithromycin. Recommendations include QT interval monitoring, withholding hydroxychloroquine and azithromycin in patients with baseline QT prolongation or known congenital long QT syndrome, correcting hypokalemia and hypomagnesemia, and avoiding other QTc-prolonging medications.

The safety and efficacy of hydroxychloroquine for the treatment of COVID-19 will be further evaluated in the ORCHID Study (NCT04332991) by the National Heart, Lung and Blood Institute. This phase 3 multicenter, placebo-controlled, randomized trial aims to enroll approximately 500 patients, and is estimated to have initial results by April 2021. There are also chloroquine studies underway in China and other countries, as there is currently limited evidence regarding the drug’s effectiveness for COVID-19. One randomized phase 2b clinical trial compared high-dose chloroquine (600 mg twice daily for 10 days) with low-dose chloroquine (450 mg for five days, twice daily only on first day) in 81 patients with severe COVID-19 in Brazil. All patients also received...
azithromycin and ceftriaxone. The fatality rate was 13.5%, with more deaths and QTc prolongation occurring in the high-dose treatment group. The study halted the high-dose treatment arm and results were posted to medRxiv, the preprint server for health sciences, but the study has not yet been peer reviewed. These results shed light on cardiac AEs potentially being dose dependent.

One man in Arizona died and his wife was hospitalized after they both ingested chloroquine phosphate, commonly used in aquariums to clean fish tanks, in an attempt to prevent COVID-19. The American Association of Poison Control Centers released a statement about AEs relating to hydroxychloroquine and chloroquine, especially nonpharmaceutical formulations that can be particularly dangerous, as exposure to these drugs has increased.

TOCILIZUMAB
Tocilizumab (Actemra), manufactured by Genentech, is a recombinant humanized monoclonal antibody that is an interleukin-6 (IL-6) receptor antagonist, with a proposed mechanism of action that combats cytokine release syndrome, or “cytokine storms,” in some severe cases of COVID-19. The drug is currently approved to treat various conditions such as rheumatoid arthritis; however, there are limited data demonstrating that tocilizumab shows benefit for severe COVID-19 symptoms and results in fever reduction and a decreased need for supplemental oxygen. Because tocilizumab is an immunosuppressive drug, it can increase the risk of serious infections.

A phase 3 randomized multicenter study is underway to evaluate the safety and efficacy of tocilizumab in hospitalized patients with severe COVID-19 pneumonia.

### TABLE Other COVID-19 Investigational Therapies

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<td>Lopinavir/ritonavir (Kaletra)</td>
<td>AbbVie Inc.</td>
<td>Mixed evidence on HIV protease inhibitor efficacy; randomized controlled trial in China with hospitalized patients with severe COVID-19 showed no benefit. RECOVERY trial in the UK is underway and will examine lopinavir/ritonavir and other therapies for COVID-19.</td>
</tr>
<tr>
<td>EIDD-2801</td>
<td>Ridgeback Biotherapeutics/Emory University</td>
<td>Oral drug has shown activity against coronaviruses in animal studies and human trials have been approved by the FDA to begin.</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Bellerophon Therapeutics</td>
<td>FDA granted emergency expanded access for the nitric oxide delivery system INOpulse to be used for COVID-19 treatment, based on positive results from 3 patients. Bellerophon Therapeutics also submitted an IND application to the FDA to study INOpulse in patients with COVID-19 in a randomized trial of approximately 500 patients.</td>
</tr>
</tbody>
</table>

IND, investigational new drug, UK, United Kingdom.
Let’s Connect.

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Network with fellow executives from across the world while you stay current on healthcare’s new developments and innovations.
A s a healthcare executive, you talk to a lot of healthcare professionals, and you talk to them often. But even as you talk, a nagging thought bubble may pop up, the same one that teachers, bosses and parents deal with: “Is anyone really listening?”

To cut through the noise and get people to listen try these four tips to help motivate providers to join forces with you as partners.

1. **Stick to high values.**
Most people choose a career in healthcare for altruistic reasons. Ken Faber, M.D., vice president of clinical care at Grand Rounds, a San Francisco company that provides healthcare navigation services, says, “A leader who fails to link the organization’s mission to the values of their providers will fail.” Mission statements on letterhead are not enough.

2. **Encourage creative thinking.**
The art and science of medicine is a cliche. Even so, you don’t want healthcare providers in your organization just trudging along. You want them excited about coming up with new ideas — ideas that could improve outcomes and help control costs. Richard S. Isaacs, M.D., FACS, CEO and executive director of The Permanente Medical Group (TPMG) and president and CEO of the Mid-Atlantic Permanente Medical Group, says the best way to encourage creativity is to cultivate an environment in which physicians and staff feel empowered. He is also big on JAMM, which stands for “joy and meaning in medicine.” Says Isaacs, “We are gathering data from our physicians to understand the factors that affect JAMM in their work, which means our physicians have a voice and role in designing initiatives to promote fulfilling careers at TPMG. For example, feedback from our physicians has prompted new performance measures that incentivize the reduction of clerical burden and broadened professional development opportunities across their career continuum.”

3. **Streamline operations to reduce administrative burden.**
Let healthcare professionals take care of patients and offload some of the administrative work to others, says Seth Cohen, CEO and co-founder of OODA Health, a healthcare technology startup in San Francisco. How do you do that? By streamlining -office operations. “That can help reduce physician burnout, ensure large systems stay competitive and encourage a focus on patient care,” he says.

Patients often struggle to manage and pay their bills, while providers must shoulder an increasing burden of bad debt, observes Cohen. “Meanwhile,” he adds, “payers depend on this flawed system to administer benefit designs and miss a critical point of engagement with patients. This creates a perfect storm of uncoordinated communications and patient confusion, resulting in poor repayment rates.”

4. **Do a 360 before you adopt an EHR.**
Improving the EHR experience will pay huge dividends in engagement and motivation. Geeta Nayyar, M.D., chief medical officer for Greenway Health, a health information technology in Tampa, Florida, says that practices should seek out products that are customizable.

“Before implementing any new technology, ask the right questions,” Nayyar says. “Get perspective from all departments within the practice, from the front office to the back, to ensure all needs will be met. Focus on the amount of training an EHR vendor provides because physicians who report poor training are over 3.5 times more likely to report that their EHR does not enable them to deliver quality care.”

**Stephanie Stephens** is a journalist and radio and television producer and host in Orange County, California.
OCREVUS® (ocrelizumab) injection, for intravenous use

1 INDICATIONS AND USAGE
OCREVUS is indicated for the treatment of:
- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults

2 CONTRAINDICATIONS
OCREVUS is contraindicated in patients with:
- Active HBV infection [see Warnings and Precautions (5.2)]
- A history of life-threatening infusion reaction to OCREVUS [see Warnings and Precautions (5.1)]

5 WARNINGS AND PRECAUTIONS
5.1 Infection Reactions
OCREVUS can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, chills, fever, rigors, hypotension, asthenia, myalgia, arthralgia, chest pain, dyspnea, cholecystitis, abdominal pain, nausea, vomiting, headache, diarrhea, respiratory tract infections, and infusion reactions. The addition of an antipyscotic (e.g., acetaminophen) may also be considered.

5.2 Infections
A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections [see Adverse Reactions (6.1)]. The rate of infections in the PPMS trial was lower than that observed in the placebo-controlled clinical trial in patients with primary progressive MS (PMPMS).

Respiratory Tract Infections
A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PMPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 9% of patients on placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis.

Herpes
In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in OCREVUS-treated patients than in REBIF-treated patients, including herpes zoster (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). The infections were predominantly mild to moderate in severity. There were no reports of disseminated herpes.

In the placebo-controlled (PMPMS) clinical trial, oral herpes was reported more frequently in the OCREVUS-treated patients than in the patients on placebo (2.7% vs. 0.8%).

Progressive Multifocal Leuкоencephalopathy (PML)
PML is a demyelinating viral infection of the brain caused by the John Cunningham (JC) virus that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Although no cases of PML were identified in OCREVUS clinical trials, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (e.g., patients with monoclonal gammopathy or multiple myeloma) and specific infections. At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confabulation and personality change.

Hepatitis B Virus (HBV) Reactivation
There were no reports of hepatitis B reactivation in MS patients treated with OCREVUS. Fulfilled hepatitis B, hepatitis D, and death caused by HBV reactivation have occurred in patients treated with other anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS to patients with active HBV infection confirmed by positive results for HBsAg or anti-HB. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+] consult liver disease experts before starting and during treatment.

Possible Increased Risk of Immunopressor Effect with Other Immunopressors
When initiating OCREVUS after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effects [see Drug Interactions (7.1)]. OCREVUS has not been studied in combination with other MS therapies.

Vaccinations
Administer all vaccinations according to immunization guidelines at least 4 weeks prior to initiation of OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines. OCREVUS may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines following OCREVUS therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

Vaccination of Infants Born to Mothers Treated with OCREVUS During Pregnancy
In infants of mothers exposed to OCREVUS during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts as measured by CD19+ B-cells. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines. You may administer non-live vaccines, as indicated, prior to recovery from B-cell depletion, but should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted [see Use in Specific Populations (8.1)].

5.3 Malignancies
An increased risk of malignancy with OCREVUS may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with OCREVUS and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

6 ADVERSE REACTIONS
The following serious adverse reactions are discussed in greater detail in other sections of the labeling:
- Infections [see Warnings and Precautions (5.1)]
- Infusions [see Warnings and Precautions (5.2)]
- Malignancies [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions 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 clinical practice. The safety of OCREVUS has been evaluated in 1311 patients across MS clinical studies, which included 825 patients in active-controlled clinical trials in patients with relapsing forms of MS (RMS) and 486 patients in a placebo-controlled study in patients with primary progressive MS (PMPMS).

Adverse Reactions in Patients with Relapsing Forms of MS
In active-controlled clinical trials (Study 1 and Study 2), 825 patients with RMS received OCREVUS 600 mg intravenously every 24 weeks (initial treatment was given as two separate 300 mg infusions at Weeks 0 and 2). The overall exposure in the 96-week controlled treatment periods was 1448 patient-years.

The most common adverse reactions in RMS trials (incidence ≥ 10%) were upper respiratory tract infections and infusion reactions. Table 2 summarizes the adverse reactions that occurred in RMS trials (Study 1 and Study 2).

Table 2 Adverse Reactions in Adult Patients with RMS with an Incidence of at least 5% for OCREVUS and Higher than REBIF

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>OCREVUS 600 mg IV Every 24 Weeks1 (n=825)</th>
<th>REBIF 44 mcg SQ 3 Times per Week (n=826)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>34</td>
<td>10</td>
</tr>
<tr>
<td>Depression</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Herpes virus-associated infections</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

1The first dose was given as two separate 300 mg infusions at Weeks 0 and 2.

Adverse Reactions in Patients with Primary Progressive MS
In a placebo-controlled clinical trial (Study 3), a total of 486 patients with PPMMS received one course of OCREVUS (600 mg of OCREVUS administered as two 300 mg infusions two weeks apart) given intravenously every 24 weeks and 239 patients received placebo intravenously. The overall exposure in the controlled treatment period was 1416 patient-years, with median treatment duration of 3 years.

The most common adverse reactions in the PPMMS trial (incidence ≥ 10%) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections. Table 3 summarizes the adverse reactions that occurred in the PPMMS trial (Study 3).

Table 3 Adverse Reactions in Adult Patients with PPMMS with an Incidence of at least 5% for OCREVUS and Higher than REBIF

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>OCREVUS 600 mg IV Every 24 Weeks1 (n=486)</th>
<th>REBIF 44 mcg SQ 3 Times per Week (n=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Infusion reactions</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Depression</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Back pain</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Herpes virus-associated infections</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

1The first dose was given as two separate 300 mg infusions at Weeks 0 and 2.
Table 3 Adverse Reactions in Adult Patients with PPMS with an Incidence of at least 5% for OCREVUS and Higher than Placebo

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Study 3 OCREVUS 600 mg IV Every 4 Weeks† (n=486)</th>
<th>Placebo (n=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upper respiratory tract infections</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Infusion reactions</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory tract infections</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Edema peripheral</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Herpes virus associated infections</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td><strong>One dose of OCREVUS (600 mg administered as two 300 mg infusions two weeks apart)</strong></td>
<td></td>
</tr>
</tbody>
</table>

Laboratory Abnormalities

Decreased Immunoglobulins

OCREVUS contains immunoglobulins with the greatest decline seen in IgM levels. In MS clinical trials, there was no apparent association between immunoglobulin decrease and risk for serious infections.

In the active-controlled (RMS) trials (Study 1 and Study 2), the proportion of patients at baseline reporting IgG, IgA, and IgM below the lower limit of normal (LLN) in OCREVUS-treated patients was 0.5%, 1.5%, and 0.1%, respectively. Following treatment, the proportion of patients at baseline reporting IgG, IgA, and IgM below the LLN at 96 weeks was 1.5%, 2.4%, and 16.5%, respectively.

In the placebo-controlled (PPMS) trial (Study 3), the proportion of patients at baseline reporting IgG, IgA, and IgM below the LLN in OCREVUS-treated patients was 0.0%, 0.2%, and 0.2%, respectively. Following treatment, the proportion of OCREVUS-treated patients reporting IgG, IgA, and IgM below the LLN at 120 weeks was 1.1%, 0.5%, and 15.5%, respectively.

Decreased Neutrophil Levels

In the PPMS clinical trial (Study 3), decreased neutrophil counts occurred in 13% of OCREVUS-treated patients compared to 10% in placebo patients. The majority of the decreased neutrophil counts were only observed once for a given patient treated with OCREVUS and were between LLN: 1.5 x 10⁹/L and 1.0 x 10⁹/L. Overall, 1% of the patients in the OCREVUS group had neutrophil counts less than 1.0 x 10⁹/L and these were not associated with infection.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication, and the underlying disease. Therefore, comparison of the incidence of antibodies to OCREVUS with the incidence of antibodies to other products may be misleading.

Patients in MS trials (Study 1, Study 2, and Study 3) were tested at multiple time points (baseline and every 6 months post-treatment for the duration of the trial) for anti-drug antibodies (ADAs). Out of 1311 patients treated with OCREVUS, 12 (1.1%) tested positive for ADAs, of which 2 patients tested positive for neutralizing antibodies. These data are not adequate to assess the impact of ADAs on the safety and efficacy of OCREVUS.

7 DRUG INTERACTIONS

7.1 Lymphoid-Modulating or Immune-Modulating Therapies

The concomitant use of OCREVUS and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of infusion reactions. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with OCREVUS. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating OCREVUS [see Warnings and Precautions (5.2)].

7.2 Vaccinations

A Phase 3b randomized, open-label study examined the concomitant use of OCREVUS and several non-live vaccines in adults 18-55 years of age with relapsing forms of MS (68 subjects undergoing treatment with OCREVUS at the time of vaccination and 34 subjects not undergoing treatment with OCREVUS at the time of vaccination). Concomitant exposure to OCREVUS attenuated antibody responses to tetanus toxoid-containing vaccines, influenza vaccine, pneumococcal conjugate vaccines, and seasonal inactivated influenza vaccines. The impact of the observed attenuation on vaccine effectiveness in this patient population is unknown. The safety and effectiveness of live-attenuated or live vaccines is not recommended during OCREVUS treatment and until B-cell recovery [see Warnings and Precautions (5.2)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

OCREVUS is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. However, transient peripheral B-cell depletion and lymphopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell levels in infants following maternal exposure to OCREVUS have not been studied in clinical trials. The potential duration of B-cell depletion in such infants, and the impact of B-cell depletion on vaccine safety and effectiveness, is unknown [see Warnings and Precautions (5.2)].

Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically, increased perinatal mortality, depletion of B-cell populations, renal, bone marrow, and testicular toxicity were observed in the offspring in the absence of maternal toxicity [see Data].

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

Data

Animal Data

Following intravenous administration of OCREVUS to monkeys during organogenesis (loading doses of 15 or 75 mg/kg on gestation days 20, 21, and 22, followed by weekly doses of 20 or 100 mg/kg), depletion of B-lymphocytes in lymphoid tissue (spleen and lymph nodes) was observed in fetuses at both doses. Intravenous administration of OCREVUS (three daily loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) to pregnant monkeys throughout the period of organogenesis and continuing through the neonatal period resulted in perinatal deaths (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow, and severe decreases in circulating B-lymphocytes in neonates. The cause of the neonatal deaths is uncertain; however, both affected neonates were found to have bacterial infections. Reduced testicular weight was observed in neonates at the high dose.

A no-effect dose for adverse developmental effects was not identified; the doses tested in monkeys were 2 and 10 times the recommended human dose of 600 mg, on a mg/kg basis.

8.2 Lactation

Risk Summary

There are no data on the presence of ocrelizumab in human milk, the effects on breastfed infants or the effects of the drug on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and there is potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for OCREVUS and any potential adverse effects on the breastfed infant from OCREVUS or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Women of childbearing potential should use contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS.

8.4 Pediatric Use

Safety and effectiveness of OCREVUS in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of OCREVUS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

17 PATIENT COUNSELING INFORMATION

Advisse the patient to read the FDA-approved patient labeling (Medication Guide).

Infusion Reactions

Inform patients about the signs and symptoms of infusion reactions, and that infusion reactions can occur up to 24 hours after infusion. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions [see Warnings and Precautions (5.1)].

Infection

Advisse patients to contact their healthcare provider for any signs of infection during treatment or after the last dose. Signs include fever, chills, constant cough, or signs of sepsis such as cool ears, or genital sores [see Warnings and Precautions (5.2)].

Advise patients that FML has happened with drugs that are similar to OCREVUS and may happen with OCREVUS. Inform the patient that FML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of FML. Inform the patient that typical symptoms associated with FML are most likely to occur over days to weeks and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes [see Warnings and Precautions (5.2)].

Advise patients that OCREVUS may cause reactivation of hepatitis B infection and that monitoring will be required if they are at risk [see Warnings and Precautions (5.2)].

Vaccination

Advisse patients to complete any required live or live-attenuated vaccinations at least 4 weeks and, whenever possible, non-live vaccinations at least 2 weeks prior to initiation of OCREVUS. Administration of live-attenuated or live vaccines is not recommended during OCREVUS treatment and until B-cell recovery [see Warnings and Precautions (5.2)].

Malignancies

Advisse patients that an increased risk of malignancy, including breast cancer, may exist with OCREVUS. Advise patients that they should follow standard breast cancer screening guidelines [see Warnings and Precautions (5.3)].

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking OCREVUS they should inform their healthcare provider [see Pregnancy (8.1)].

OCREVUS* [ocreliumab]”

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Opportunity Calling.
Will COVID-19 Bring Telehealth Into the Mainstream of American Healthcare?

by SUSAN LADIKA

It took American Family Care, an urgent care and primary care company headquartered in Birmingham, Alabama, just 36 hours to roll out its telemedicine service, AFC TeleCare, after the COVID-19 outbreak struck. "We had been thinking about it and deciding when we wanted to venture into it (telemedicine) prior to the pandemic," says Benjamin Barlow, M.D., the company's chief medical officer (CMO). "We met on a Monday, and the next day it was a go." Since AFC TeleCare's launch in March, many of the calls the company has received involve medication management for established patients, Barlow says.

If American healthcare does wind up getting divided into pre- and post-COVID-19 eras, the migration from in-person visits to telehealth ones will likely be one of the biggest developments on the right-hand side of the inflection. Population health experts and advocates have been eyeing telehealth for some time as a way to monitor patients, encourage healthy behaviors and increase adherence to medications. "It's recognized as an effective and often more efficient means to connect with patients to provide healthcare and chronic disease management," says Mitchell Kaminski, M.D., MBA, a family physician and program director of population health at Jefferson College of Population in Philadelphia. The COVID-19 outbreak moved thought, research and pilot projects into full-on implementation mode. "We've gone from incremental change in 10 years to very rapid, transformative change" because of COVID-19, Kaminski says, as virtual care gives providers the opportunity to offer much needed care during the pandemic while keeping patients safe by not making them come in person and wait in a doctor's office.

As a family physician and leader in population health, Kaminski says he had long thought that he should provide virtual care for his own patients, but it languished on the to-do list. He envisioned a steep learning curve. And like many physicians, especially those who deliver primary care, he assumed that telehealth visits couldn't measure up to the in-person ones in establishing a strong doctor-patient relationship.

But he has been pleasantly surprised. "I have been amazed at the connection I feel, even with patients I've never met before," says Kaminski, who has been seeing patients remotely through JeffConnect, an app set up by the Thomas Jefferson University Hospitals system, as well as having telehealth visits with his own patients.

Pre-COVID-19
Before the COVID-19 outbreak, telehealth had been edging its way into American healthcare delivery. The convenience of being able to receive immediate care online via a mobile device has undeniable appeal for patients, especially compared with having to wait days, even weeks, to be seen. In many cases, the virtual visits had a lower copay. In some cases, the services were provided by hospital and healthcare systems. In others, they were the reason to be for so-called direct-to-consumer companies such as Teladoc Health and were offered as an add-on benefit to employer-based health insurance.

A 2019 J.D. Power survey found about 10% of respondents had used telemedicine in the previous 12 months. Two years ago, Michael Barnett, M.D., an assistant professor at the Harvard T.H. Chan School of Public Health, and his colleagues reported the results of...
a study of telehealth usage in an
unnamed health plan in JAMA. (Al-
though the plan is not named, the
de-identified claims that Barnett
and his co-authors used came from
OptumLabs.)

From 2005 to 2017, those health
plan members made almost 385,000
virtual visits, and usage climbed
from 0.02 visits per 1,000 members
in 2005 to 6.57 visits per 1,000 mem-
bers in 2017. More than half the
visits were for mental healthcare,
and almost 40% were for primary
care. Barnett’s report shows a steep
increase in telehealth use starting
in 2015.

Teladoc, which stakes a claim to
being the country’s most expe-
rienced and largest telehealth
provider, reported that its number
of virtual visits reached 4.1 million
in 2019, a 57% increase over the pre-
vious year.

On March 13 of this year
the company reported that virtual
visits had increased by 50% in the
previous seven days compared with
the week before. Teladoc provided
about 100,000 virtual visits during
that time. Its stock price shot up
from $128 per share on March 13 to
$167 on March 23.

Maven Clinic, a digital health
startup that focuses on women’s
health, has seen virtual mental
healthcare increase more than
500% since the pandemic began,
says CEO Katherine Ryder. Virtual
care is “dramatically reshaping”
healthcare delivery, she says.

Kaminski says that Jefferson
emergency department physicians
set up the JeffConnect app about
three years ago. Patients were
charged a relatively small copay.
“They were providing about 50
telemedicine visits per day until the
pandemic hit, and suddenly they
found themselves dealing with over
3,000 visits a day, a 60-fold increase.”

Reimbursement matters
“The slow adoption of telemedicine
tools really has been reflective
of the lack of payment or limited
payment for visits,” notes Kaminski.
Prior to COVID-19, CMS had been
slowly relaxing restrictions on the
telehealth services that Medicare
would pay for. For example, start-
ing this year, Medicare Advantage
plans were allowed to offer tele-
health as a basic benefit. Last year,
Medicare started paying for brief
virtual check-ins with patients with
whom a physician has an estab-
lished relationship. But in March,
CMS swept away many restrictions
and agreed to pay for telehealth
visits at the same rate as in-per-
son visits. Rules that had required
in-person visits with nursing home
residents and hospice and end-
stage renal disease patients have
been waived.

For commercial payers, a 2019
report by the law firm Foley & Lard-
ner LLP found only 10 states had
payment parity laws requiring equal
reimbursement for virtual visits
and in-person care. But amid the
COVID-19 outbreak, some states
have ordered private insurers to
reimburse providers for telehealth
services at rates no lower than what
they pay for in-person care. Some
insurers have waived cost sharing
for telehealth visits, and a few —
Aetna, most prominently — are
matching the CMS policy of paying
for telehealth visits at the same rate
as in-person visits.

Prior to the reimbursement
changes, “it just wasn’t worth it”
to have American Family Care
doctors offer telemedicine services,
says Barlow, the CMO. “You lost
money.” But that has changed now
that some insurers “are recognizing
the value and need for this and are
paying us for it,” he adds.
CMS could relax its telehealth rules because COVID-19 was declared a public health emergency. Once that the emergency is over, legally, the rules will go back into effect. There's also a chance that the current appetite for telehealth is particular to the COVID-19 outbreak and to the social distancing designed to mitigate its worst effects. Kaminski says a large percentage of his telehealth visits have been about easing people's COVID-19 fears. Still, he doesn’t see a return to the pre-COVID-19 era of telehealth when it was largely on the margins of American healthcare.

“I think of it as opening Pandora’s box. We see all the benefits of this technology patients are experiencing: greater access and convenience for care. And we’re finding that it’s effective for their care.

“When the pandemic is over,” Kaminski continued, “I don’t think anyone can predict what is going to happen. But it’s hard to imagine that we can put Pandora back into the box and say, ‘Let’s go back to this less efficient, more costly, fee-for-service-based, RVU (relative value unit) system that we had before.’

There is a question, though, about who will be providing telehealth. Part of the appeal of the direct-to-consumer providers is that they make their service available around the clock. Many traditional, office-based providers will presumably add telehealth visits as a service, but it is hard to imagine their having 24/7 coverage.

Another question centers on what exactly post-COVID-19 telehealth will be used for. Amid the outbreak, it helps people stay home. But what happens afterward? Population health experts like Kaminski worry about weakening the already tenuous continuity of American healthcare if people depend too heavily on the direct-to-consumer providers. Kaminski is also concerned about loss of data. “When a patient has a visit with a nonaffiliated service or provider, whether it’s at a drugstore or through a virtual telemedicine visit, does that information get back to that patient’s primary medical record? It will matter if it affects the medications they take for their illnesses.

So where there’s concern about the continuity with providers, you also have to think about continuity of data,” he says.

The digital divide between low- and middle-income Americans and the affluent may be a fault line in the future of telehealth. Enthusiasts for online endeavors of all kinds sometimes gloss over the fact that reliable, high-speed internet access is not available to everyone for economic, geographic and other reasons.

Some observers also see a generational split. Baby boomers may still be attached to the in-person visit, partly because they are aging and will therefore tend to have more complex medical problems. In a webinar in March sponsored by Brookings Institution and the Leonard D. Schaeffer Center for Health Policy & Economics at the University of Southern California, Deutsche Bank analyst George Hill said he expects demand for telehealth care to continue, particularly among younger patients, who are “provider agnostic.” Instead, in this convenience-driven society, they want “a doctor serving you on your terms, when you’re ready,” he said.

Susan Ladika is a health and business writer in Tampa, Florida.

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**“We’ve gone from incremental change in 10 years to very rapid, transformative change” because of COVID-19.”**

—MITCHELL KAMINSKI, M.D., M.B.A., A FAMILY PHYSICIAN AND PROGRAM DIRECTOR OF POPULATION HEALTH AT JEFFERSON COLLEGE OF POPULATION IN PHILADELPHIA
When COVID-19 started to sweep across this country, much of the attention focused on New York, New Jersey, the city of New Orleans and a fewer other hot spots.

But from the start of the outbreak in this country in February, when residents of the Life Care Center in suburban Seattle started to fall ill and die, it was evident that nursing home residents would be among those most vulnerable to infection by the SARS-CoV-2 virus and serious illness and death from COVID-19. By late April, news organizations had tallied 7,000 COVID-19-related deaths among nursing home residents and people connected to nursing homes. That was about 20% of the total number of COVID-19-related deaths in the country at that time. State and federal government officials have been slow to release nursing home-specific COVID-19 statistics, citing privacy and other concerns. Some critics say that reluctance has obscured the scope of the problem and delayed actions to mitigate it. CMS Administrator Seema Verma changed the reporting procedures in April so nursing home deaths would be reported directly to the CDC rather than local health officials.

The deaths in nursing homes have led to some horrifying situations, such as one in Sussex County, New Jersey, where an overwhelmed nursing home piled 17 bodies in a morgue meant for just a few. The deadliest outbreak was in the Canterbury Rehabilitation & Healthcare Center outside Richmond, Virginia, where 46 deaths had occurred by the end of April. As COVID-19 flared up in nursing home after nursing home, evidence of a history of poor infection control surfaced for some facilities. Especially damning was a report by the Washington Post that found that 40% of the 650 homes with publicly reported COVID-19 cases had been cited more than once for infection control violations.

CMS has responded in several ways. In mid-March, the agency issued a memo restricting all but a few people from visiting nursing homes and ordered the cancellation of group activities and communal dining. About a week later, the agency suspended routine inspections to focus on infection control. The agency also relaxed transfer and other rules so residents with COVID-19 could be grouped together and separated from residents without the disease. And in April, CMS increased the reimbursement rate for testing, partly to accelerate the pace of testing of nursing home patients and staff.

"People will end up blaming nursing homes and talking about how terrible we are, but it is the complete lack of prioritization that has put us in the position we are in," tweeted Mark Parkinson, former governor of Kansas and now president and CEO of the American Health Care Association and National Center for Assisted Living (AHCA/NCAL), a federation of state groups for nursing homes and assisted living facilities. Beth Martino, a spokesperson for the organization, says nursing homes are doing everything they can with the resources they have been given to slow the spread of the virus. "Our providers are struggling due to lack of testing, insufficient personal protective equipment (PPE) and a workforce shortage due to school closures and employee illness," she says. "We desperately need more PPE in nursing homes, priority testing for our healthcare workers and residents, and the ability to quickly recruit and hire more staff."

Richard Feifer, M.D., M.P.H., FACP, senior vice president and chief medical officer for Genesis HealthCare in Kennett Square,
Pennsylvania, has been working nonstop with the employees across the for-profit company’s network of 381 skilled nursing and assisted living facilities. “This is a deadly, highly contagious virus with a high mortality rate in nursing homes; in fact, up to 20%,” he says. “These are frail ... seniors who are the least able to withstand even common infections, let alone a virus like this. The cruel reality is that once COVID-19 enters a nursing home, its spread is incredibly challenging to prevent, no matter how many precautions and controls you have in place — and we have been very rigorous.” Genesis’ stock price at the end of April was half what it was at the beginning of March.

Feifer says the company has had to be resourceful and at times creative in determining ways to protect Genesis’ patients, residents and employees. He says nursing homes need help from federal and state health officials in three areas: prioritizing broader, faster testing; allocating PPE; and charting a sensible, collaborative approach to addressing a shortage of hospital beds without introducing the virus into the nursing homes.

“We need to make sure we are helping our elderly community, as well as the employees who are the true heroes,” says Feifer. “They are putting themselves at risk every shift they work to serve their patients and residents each and every day.”

Eric T. Mizuno, M.D., medical director at The Admiral at the Lake, a continuing care facility in Chicago, says that nursing homes aren’t equipped with the screening necessary to keep the SARS-CoV-2 virus out of their facilities. “Many of these facilities are less sophisticated than hospitals and are not used to dealing with infection control at the same level. If it gets in, it’s like setting the match to gasoline. The staff isn’t trained on how to not spread it, and there are more mortalities.”

Kristen Knapp, director of communications for the Florida Health Care Association, which represents approximately 560 nursing homes throughout Florida, says the organization has been pushing out regular updates to its facilities and providing guidance from the local, state and federal levels. “Right now, everyone working in a nursing home and long-term care facility is required to wear a mask and gloves, and we did that even before it became a mandate by the federal government,” she says. Nursing homes have also set up areas in their facilities to isolate any residents with COVID-19, she adds. In addition, the association has an infection prevention specialist on staff who has been training nursing home workers, providing guidance on everything from cleaning solutions to the best way to do laundry to proper PPE use. “The problem,” says Knapp, “is that we are at crisis-level supply shortages, and many facilities are utilizing hand-sewn masks from the community or wearing bandannas. There is just not enough supply, and it’s getting concerning.”

**Controlling the spread**

Before COVID-19, nursing homes held group social activities to engage residents and provide some social and intellectual stimulation. Families were encouraged to visit as often as possible. All of that has stopped because of COVID-19.

The AHCA/NCAL has suggested that nursing homes “cohort” residents who are positive for or suspected of having COVID-19 by setting aside separate wings, units or floors for them. “Governors and public health officials should be directing nursing homes to create segregated units, in areas where it makes sense, right now,” says Martino, the organization’s spokesperson.

“They should also explore creating dedicated COVID-19 facilities that can accept hospital discharges. As a profession, we have made these recommendations, but we need state officials to waive regulations that limit our actions. We also need to find ways to work with state public health agencies to get the necessary support to nursing homes so they can accept positive patients.” At the end of March, CMS waived discharge rules to allow facilities to isolate COVID-19 patients.

Feifer says it’s better to overreact than underreact to COVID-19. “We have been extremely stringent on visitation restrictions, use of personal protective equipment and many other precautions across all our centers from early on,” he says. “We’ve followed guidelines and protocols set by CDC and CMS, in some cases getting out in front of them.” First and foremost, says Feifer, Genesis has required all staff to wear PPE in patient areas.

“We are also vigilantly screening residents for symptoms, first daily, then twice daily and, since March 26, three times daily,” Feifer says. “We are also actively screening and taking temperatures of all staff upon building entry, and we have canceled all outside medical appointments, except for lifesaving treatments, like dialysis and chemotherapy.”

Tracy Humble, RN, vice pres-
ident of clinical services for The Compliance Store in Montgomery, Alabama, a company that advises nursing homes on regulatory and other issues, says suspending visits has been the hardest adjustment for residents and staff. Facilities have been getting creative and using technology like video chat to maintain connections between residents and their loved ones.

"Implementation of the suggestions made by CMS and the CDC are paramount in protecting residents," says Humble. "As new information is released, facilities have to learn more and adapt as indicated."

CMS Administrator Seema Verma has appeared at several of the daily White House coronavirus briefings, and her agency has issued a barrage of guidances and regulatory waivers designed to help nursing homes respond to COVID-19. "It’s clear that CMS shares our goal of containing the virus and limiting the spread as much as possible," says AHCA/NCAL’s Martino. "We appreciate CMS targeting surveys and inspections to only critical issues, which will greatly help our staff focus on resident care and fighting this virus."

The emotional toll
Doctors and nurses have been celebrated as the heroes of the COVID-19 outbreak. But the people working in nursing homes, many of whom are in low-paying jobs and traveling long distances to get to work, have also been heroic. "We have seen the incredible dedication our staff has had during this pandemic, many coming to work even when COVID-19 is in the building and masks and other supplies are low or unavailable," Martino says. "It’s important to keep in mind that like all other healthcare facilities, nursing homes have to delicately balance ensuring that there are enough caregivers to properly aid residents and patients, while also making sure sick employees do not create unnecessary, additional risks to residents."

The pandemic has created other challenges for staff, according to Martino. Many have had to scramble to find child care because schools are closed. The deaths in the facilities take an emotional toll. The most helpful thing any advocacy group or media outlet can do right now is encourage people not to visit long-term care facilities, she says — and to stay home to reduce transmission.

Feifer, speaking in early April, said testing of nursing home residents and employees should be priority. "Where we have had access to test kits and swabs, results have been taking too long, usually three to nine days or more," Feifer said. "We know it can be done faster because we’ve had residents transferred to the hospital and seen results come back in a few hours."

Maryland, Massachusetts and Rhode Island have accelerated testing in nursing homes. A CDC guidance on April 15 mentioned that nursing home residents with COVID-19 may not have typical symptoms like fever or a cough. The guidelines for reopening businesses and other parts of the economy issued by the White House say that nursing homes should continue to prohibit visitors during the first two of the three phases outlined in the document. Feifer emphasized the need for testing: "In the absence of the ability to test everyone, and potentially more than once, nursing homes are sure to see further spread."

Mizuno, of The Admiral at the Lake, says until a screening test for COVID-19 is available, keeping the coronavirus out of nursing homes will be impossible. "That does not preclude you from morally or legally making every effort you can to keep this thing from coming in, but you will not be successful," he says. "You are trying to fight a war with rubber bands and rocks, and that’s not how you fight a war in the 21st century."
Medical and dental care in the United States are like estranged colleagues: nominally on the same team but rarely, if ever, in touch with each other. Some value-based payment arrangements may start to mend the rift, which could both improve overall health and reduce healthcare costs. “Health system leaders now have evidence that was not around five years ago showing that investing in dental care can have offsetting medical care cost savings,” says Marko Vujicic, Ph.D., chief economist and vice president at the American Dental Association’s Health Policy Institute. Vujicic has published research showing that periodontal care can lower the healthcare costs of people with Type 2 diabetes.

One notable value-based dental agreement is between Blue Cross Blue Shield of Massachusetts (BCBSMA) and 42 North Dental, a large dental group headquartered in Waltham, Massachusetts, outside Boston, comprising 24 practices. The two organizations signed a value-based contract, which they announced in February.

Under the agreement, BCBSMA will pay an incentive to 42 North Dental for the provider’s delivery of dental services to members with several conditions, including diabetes, some heart conditions and oral cancer, says Robert Lewando, D.D.S., MBA, executive director of BCBSMA’s Dental Blue plan. Pregnant women are also included. The additional services include extra dental cleanings and periodontal treatments, according to Lewando.

In September 2019, 17.8% of BCBSMA’s patients with diabetes received periodontal treatment at 42 North Dental, says Michael Scialabba, D.D.S., vice president of clinical affairs at 42 North Dental. By January 2020, that percentage had edged up to 20.5%. Scialabba wants it to improve to 50%. Incentive payments will be commensurate with 42 North Dental’s ability to improve that and other metrics, says Lewando.

Scialabba says 42 North Dental promotes the program in several ways: posters, automated messages and, among the staff, at team huddles. He notes that each practice includes periodontists and oral surgeons, in addition to general practice dentists, which encourages accountability across the team. “If you have five other colleagues in the group practice, you get criticized a lot. It holds you to a higher standard,” he adds. Typically, each 42 North Dental practice has about a dozen BCBSMA patients with these conditions, so the numbers aren’t overwhelming, says Scialabba.

Lewando says the agreement with 42 North Dental is a pilot project. If it’s successful, he hopes to expand it to all 6,300 dental providers in Massachusetts that have contracts with BCBSMA.

DentaQuest

DentaQuest, a dental and vision benefits company headquartered in Boston, has set up value-based metrics for 323,000 members in Oregon’s Medicaid program; the metrics are designed to emphasize preventive care, such as additional cleanings for people with diabetes. The program has been in place since 2012.

Advantage Dental, which is part of DentaQuest, contracts with 200 dentists to provide dental assessments, sealants and fluoride varnish to 50,000 children in schools and other settings in Oregon. Dentists are rewarded for achieving certain metrics, such as providing children and adults with access to dental services, timely dental assessment for children in foster care and comprehensive dental care for adults with diabetes. Kevin Boie, chief operations officer at Advantage Dental, says the practice has seen a 35% increase in dental sealants delivered to children over the past four years.

Aine Cryts is a healthcare writer based in Boston.
Cancer Care in the Time of COVID-19 and After

Patients and their oncologists are weighing the pros and cons of delaying treatment. Once the outbreak subsides, how might the practice of oncology change? by AINE CRYTS

COVID-19 is not an equal-opportunity illness. Older people and patients with chronic conditions are, on average, far more vulnerable to suffering serious illness and death from the disease than younger people without ongoing health problems. Although the data are not as clear, cancer patients are also among those vulnerable to the SARS-CoV-2 virus that causes COVID-19 and more likely to suffer its serious consequences.

Oncologists around the country, supported and informed by guidance from healthcare leaders and professional associations, are reviewing the available research and carefully weighing treatment decisions. Many patients, with their physician are wrestling with question of whether the risks associated with putting off their cancer treatment are greater than the risk of COVID-19.

Randall Oyer, M.D., a medical oncologist at Lancaster General Health, a health system in Lancaster, Pennsylvania, says that in addition to understanding that cancer patients are a vulnerable group, healthcare leaders need to recognize that cancer patients are at heightened risk of contracting COVID-19 in the hospital.

Oyer says research from early COVID-19 hot spots such as China, Italy and the Seattle area suggests that patients with lung, liver and some types of gastrointestinal tumors, as well as hematologic malignancies, are at greater risk of suffering COVID-19 than patients with other kinds of cancer. Sparse as these data may be, they should still guide decision-making by oncologists and healthcare leaders, Oyer says. Many professional associations are providing guidance to oncologists during the outbreak, including the Association of Community Cancer Centers (Oyer is the president), the American Society of Clinical Oncology, the American Society of Hematology, the American Society for Radiation Oncology and the American College of Surgeons.

‘Agility and collaboration’

Patients with cancers of the lung, the liver and possibly the gastrointestinal system are at increased risk of COVID-19 because the SARS-CoV-2 virus attaches to the angiotensin-converting enzyme 2 (ACE2) that is highly expressed in these organs and system, explains Oyer. ACE2 “paves the way” to cancer cells in these areas and acts a “welcome mat” for SARS-CoV-2, he says.

It’s a different story with hematologic cancers, which include the leukemias, the lymphomas and multiple myeloma. The cancers themselves reduce immunity and make people vulnerable to infection because they interfere with the production of healthy levels of lymphocytes. In addition, the treatment of hematologic cancers targets the immune system and the bone marrow to get rid of the malignant cells, but it also affects noncancerous cells, further suppressing the patient’s immunologic defenses.

Oyer describes the process as one in which “the bouncer’s been removed from the door” and can’t defend against the virus.

Masumi Ueda, M.D., M.A., assistant medical director for inpatient blood and bone marrow transplant at the Seattle Cancer Care Alliance, a hospital in its namesake city, says patients with compromised immune systems should adhere to the core recommendations for preventing COVID-19: Wash your hands, and maintain social distancing. “Aside from that, there’s not much more than we can do in the absence...”
of a vaccine,” she says.

Ueda was the lead author of an article in the April 2020 issue of the Journal of the National Comprehensive Cancer Network describing the changes that the Seattle cancer hospital made in response to the COVID-19 outbreak. The title is telling: “Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal.” Ueda and her colleagues mingled advice with brief accounts of the steps they took to respond to COVID-19:

- The first step is robust infection and environmental control. Patients with respiratory symptoms need to be triaged. In Seattle, wrote Ueda and her colleagues, they had early access to testing and could perform nasopharyngeal swabs on symptomatic patients that met COVID-19 testing criteria.

- Healthcare leaders need to strictly reinforce “stay at home when ill” policies and establish other policies for testing staff, tracking exposures and defining when people can return to work.

- Forming an “incident command” structure is necessary to centralize information. Leaders need to hold virtual town halls.

- Outpatient well visits were rescheduled or handled through telemedicine visits, and telemedicine capabilities and training were ramped up. Hours of operation were added to make sure that emergency departments and hospital resources were used only by those needing high-level care.

- Adjuvant therapy with curative intent for patients with solid tumors should likely proceed.

- Decisions about delaying treatment should factor in whether delays may lead to inpatient admissions for symptom palliation that would burden hospitals.

- Stem cell transplants and cellular immunotherapies provide curative treatment and can’t be delayed in many cases.

- By speaking to patients on the phone, surgeons optimized decision-making about delays in surgery.

- Oncology disease groups were given the job of determining which treatments might reduce the risks of immunosuppression. They also weighed whether treatments might be moved from an inpatient to outpatient setting or delayed.

Ueda’s area of expertise is in stem cell transplant. She says not much data exist about whether patients undergoing the procedure, which involves a period of severe immunosuppression, do in fact need intensive care, be put on a ventilator, or die than people without any comorbidities.

The prevalence of cancer in patients with COVID-19 is 2%.

The COVID-19 case-fatality rate among people with cancer is 7.6%.

Source: Guan et al., European Respiratory Journal, April 2020.

Source: Desai et al., JCO Global Oncology, published online on April 6, 2020.

Healthcare organizations should start planning now for when the worst of the outbreak is over.

“There’s going to be an incredible rush to the door of patients seeking treatment.”

J. Leonard Lichtenfeld, M.D., MACP, Deputy Chief Medical Officer at the American Cancer Society in its Atlanta headquarters

To delay or not to delay

The COVID-19 outbreak has put nearly every medical service on hold and forced patients and physicians to do some cost-benefit thinking about diagnosis and treatment, now and later. But the decision to delay cancer treatment is especially fraught, and the seesaw of cost-benefit, huge. Delay could give an aggressive cancer an opportunity to progress, but treatment may lower immunity. J. Leonard Lichtenfeld, M.D., MACP, deputy chief medical officer at the American Cancer Society in its Atlanta headquarters, says the society’s around-the-clock call center has received questions from many patients whose cancer treatments have been stopped or put on hold. “Every cancer center is struggling with this,” he says.

Richard Van Etten, M.D., Ph.D., a stem cell transplant specialist at the University of California, Irvine, and director of its Chao Family Comprehensive Cancer Center, says the decision to delay care depends on the type of treatment. For autologous stem cell transplants, which involve using the patient’s stem cells, continuing treatment is plausible if the patient doesn’t have COVID-19. Maintenance therapy is also an option for these patients and would allow them to undergo the procedure later.

Allogeneic stem cell treatment, which involve using stem cells from a donor, presents a greater challenge, says Van Etten, because these patients can be profoundly immunosuppressed for up to a year after treatment. Many of these patients can’t wait long for a transplant, so moving forward with the procedure, and ensuring the patient is isolated afterward, may make sense, provided they don’t have COVID-19.

Post-COVID-19 oncology

Oyer, a practicing oncologist for 40 years, describes himself as an optimist. He is challenging healthcare leaders and oncologists to use this experience with COVID-19 to transform cancer care. For example, patients undergoing treatment might be given the option of checkups using telehealth, which will increase convenience, he says. Oyer also notes how quickly medical journals have published articles about COVID-19. The evidence they have presented has helped professional organizations keep their guidelines timely and relevant.

Healthcare organizations should start planning now for when the worst of the outbreak is over, says Lichtenfeld. “There’s going to be an incredible rush to the door of patients seeking treatment,” he notes, and careful triage of patients is going to be important. He also recommends proactive communication with patients about when they will resume treatment. In addition, healthcare leaders must support staff members with employee assistance programs, he says.

“Everyone has a story,” Lichtenfeld says. “Everyone wants to be comforted, and staff will have emotional and community-based issues they have to deal with.”

Aine Cryts is a healthcare writer based in Boston.
Martin VanTrieste is not your typical CEO. When the 35-year veteran of the healthcare industry was offered the top role at Civica Rx in 2018, he agreed to come out of retirement on two conditions. First, he wasn’t going to uproot his family from Florida. Second, he would work only pro bono. “I think it adds a lot of credibility for a nonprofit company, especially when no one has ever heard of a nonprofit pharmaceutical company,” VanTrieste says. “It also put me on equal footing with our board of directors. I wanted them to understand that I was coming to them with the best interest of patients and our members.”

VanTrieste was hired after a phone call from Dan Liljenquist, senior vice president and chief strategy officer for Utah-based Intermountain Healthcare. Liljenquist had asked him a year earlier to come to Salt Lake City to be part of a group of 30 advisers to health systems looking to start their own generic drug company as a way of ending hospital drug shortages. Civica is Liljenquist’s brainchild, and he chairs its board. When he asked VanTrieste to become Civica’s leader, VanTrieste was reluctant. He said no multiple times because he wasn’t really looking for any post-retirement challenges. “I told him, ‘I really liked retirement, but more importantly, I am a manufacturing guy, not a CEO, and I don’t have those polished CEO skills,’” says VanTrieste. “He called me back and once again said he wanted me to be the CEO.” Eventually, VanTrieste’s wife, Cynthia, who is also a pharmacist, told him the mission was so important and persuaded him to take the job.

VanTrieste himself was impressed with the mission of the company, which is located in Lehi, Utah, just outside Salt Lake City. The company’s goal is to be an FDA-approved manufacturer that will either directly manufacture generic drugs or subcontract manufacturing to reputable contract organizations. American hospitals have been dealing with drug shortages off and on for the better part of two decades. Here at last was a solution. VanTrieste has long cared about the problem, and his resume, despite the lack of CEO sheen, made him a good fit for the top role at Civica.

Drugstore dream
So many career paths have accidental trailheads in summer jobs and seemingly random influences. “It’s a little bit of serendipity,” says VanTrieste. “When I was in high school, I got to work in a pharmacy as a short-order cook. The older pharmacist took a liking to me and brought me into the back and taught me what pharmacy was all about.” VanTrieste was so interested, he applied to pharmacy school at Temple University in Philadelphia. “My goal was to own my own drugstore, but the year before I graduated, I was offered a summer internship at Abbott Laboratories to do research and development (R&D),” VanTrieste explains. “That’s where I fell in love with industrial pharmacy.” His impressive resume includes a decade as chief quality officer at Amgen, plus stints as vice president of worldwide quality for Bayer Healthcare’s biological products division and vice president of quality assurance for Abbott Laboratories’ hospital products division.

“A key moment of my career was when I was approached to move out of an R&D role and go into manufacturing,” VanTrieste says. “It was in the hospital products division that I got all the experience and love for what we do at Civica, because many of the drugs that are on drug shortage today I formulated when I was a formulation pharmacist and I manufactured when I was in this division of Abbott.”

VanTrieste is also the founder of Rx-360, an international nonprofit based in Philadelphia that enhances patient safety by increasing security and quality in the biopharmaceutical supply chain. He has also served as chair of the Parenteral Drug Association’s board of directors.

Early days at Civica
Last year was Civica’s first full year in operation, and VanTrieste has helped the nonprofit grow to serve over 45 health systems comprising about 1,200 hospitals across the
country. He says the three goals he had for 2019 were to hire a high-performance leadership team (the company now has 28 employees), lay the groundwork for a company culture to serve patients and bring quality products into the market that are available and affordable, and get Civica’s first products launched. “We set a goal to launch 14 products, and we overachieved, with 19 products available to the marketplace by the end of 2019,” VanTrieste says.

VanTrieste says he and others at Civica have studied the drug shortage problem. “We realized that because of how the marketplace evolved and how the entire economics were broken, people awarded single-source contracts to the lowest possible bidder, who then had to cut costs and move supply chains to faraway lands. And when it broke, there was no other manufacturer that had the capacity or was ready to fill in that gap.” They contacted a number of manufacturers who did not get those exclusive contracts and who weren’t actively participating in the marketplace, and presented their unique business model.

Civica promised five-year guaranteed contracts in take-or-pay arrangements at fixed prices, an attractive offer to the manufacturers. Those terms meant the manufacturers Civica were more willing to invest in their operations. So the win-win cliche rang true, in this case a win for the manufacturers with which Civica contracts and another one for the health systems it supplies.

“We’re doing the research and development to get the FDA to approve our own abbreviated new drug applications (ANDAs), and we’re going to use contract manufacturers to make the product for us,” VanTrieste says. At the same, Civica is “actively engaged” in trying to buy a manufacturing facility and conferring with architectural firms about building its own manufacturing facility, he says.

Of course Civica is dealing with the COVID-19 epidemic. VanTrieste says demand has increased for broad-spectrum antibiotics, sedatives, pain management medications, neuromuscular blocking agents, and a variety of medications for comorbidities. “This a defining moment for Civica,” VanTrieste says, “one that demonstrates the model is working as designed to help stabilize the supply of essential generic medicines.”

Money matters
Civica’s member organizations make a one-time donation, with each of the seven healthcare systems and three philanthropies on the board committing $10 million. The second tier of members, known as founding members, puts up a one-time capital investment of $5 million and is part of the drug selection advisory and medical trends advisory committees. The next tier, known as partnering members, is open to all health systems and is priced at $300 per licensed hospital bed, with a cap of $1 million. “We raised a significant amount of capital, just shy of $200 million,” says VanTrieste.

Money will also come from a new Blue Cross Blue Shield Association partnership, which will put $100 million on the table for Civica to bring seven to 10 drugs to the retail market. The plan for this year is to bring 20 drugs to market and submit a series of products to the FDA for ANDA approval. Civica hopes to have 100 drugs on the market within five years.

Civica was conceived as the answer to hospital drug shortages. But VanTrieste says the organization is eyeing the retail side of the drug market carefully. “Another thing 2020 brings is a partnership with Blue Cross Blue Shield Association, and they want us to explore using Civica in the retail space,” he says. “We are actively studying what’s causing that high price and looking at developing a business model to fix that marketplace.”

Keith Loria is a freelance writer in northern Virginia.
Have pain? For many years, the answer has been to take a pill. But the opioid epidemic has shown the limitations — dangers — of sticking to just pharmacological approaches to one of the most common, fearsome health problems that people have, especially when the pain settles in as a chronic problem. Clinicians and entrepreneurs — and some patients — have a growing interest in nonpill approaches to pain treatment that use device technologies.

Virtual reality
Multiple virtual reality (VR) solutions now available have been effective in helping patients cope with acute pain. VR can be so absorbing that it takes people’s minds off their pain. For instance, VR applications can help women manage labor pains and even help with the sharp pain caused by removing a bandage. But chronic pain is complex and VR applications to help with it are still very much under development.

“Acute pain has been proved many times over to be treated very well through VR via distraction therapy,” says Sandra Marshall, a senior associate at the consulting firm Booz Allen Hamilton, who focuses on VR and other augmented reality technologies. “I’ll be curious to see where chronic pain goes in the VR space. It’s a newer application for VR technology, and, as chronic pain manifests itself differently in everyone, what might work for one individual might not work for the next,” she says.

Marshall says at-home mindfulness, meditation and breathing treatments coupled with VR in the office could help patients with pain. “There is a difference between a wellness app and a clinically prescribed pain management application. If people want to get a wellness app, they can easily get one and use that in the comfort of their home,” she says. “But if they want to use a clinical app specific to treating chronic pain, then it has to be prescribed and monitored by their doctor. Chronic pain therapy can be used both in a clinical setting and at home through a prescription service. That being said, acute pain management is more often used in just a clinical setting.”

For now, Marshall says, practitioners should implement VR in a pain management plan on a case-by-case basis. The devices are getting smaller, although most models are still about the size of a snorkeling mask, and they’re becoming more affordable. VR headsets on Amazon are priced as low as $35. Treating pain with VR “really has to be tailored to the patient, and we are still exploring what types of therapies we can offer in the form of VR treatment that will best help individuals suffering from chronic pain,” says Marshall. She also notes that gathering and analyzing data about chronic pain will help with the development of VR techniques.

Implant technology
Spinal cord stimulators are devices that involve placing electrodes between the spinal cord and the vertebrae in the epidural space. Why they relieve pain isn’t completely understood, but researchers believe that the electrical impulses

New Tech Delivers Needed Options for Treating Pain
The opioid epidemic has led doctors and patients to look for other ways to control pain, and they’re turning to technology for answers. by DONNA MARBURY

“We have studied and found that psychologically, it is very advantageous for chronically ill patients to get control of their chronic symptoms but not have constant reminders that they have a chronic illness.”
— ALLEN BURTON, M.D., MEDICAL DIRECTOR FOR NEUROMODULATION AT ABBOTT.
modulate dysregulated pain pathways. The impulses may also dilate blood vessels, thereby relieving ischemic pain. In this country, the most common indication is for chronic pain after failed back surgery. In Europe, practitioners use spinal stimulators to treat peripheral vascular disease. Yet studies of the efficacy of spinal cord stimulators have produced mixed results. Calculations of how many patients suffer complications vary greatly, from small minority to as many as 40%. Lead migration, when the electrodes move out of place, is one of the most common complications.

Medtronic, Boston Scientific and other large medical device companies offer spinal stimulators. One of the newest is Abbott’s Proclaim XR recharge-free device, which the FDA approved in September 2019. A key selling point is that it works at low doses, so the battery can go without recharging for 10 years, according to Abbott.

“Our device has a lot of unique aspects to it that are very patient centric,” notes Allen Burton, M.D., medical director for neuromodulation at Abbott. The stimulator works with Bluetooth and Apple iOS, allowing patients to fine-tune the settings within limits set by the physician. “The device controls patients’ pain and brings their symptoms down to a very tolerable level. The patient goes on about their life, and they don’t have to spend a lot of time making those subtle adjustments with the device,” he says.

Burton says the Proclaim XR is for patients with chronic pain who are stuck in a “chronic care cycle where they’re having a terrible quality of life and consuming lots of healthcare resources.” He adds, “We have studied and found that psychologically, it is very advantageous for chronically ill patients to get control of their chronic symptoms but not have constant reminders that they have a chronic illness. We’ve really taken time to engineer this in a very patient-centered way to achieve those goals.”

**Auricular vagus nerve stimulator**

The vagus nerve, the longest cranial nerve, travels down the body from the brainstem to the pharynx, larynx, trachea, heart and the entire gastrointestinal tract. But it also has two branches that go out to the auricle, or the external part of the ear. Transcutaneous auricular vagus nerve stimulators take advantage of this structure and the access it provides to the vagus nerve. They work by stimulating the vagus nerve with electrodes placed on the auricle.

The first auricular nerve stimulator to get the go ahead from the FDA was approved for acupuncture-like treatment in 2014. The IB-Stim device is a version of a transcutaneous auricular vagus nerve stimulator for the treatment of pain from irritable bowel syndrome. The FDA approved it last year for use in patients 11 to 18 years old. Innovative Health Solutions, a device company headquartered in Versailles, Indiana, markets IB-Stim and a similar device, sold as NSS-2 Bridge, for treating the symptoms of opioid withdrawal.

Katja K. Kovacic, M.D., a pediatric gastroenterologist at Children’s Hospital of Wisconsin in Milwaukee, says patients wear the IB-Stim device for five days straight, day and night, and then take it off for two days before seeing their doctor the following week for evaluation. She adds that depending on individual needs, a patient can use the device on this schedule for several months. Transcutaneous auricular vagus nerve stimulators are an attractive choice for younger people because many parents, as well as the patients themselves, don’t want to involve strong pain medications, observes Kovacic. Practitioners have so far treated more than 500 patients with the device, according to Kovacic.

Donna Marbury is a writer in Columbus, Ohio.

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Treating pain with VR “really has to be tailored to the patient, and we are still exploring what types of therapies we can offer in the form of VR treatment that will best help individuals suffering from chronic pain.” —SANDRA MARSHALL, A SENIOR ASSOCIATE AT THE CONSULTING FIRM BOOZ ALLEN HAMILTON
Let’s Remember That This Brought Out the Best in Us

As I sit at home, like most of you, I am amazed at how quickly the world has evolved from what we always knew and trusted to a new, unprecedented state of uncertainty in which we have no idea what the future will hold. In the six weeks that most of us have been sequestered in our homes, so much has happened. The whole world has seemingly closed down. In healthcare, we’ve seen a startling dichotomy: Emergency departments and ICUs in hot spot areas have been overrun, while elective surgeries have been canceled and hospitals and many physician offices avoided, except by individuals with COVID-19.

The pandemic and the need for us to all be #alonetogether have accelerated the acceptance and implementation of many ideas and models that prior to COVID-19 were considered back burner — potentially helpful but hardly top priority. The current situation has highlighted what has always been true: Being in an environment with potential exposure to infection, including and especially hospitals and physician offices, can be dangerous to one’s health. Now, more than ever, we must do everything we can to protect ourselves — and each other — from unnecessary exposure to infection.

To that end, an unprecedented amount of medical service has transitioned to telehealth. In the span of just days or weeks, many small and large practices with no prior telecare capability have pivoted to offering services via an electronic visit platform. They did so because the current situation of doing what we can to reduce transmission of the SARS-CoV-2 virus demanded it. In further efforts to support patients, insurance companies are waiving copays, relaxing prior authorization and other processes used to manage inappropriate utilization, and providing easier and more access for patients throughout the country. The pandemic presents a difficult situation for these companies. While many businesses are struggling to pay their premiums, resulting in lost revenue, health plans are simultaneously being asked to provide multimillion-dollar loans to support physician practices that have been financially decimated by the lack of procedures and in-person visits.

Many of these dynamics are largely invisible to the American public. Except for those on the front lines, the rest of us are on computers in our home offices or dining rooms, juggling home-schooling kids while preparing for Zoom calls, quieting barking dogs, looking professional (at least on top; it may be pajamas on the bottom), trying to master the art of video visiting (and wondering why we have not done this before)... the list goes on. We are attempting to maintain the normal in a situation that is anything but.

As a result, some remarkable things have happened. We have figured out creative ways to stay connected. We have softened. There’s more generosity of spirit, forgiveness, acceptance, understanding, compassion, gratitude — expressed all day, every day, in interactions between people all over the world. There’s laughter at our individual and collective lack of grace in figuring out how to manage in this time of uncertainty and use new (to many of us) technology.

We are cheering for healthcare workers, silently and out loud, alone but together. Every meeting begins with empathetic questions about how others are doing, and not just the toss-away “How are you?” of pre-COVID-19 times but a heartfelt “How are you, really?” And, in my experience, each meeting ends with genuine wishes of good health and safety. The outbreak has kindled a collective spirit.

We must, though, take care to protect those at greater risk and recognize that we are not all evenly affected by the virus. Those living with preexisting chronic and other conditions are at heightened risk, and older people, those living in nursing homes and African Americans have been disproportionately affected by suffering and death.

Let us remember the interconnectedness and dependency we feel today. And let us hold on to the generosity of spirit and the lessons we have learned as we move forward. We must bring both to our collective and ongoing work of managing healthcare. These respectful, thoughtful interactions are precisely what will spark our collaborative innovation and ensure the best care for all of us.

Lili Brillstein is CEO of BCollaborative, which provides strategic advisory services to stakeholders across the healthcare continuum, and a member of the Managed Healthcare Executive editorial advisory board.
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