JOURNAL of MANAGED CARE MEDICINE

Vol. 26, No. 3, 2023

Educating Medical Directors of Employers, Health Plans and Provider Systems

FEATURED ARTICLES INCLUDE:

Innovative Approaches in the Treatment and Management of HER2-Positive Advanced Breast Cancer: Key Considerations in Managed Care Decision-Making

Managed Care Considerations in the Treatment of Hereditary Angioedema: Optimizing Decision-Making Strategies for Improved Clinical and Economic Outcomes

Recent Advances in the Management of Amyotrophic Lateral Sclerosis

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JOURNAL OF MANAGED CARE MEDICINE

4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
Thomas Morrow, MD

PUBLISHER
Jeremy Williams

ADVERTISING REPRESENTATIVE
Maria Sercia
American Medical Communications, Inc.
msercia@americanmedicalcomm.com
(267) 614-6809

JOURNAL MANAGEMENT
Douglas Murphy Communications
Richmond, Virginia
(804) 387-7580

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
Douglas Murphy Communications

ISSN: 1094-1525. The ***Journal of Managed Care Medicine*** is published by NAMCP Medical Directors Institute. Corporate and Circulation offices: 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060; Tel (804) 527-1905; Fax (804) 747-5316. Editorial and Production offices: 15 Bridgehampton Place, Richmond, VA 23229; Tel (804) 387-7580. Advertising offices: Sloane Reed, 4435 Waterfront Drive Ste 101, Glen Allen, VA 23060 Tel (804) 527-1905, Fax (804) 747-5316.

POSTMASTER: Send address changes to The Journal of Managed Care Medicine, 4435 Waterfront Drive, Suite 101, Glen Allen, VA 23060.

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Journal of Managed Care Medicine

The Official Journal of the NAMCP MEDICAL DIRECTORS INSTITUTE

A Peer-Reviewed Publication

Vol. 26, No. 3, 2023

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FOR ADULTS WITH SCHIZOPHRENIA OR BIPOLAR I OR II DISORDER,

LET'S FIND COMMON GROUND IN THE TREATMENT OF AGITATION

Not an actual patient or healthcare provider.

IGALMI is a sublingual film purposefully designed to support a cooperative approach to agitation intervention[1,2]

INDICATION

IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. **Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension. Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death, including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia, or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions, Tolerance, and Tachyphylaxis: IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence, a withdrawal syndrome, tolerance, and/or tachyphylaxis if IGALMI is used in a manner other than indicated.

IGALMI IS THE FIRST AND ONLY SUBLINGUAL FILM FORMULATION OF DEXMEDETOMIDINE

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg, 180 mcg

- **TARGETS** a key mediator of agitation[1,3,4]*
- **NONINVASIVE** sublingual film with a mucoadhesive design, so it cannot be spit out[1,4]
- **PATIENT ADMINISTERED** under the supervision of a healthcare provider[1]

Learn more about the proven reduction in agitation related to schizophrenia and bipolar I or II disorder at IGALMIhcp.com

*IGALMI reduces the release of norepinephrine, a key mediator among other neurotransmitters thought to be involved in agitation.[1,3,4]

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

DRUG INTERACTIONS

Drugs That Prolong the QT Interval: Avoid use. Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use may cause enhanced CNS-depressant effects. Reduction in dosage of IGALMI or the concomitant medication should be considered.

USE IN SPECIFIC POPULATIONS

Hepatic Impairment and Geriatric Patients (≥65 years old): A lower dose is recommended in patients with hepatic impairment and geriatric patients. See the full Prescribing Information for the recommended dosage depending on the agitation severity.

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

To report SUSPECTED ADVERSE REACTIONS, contact BioXcel Therapeutics, Inc. at 1-833-201-1088 or medinfo@bioxceltherapeutics.com, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References: 1. IGALMI. Package insert. BioXcel Therapeutics, Inc.; 2022. **2.** Wilson MP, et al. *West J Emerg Med*. 2012;13(1):26-34. doi:10.5811/westjem.2011.9.6866 **3.** Miller CWT, et al. *West J Emerg Med*. 2020;21(4):841-848. doi:10.5811/westjem.2020.4.45779 **4.** Data on file. BXCL501-301 CSR (SERENITY I). BioXcel Therapeutics, Inc.; January 2021.

bioxcel therapeutics®

Igalmi™
(dexmedetomidine)
sublingual film · 120 mcg,180 mcg

IGALMI™ (dexmedetomidine) sublingual film, for sublingual or buccal use. Rx Only. Brief Summary of Prescribing Information (PI) for IGALMI. See full PI.

Indication: IGALMI is indicated for the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder in adults. Limitations of Use: The safety and effectiveness of IGALMI have not been established beyond 24 hours from the first dose.

Important Recommendations Prior to Initiating IGALMI and During Therapy: IGALMI should be administered under the supervision of a healthcare provider. A healthcare provider should monitor vital signs and alertness after IGALMI administration to prevent falls and syncope.

IGALMI is for sublingual or buccal administration. Do not chew or swallow IGALMI. Do not eat or drink for at least 15 minutes after sublingual administration, or at least one hour after buccal administration.

Recommended Dosage: The initial dose of IGALMI is based on agitation severity, with lower doses recommended in patients with hepatic impairment and geriatric patients. If agitation persists after the initial dose, up to two additional doses may be administered at least two hours apart, depending upon the patient population and agitation severity. Assess vital signs including orthostatic measurements prior to the administration of any subsequent doses. Due to risk of hypotension, additional half-doses are not recommended in patients with systolic blood pressure (SBP) less than 90 mmHg, diastolic blood pressure (DBP) less than 60 mmHg, heart rate (HR) less than 60 beats per minute, or postural decrease in SBP ≥ 20 mmHg or in DBP ≥ 10 mmHg.

The recommended dose in adults is 120 mcg for mild or moderate agitation and 180 mcg for severe agitation. Patients with mild or moderate hepatic impairment and mild to moderate agitation should receive 90 mcg. Patients with mild or moderate hepatic impairment and severe agitation should receive 120 mcg. Patients with severe hepatic impairment and mild to moderate agitation should receive 60 mcg. Patients with severe hepatic impairment and severe agitation should receive 90 mcg. Geriatric patients (patients ≥65 years old) with mild, moderate or severe agitation should receive 120 mcg. See Full Prescribing Information for recommendations on administering up to two additional doses and maximum recommended dosages.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Hypotension, Orthostatic Hypotension, and Bradycardia: IGALMI causes dose-dependent hypotension, orthostatic hypotension, and bradycardia. In clinical studies, 18%, 16%, and 9% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced orthostatic hypotension (defined as SBP decrease ≥ 20 mmHg or DBP decrease ≥ 10 mmHg after 1, 3, or 5 minutes of standing) at 2 hours post-dose. In those studies, 7%, 6%, and 1% of patients treated with 180 mcg of IGALMI, 120 mcg of IGALMI, and placebo, respectively, experienced HR ≤ 50 beats per minute within 2 hours of dosing. In clinical studies with IGALMI, patients were excluded if they had treatment with alpha-1 noradrenergic blockers, benzodiazepines, other hypnotics or antipsychotic drugs four hours prior to study drug administration; had a history of syncope or syncopal attacks; SBP < 110 mmHg; DBP < 70 mmHg; HR < 55 beats per minute; or had evidence of hypovolemia or orthostatic hypotension.

Reports of hypotension and bradycardia, including some resulting in fatalities, have been associated with the use of another dexmedetomidine product given intravenously (IGALMI is for sublingual or buccal use and is not approved for intravenous use). Clinically significant episodes of bradycardia and sinus arrest have been reported after administration of this other dexmedetomidine product to young, healthy adult volunteers with high vagal tone and when this product was given by rapid intravenous or bolus administration.

Because IGALMI decreases sympathetic nervous system activity, hypotension and/or bradycardia may be more pronounced in patients with hypovolemia, diabetes mellitus, or chronic hypertension, and in geriatric patients. Avoid use of IGALMI in patients with hypotension, orthostatic hypotension, advanced heart block, severe ventricular dysfunction, or history of syncope. After IGALMI administration, patients should be adequately hydrated and should sit or lie down until vital signs are within normal range. If a patient is unable to remain seated or lying down, precautions should be taken to reduce the risk of falls. Ensure that a patient is alert and not experiencing orthostatic hypotension or symptomatic hypotension prior to allowing them to resume ambulation.

QT Interval Prolongation: IGALMI prolongs the QT interval. Avoid use of IGALMI in patients at risk of torsades de pointes or sudden death including those with known QT prolongation, a history of other arrhythmias, symptomatic bradycardia, hypokalemia or hypomagnesemia, and in patients receiving other drugs known to prolong the QT interval.

Somnolence: IGALMI can cause somnolence. In placebo-controlled clinical studies in adults with agitation associated with schizophrenia or bipolar I or II disorder, somnolence (including fatigue and sluggishness) was reported in 23% and 22% of patients treated with IGALMI 180 mcg and 120 mcg, respectively, compared to 6% of placebo-treated patients. Patients should not perform activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery, for at least eight hours after taking IGALMI.

Risk of Withdrawal Reactions: Symptoms of withdrawal have been observed after procedural sedation with another dexmedetomidine product administered intravenously. In this study, 12 (5%) adult patients who received intravenous dexmedetomidine up to 7 days (regardless of dose) experienced at least 1 event related to withdrawal within the first 24 hours after discontinuing dexmedetomidine and 7 (3%) adult patients who received intravenous dexmedetomidine experienced at least 1 event related with withdrawal 24 to 48 hours after discontinuing dexmedetomidine. The most common withdrawal reactions were nausea, vomiting, and agitation. In these subjects, tachycardia and hypertension requiring intervention occurred at a frequency of <5% in the 48 hours following intravenous dexmedetomidine discontinuation. IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated.

Tolerance and Tachyphylaxis: Use of another dexmedetomidine product administered intravenously beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions. IGALMI was not studied for longer than 24 hours after the first dose. There may be a risk of tolerance and tachyphylaxis if IGALMI is used in a manner other than indicated.

ADVERSE REACTIONS, Clinical Studies 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 clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IGALMI was evaluated in 507 adult patients with agitation associated with schizophrenia (N=255) or bipolar I or II disorder (N=252) in two randomized, placebo-controlled studies (Studies 1 and 2). In both studies, patients were admitted to a clinical research unit or a hospital and remained under medical supervision for at least 24 hours following treatment. Patients were 18 to 71 years of age (mean age was 46 years old); 45% were female and 55% were male; 66% were Black, 31% were White, 2% were multiracial, and 1% were other.

In these studies, patients received an initial dose of IGALMI 180 mcg (N=252), IGALMI 120 mcg (N=255), or placebo (N=252). Patients who were hemodynamically stable (i.e., those with systolic blood pressure (SBP) > 90 mmHg, diastolic blood pressure (DBP) > 60 mmHg, and heart rate (HR) > 60 beats per minute) and without orthostatic hypotension (i.e., reduction in SBP < 20 mmHg or DBP < 10 mmHg upon standing) were eligible for an additional dose after 2 hours. An additional half dose (90 mcg, 60 mcg, or placebo) was given to 7.1% (18/252), 22.7% (58/255) and 44.0% (111/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg or placebo arms, respectively. After at least an additional 2 hours, an additional second half dose (total IGALMI dose of 360 mcg, total IGALMI dose of 240 mcg, or placebo, respectively) was given to 3.2% (8/252), 9.4% (24/255), and 21.0% (53/252) of patients in the IGALMI 180 mcg, IGALMI 120 mcg or placebo arms, respectively.

In these studies, one patient discontinued treatment due to an adverse reaction of oropharyngeal pain.

The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) were: somnolence, oral paresthesia or oral hypoesthesia, dizziness, dry mouth, hypotension, and orthostatic hypotension.

Adverse reactions that occurred in IGALMI-treated patients at a rate of at least 2% and at a higher rate than in placebo-treated patients in Studies 1 and 2 were as follows (adverse reaction is followed by percentage of patients treated with IGALMI 180 mcg (n = 252), IGALMI 120 mcg (n = 255) and placebo (n = 252): Somnolence, includes the terms fatigue and sluggishness, (23%, 22%, 6%); Oral paresthesia or oral hypoesthesia (7%, 6%, 1%); Dizziness (6%, 4%, 1%); Hypotension (5%, 5%, 0%); Orthostatic hypotension (5%, 3%, <1%); Dry Mouth (4%, 7%, 1%); Nausea (3%, 2%, 2%); Bradycardia (2%, 2%, 0%); Abdominal discomfort, including dyspepsia, gastroesophageal reflux disease (2%, 0%, 1%).

Hypotension, Orthostatic Hypotension, and Bradycardia in Two Placebo-Controlled Studies: In clinical studies, patients were excluded if they were treated with alpha-1 noradrenergic blockers, benzodiazepines, antipsychotic drugs, or other hypnotics four hours prior to study drug administration; had a history of syncope or syncopal attacks; their SBP was less than 110 mmHg; their DBP was less than 70 mmHg; their HR was less than 55 beats per minute; or they had evidence of hypovolemia or orthostatic hypotension. In these studies, vital signs were monitored (at 30 minutes, 1-, 2-, 4-, 6-, and 8- hours post-dose), including orthostatic vital signs at 2-, 4-, and 8-hours post-dose. Maximum positional decreases in SBP and DBP after standing were observed at two hours post-dose. Maximal reductions on BP and HR were observed two hours post-dose.

The mean BP (in mmHg) and HR decrease (in bpm) across all patients from both studies at 2 hours post-dose were as follows for patients treated with IGALMI 180 mcg (n = 252), IGALMI 120 mcg (n = 255) and placebo (n = 252): Mean SBP Decrease (15, 13, 1), Mean DBP Decrease (mmHg) (8, 7, <1), Mean Heart Rate Decrease (9, 7, 3). In the clinical studies: 13%, 8%, and <1% of patients in the single dose 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, experienced SBP ≤ 90 mmHg and a decrease ≥ 20 mmHg of SBP within 24 hours of dosing; 19%, 17%, and 2% of the patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a DBP ≤ 60 mmHg and a DBP decrease ≥ 10 mmHg within 24 hours of dosing; 4%, 3%, and 0% of patients in the 180 mcg IGALMI, 120 mcg IGALMI, and placebo groups, respectively, had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute within 24 hours of dosing.

At 8 hours post-dose, 2% of patients in the IGALMI 180 mcg group experienced a SBP ≤ 90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 24 hours, none of the patients in the IGALMI 180 mcg group experienced a SBP ≤90 mmHg and decrease ≥ 20 mmHg compared with one patient (<1%) in the IGALMI 120 mcg group and none in the placebo group. At 8 hours post-dose, none of the patients in the IGALMI 180 mcg group had a HR ≤ 50 beats per minute and a HR decrease ≥ 20 beats per minute compared with one patient in the 120 mcg group (<1%) and none in the placebo group.

Postmarketing Experience

The following adverse reactions have been identified during post approval use of another dexmedetomidine product given intravenously (IGALMI is not approved for intravenous use). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Anemia; *Cardiac Disorders:* Arrhythmia, atrial fibrillation, atrioventricular block, bradycardia, cardiac arrest, cardiac disorder, extrasystoles, myocardial infarction, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular tachycardia; *Eye Disorders:* Photopsia, visual impairment; *Gastrointestinal Disorders:* Abdominal pain, diarrhea, nausea, vomiting; *General Disorders and Administration Site Conditions:* Chills, hyperpyrexia, pain, pyrexia, thirst; Hepatobiliary Disorders: Hepatic function abnormal, hyperbilirubinemia; Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood urea increased, electrocardiogram T wave inversion, gammaglutamyltransferase increased, electrocardiogram QT prolonged; *Metabolism and Nutrition Disorders:* Acidosis, hyperkalemia, hypoglycemia, hypovolemia, hypernatremia; *Nervous System Disorders:* Convulsion, dizziness, headache, neuralgia, neuritis, speech disorder; *Psychiatric Disorders:* Agitation, confusional state, delirium, hallucination, illusion; *Renal and Urinary Disorders:* Oliguria, polyuria; *Respiratory, Thoracic and Mediastinal Disorders:* Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion, respiratory acidosis; *Skin and Subcutaneous Tissue Disorders:* Hyperhidrosis, pruritus, rash, urticaria; *Surgical and Medical Procedures:* Light anesthesia;

Vascular Disorders: Blood pressure fluctuation, hemorrhage, hypertension, hypotension

DRUG INTERACTIONS

Drugs that Prolong the QT Interval: Concomitant use of drugs that prolong the QT interval may add to the QT-prolonging effects of IGALMI and increase the risk of cardiac arrhythmia. Avoid the use of IGALMI in combination with other drugs known to prolong the QT interval.

Anesthetics, Sedatives, Hypnotics, and Opioids: Concomitant use of IGALMI with anesthetics, sedatives, hypnotics, or opioids is likely to lead to enhanced CNS depressant effects. Specific studies with another dexmedetomidine product given intravenously have confirmed these effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. Due to possible enhanced CNS effects when given concomitantly with IGALMI, consider a reduction in dosage of IGALMI or the concomitant anesthetic, sedative, hypnotic, or opioid.

USE IN SPECIFIC POPULATIONS

Pregnancy, Risk Summary: There are no available data on IGALMI use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal effects. Available data from published randomized controlled trials and case reports over several decades of use with intravenously administered dexmedetomidine during pregnancy have not identified a drug-associated risk of major birth defects or miscarriage; however, the reported exposures occurred after the first trimester. Most of the available data are based on studies with exposures that occurred at the time of cesarean-section delivery, and these studies have not identified an adverse effect on maternal outcomes or infant Apgar scores. Available data indicate that dexmedetomidine crosses the placenta.

In animal reproductive studies fetal toxicity occurred in the presence of maternal toxicity with subcutaneous administration of dexmedetomidine to pregnant rats during organogenesis at doses 5 times the maximum recommended human dose [MRHD] of 360 mcg/day based on mg/m^2 body surface area. Adverse developmental effects, including early implantation loss and decreased viability of second generation offspring, occurred when pregnant rats were subcutaneously administered doses less than or equal to the MRHD based on mg/m^2 from late pregnancy through lactation and weaning *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population 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 to 4% and 15 to 20%, respectively.

Data: *Animal Data*: Increased post-implantation losses and reduced live pups in the presence of maternal toxicity (decreased body weight) occurred in a rat embryo-fetal development study in which pregnant dams were administered subcutaneous doses of dexmedetomidine of 200 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (Gestation Day (GD) 5 to 16). No embryo-fetal toxicity was observed at 20 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2). No malformations were reported at any dose level.

No malformation or embryo-fetal toxicity were observed in a rabbit embryo-fetal developmental study in which pregnant dams were administered dexmedetomidine intravenously at doses up to 96 mcg/kg/day (equivalent to 5 times the MRHD of 360 mcg/day based on mg/m^2) during the period of organogenesis (GD 6 to 18).

Reduced pup and adult offspring weights and grip strength were reported in a rat developmental toxicology study in which pregnant females were administered dexmedetomidine subcutaneously at 8 mcg/kg/day (less than the MRHD of 360 mcg/day based on mg/m^2) during late pregnancy through lactation and weaning (GD 16 to postnatal day [PND] 25). Decreased viability of second generation offspring and an increase in early implantation loss along with delayed motor development occurred at 32 mcg/kg/day (equivalent to the MRHD of 360 mcg/day based on mg/m^2) when first generation offspring were mated. This study limited dosing to hard palate closure (GD 15-18) through weaning instead of standard dosing from implantation (GD 6-7) to weaning (PND 21).

Lactation, *Risk Summary*: Available published literature report the presence of dexmedetomidine in human milk following intravenous administration. There is no information regarding the effects of dexmedetomidine on the breastfed child or the effects on milk production. Advise women to monitor the breastfed infant for irritability. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IGALMI and any potential adverse effects on the breastfed child from IGALMI or from the underlying maternal condition.

Pediatric Use: The safety and effectiveness of IGALMI have not been established in pediatric patients.

Geriatric Use: Fifteen geriatric patients (≥ 65 years of age) were enrolled (no patients were 75 years of age and older) in the clinical studies for acute treatment of agitation associated with schizophrenia or bipolar I or II disorder. Of the total number of IGALMI-treated patients in these clinical studies, 11/507 (2.2%) were 65 years of age and older. Dosage reduction of IGALMI is recommended in geriatric patients. A higher incidence of bradycardia and hypotension was observed in geriatric patients compared to younger adult patients after intravenous administration of another dexmedetomidine product. The pharmacokinetic profile of intravenous dexmedetomidine was not altered in geriatric subjects. Clinical studies of IGALMI did not include sufficient numbers of patients 65 years of age and older to determine whether there were differences in the effectiveness of IGALMI in the acute treatment of agitation associated with schizophrenia or bipolar I or II disorder compared to younger adult patients.

Hepatic Impairment: Dexmedetomidine clearance was decreased in patients with hepatic impairment (Child-Pugh Class A, B, or C). Thus, a dosage reduction of IGALMI is recommended in patients with hepatic impairment compared to patients with normal hepatic function.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: IGALMI contains dexmedetomidine, which is not a controlled substance.

Dependence, Physical Dependence: Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. The dependence potential of dexmedetomidine has not been studied in humans. However, because studies in rodents and primates have demonstrated that intravenous dexmedetomidine exhibits pharmacologic actions similar to those of clonidine, it is possible that dexmedetomidine may produce a clonidine-like withdrawal syndrome upon abrupt discontinuation. IGALMI was not studied for longer than 24 hours after the first dose. There may be risk of physical dependence and a withdrawal syndrome if IGALMI is used in a manner other than indicated.

Tolerance: Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). IGALMI has not been studied for longer than 24 hours after the first dose. There may be a risk for tolerance if IGALMI is administered in a manner other than indicated.

OVERDOSAGE: In a tolerability study of intravenous dexmedetomidine in which healthy adult subjects were administered doses at and above the recommended dose of 0.2 to 0.7 mcg/kg/hour, the maximum blood concentration was approximately 13 times the upper boundary of the therapeutic range for the intravenous dexmedetomidine (IGALMI is not approved for intravenous use). The most notable effects observed in two subjects who achieved the highest doses were first degree atrioventricular block and second-degree heart block.

Five adult patients received an overdose of intravenous dexmedetomidine in intensive care unit sedation studies. Two patients who received a 2 mcg/kg loading dose (twice the recommended loading dose) over 10 minutes, experienced bradycardia and/or hypotension. One patient who received a loading intravenous bolus dose of undiluted dexmedetomidine (19.4 mcg/kg), had cardiac arrest from which he was successfully resuscitated.

Consider contacting a Poison Center (1-800-222-1222) or a medical toxicologist for overdosage management recommendations for IGALMI.

Distributed by: BioXcel Therapeutics, Inc., 555 Long Wharf Drive 12th Floor New Haven, CT 06511

US-IGA-2300016 February 2023

Innovative Approaches in the Treatment and Management of HER2-Positive Advanced Breast Cancer: Key Considerations in Managed Care Decision-Making

Jane Lowe Meisel, MD

This journal article is supported by educational grants from AstraZeneca; Daiichi Sankyo; Seagen.

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

The treatment of HER2-positive metastatic breast cancer has been transformed by targeted therapy; although previously associated with poor outcomes and higher mortality rates compared with other breast cancer subtypes, survival is now equivalent to hormone receptor positive disease. Due to the new treatment options available, patients can undergo many lines of therapy all of which provide some improvement in survival.

Key Points

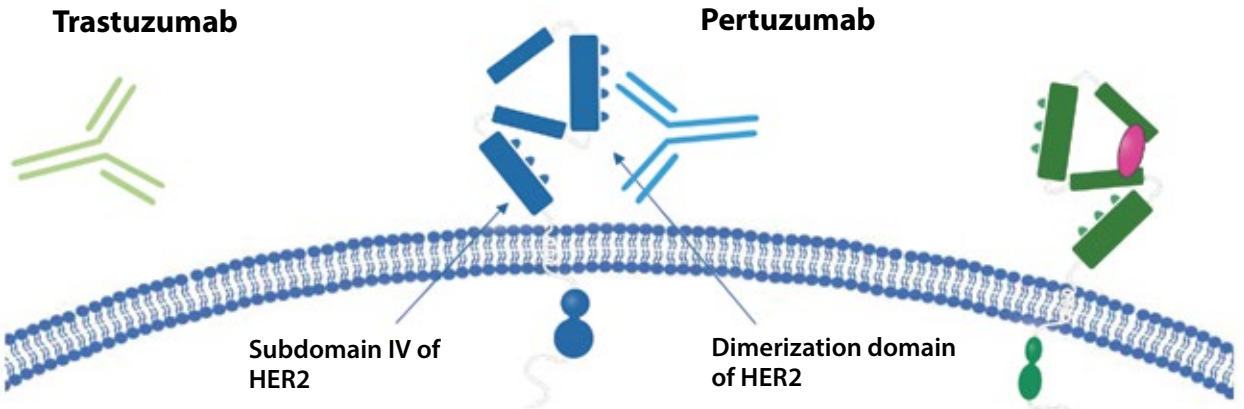
- Several new treatment options are now available.
- Given all the options available, shared decision making and optimization of adverse events becomes even more important.
- Choosing the right treatment for the right patient, and maximizing communication and adverse event management, cuts costs for all.

PRODUCTION OF HIGH LEVELS OF THE protein HER2 (human epidermal growth factor 2) is present in 14 percent of breast cancers.[1] According to Surveillance, Epidemiology, and End Results (SEER) data, approximately 55,000 new cases of HER2-positive breast cancer will be diagnosed in the United States in 2022.

Knowing HER2 status can impact treatment and help predict patterns of disease progression and prognosis. HER2-positive breast cancer is aggressive and fast-growing and was previously associated with poor outcomes and higher mortality rates than other breast cancer subtypes. HER2-positive metastatic breast cancer is more likely to metastasize to the liver and lungs and has a high propensity for metastasis to the brain compared to other subtypes of breast cancer. Due to the development of HER2-targeted agents, HER2-positive metastatic breast cancer (mBC) is now a treatable disease and outcomes have dramatically improved for these patients. Survival is now equivalent to those with hormone receptor positive disease. HER2 testing is routinely performed for newly diagnosed and metastatic breast cancer.

Trastuzumab, the first HER2-targeted therapy, was approved in 1998 and revolutionized treatment of HER2-positive disease; pertuzumab was approved in 2012 and further improved treatment. Exhibit 1 illustrates how these two monoclonal antibodies target HER2-positive breast cancer cells in diverse ways. These two agents are now given together along with chemotherapy as standard treatment for HER2-positive mBC because of improved overall survival (OS). In a pivotal trial (Cleopatra), median OS was 57.1 months in those receiving pertuzumab/

Exhibit 1: HER2 Targeted Therapy



- Trastuzumab does not inhibit HER2 dimerization, thus, blocking HER2:HER3
- Trastuzumab prevents HER2 receptor shedding
- Trastuzumab blocks HER2 signaling and flags cells for destruction by the immune system

- Pertuzumab inhibits HER2 from forming dimer pairs
- Flags cells for destruction by the immune system
- Pertuzumab does not prevent HER2 receptor shedding

trastuzumab/docetaxel and 40.8 months in those receiving placebo/trastuzumab/docetaxel (hazard ratio [HR] 0.69); eight-year landmark overall survival rates were 37 percent in the pertuzumab group and 23 percent in the placebo group.[2] Usually taxane chemotherapy is stopped after six to eight cycles and trastuzumab/pertuzumab is continued every three weeks until disease progression. The National Comprehensive Cancer Network (NCCN) Guidelines recommendations for treating HER2-positive mBC are shown in Exhibit 2.[3]

With disease progression, there are several treatment options. Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate, where a chemotherapy drug is linked to trastuzumab. The chemotherapy is carried to the cancer cell overexpressing HER2 and released there, causing cell death. This conjugate has been shown to be more effective than other drugs after patients have progression on trastuzumab/pertuzumab-based combinations.[4,5] Fam-trastuzumab deruxtecan (TDxd) is a newer antibody-drug conjugate that also kills HER2-positive cancer cells by delivering chemotherapy directly into HER2-positive cells but also has the ability to kill neighboring non-HER2-positive tumor cells (bystander killing) due to high cell membrane permeability. The bystander killing has led to it also being evaluated in non-HER2-positive breast cancer. It also delivers a higher chemotherapy payload than ado-trastuzumab emtansine. In a heavily pretreated HER2-positive mBC population, there was a 61 percent response rate with this agent with a 6 percent complete response and a 14.8-month duration of response in a nonrandomized study which led to FDA-accelerated approval.[6] The estimated median OS was 24.6 months with 85 percent of patients alive at 12 months and 74 percent at 18 months. In a trial comparing fam-trastuzumab deruxtecan and ado-traztusumab emtansine in patients with HER2-positive mBC previously treated with trastuzumab and a taxane, the percentage of those who were alive without disease progression at 12 months was 75.8 percent with trastuzumab deruxtecan and 34.1 percent with trastuzumab emtansine (HR for progression or death from any cause, 0.28; $p < 0.001$).[7] The percentage of patients who were alive at 12 months was 94.1 percent and 85.9 percent, respectively (HR for death, 0.55; prespecified significance boundary not reached). An overall response (a complete or partial response) occurred in 79.7 percent and 34.2 percent, respectively. The incidence of adverse events of any grade was 98.1 percent with trastuzumab deruxtecan and 86.6 percent with trastuzumab emtansine, and the incidence of drug-related adverse events of Grade 3 or 4 was 45.1 percent and 39.8 percent, respectively. Interstitial lung diseases are known adverse events of these two agents. Adjudicated drug-related

Exhibit 2: NCCN Guidelines for Advanced HER2-positive Breast Cancer[3]

Setting	Regimen
First-Line	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second-Line	Fam-trastuzumab deruxtecan (Category 1, preferred)
Third-Line	Tucatinib + trastuzumab + capecitabine (Category 1, preferred, option for 2nd line)
	Ado-trastuzumab emtansine (T-DM1)
Fourth-Line and Beyond (optimal sequence is not known)	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents
	Neratinib + capecitabine
	Margetuximab + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)

interstitial lung disease occurred in 10.5 percent of the patients in the trastuzumab deruxtecan group and in 1.9 percent of those in the trastuzumab emtansine group; none of these events were of Grade 4 or 5. The results of this trial led to fam-trastuzumab deruxtecan being recommended over trastuzumab emtansine for second-line treatment. Once patients progress on the triple regimen of pertuzumab/trastuzumab/taxane, fam-trastuzumab deruxtecan is the NCCN preferred option, unless the patient has central nervous system (CNS) metastases. [3] The NCCN Guidelines also note that fam-trastuzumab deruxtecan can be considered as first-line treatment for those patients with rapid progression within six months of neoadjuvant or adjuvant therapy (12 months for pertuzumab containing regimen).[3] Trastuzumab emtansine has moved from a second-line option to third-line.

Oral tyrosine kinase inhibitors (tucatinib, neratinib, lapatinib) are treatment options in the third-line. Tucatinib in combination with trastuzumab and capecitabine is preferred in the NCCN Guidelines in those with both systemic and CNS progression for third-line treatment.[3] This combination is also an option instead of fam-trastuzumab deruxtecan in second-line treatment if CNS disease is present. Tucatinib is preferred over the other agents because of increased specificity for HER2, demonstrated CNS activity, and improved OS compared to a regimen without tucatinib. The HER2 specificity reduces off target adverse events, particularly those related to epidermal growth factor receptor effects (rash, diarrhea). CNS activity is important because up to 50 percent of those with HER2-positive mBC will develop brain metastases. In the HER2Climb trial, tucatinib/trastuzumab/capecitabine treatment produced a median duration of OS of 24.7 months versus 19.2 months for placebo/trastuzumab/capecitabine (HR for death: 0.73, p = 0.004) and OS at two years was 51 percent and 40 percent, respectively.[8] Hazard ratios for OS across prespecified subgroups (including stable and active brain metastases) were consistent with the HR for the overall study population.

Toxicity is minimal due to tucatinib's targeted nature. The most common side events with tucatinib/trastuzumab/capecitabine are diarrhea and hand-foot syndrome and can be alleviated by capecitabine dose reduction. Choice of this regimen versus fam-trastuzumab deruxtecan in the second-line must take multiple factors into account including presence of brain metastases, how much disease is present in the body, what kind of symptoms patients have, and patient preferences regarding adverse event profiles, pill burden, and dosing schedules.

Another new option for third-line or later is margetuximab in combination with chemotherapy. Margetuximab is an Fc-engineered monoclonal antibody with an improved binding to FcγRIIIA receptor, which leads to a greater antibody-

dependent cellular cytotoxicity (ADCC) activation compared with trastuzumab. It has the same specificity and affinity to HER2 as trastuzumab, with similar ability to disrupt cell signaling. The unique feature of this agent is due to differential affinities for certain antibodies involved in immune recognition of foreign cells, margetuximab may enhance the immune system's ability to help fight cancer as well. In the Sophia trial, margetuximab was shown to slightly improve progression-free survival (PFS) compared with trastuzumab for the treatment of HER2-positive mBC patients but provided no difference in median OS (21.6 versus 21.9 months).[9] The place for this therapy is currently third-line and beyond but data are accumulating that it may be more effective in patients with a CD16A F allele, especially those who are homozygous (CD16A FF). In the Sophia trial, the median OS in those with CD16A FF was 23.6 months with margetuximab versus 19.2 months with trastuzumab ($p = 0.052$).[9] Given cost and modest benefits over trastuzumab, this is reserved for later lines of treatment.

The most recent advance in HER2-related disease is the approval of fam-trastuzumab deruxtecan for HER2-low disease. The HER2-low category includes those who have borderline immunohistochemistry (IHC) scores of 1+ and 2+; HER2-positive is defined as a score of 3+. Approximately 60 percent of people with HER2-negative breast cancer fall into this HER2-low category.[10] Low HER2 expression occurs in both hormone receptor positive and negative breast cancer and has previously not been actionable. In the DESTINY-Breast04 trial, patients with previously treated HER2-low mBC who were treated with fam-trastuzumab deruxtecan had significant improvements in survival compared to those treated with chemotherapy alone.[11] The median PFS was 10.1 months in the trastuzumab deruxtecan group and 5.4 months in the physician's choice chemotherapy group (HR for disease progression or death, 0.51; $p < 0.001$), and OS was 23.9 months and 17.5 months, respectively (HR for death, 0.64; $p = 0.003$). Based on this study, this agent is now FDA approved for adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/in situ hybridization) breast cancer, as determined by an FDA-approved test, who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

Given all the options available, shared decision making and optimization of adverse events becomes even more important. For example, with fam-trastuzumab deruxtecan, it is important to prepare patients for adverse events including nausea, low white blood cell counts, fatigue, and hair loss. Prescribing prophylactic medications such as antiemetics can minimize adverse event impact and checking in with the patient seven to ten days into cycle one so that problems can be addressed proactively. Patients need to understand the low but real risk of interstitial lung disease and what symptoms to bring to their care provider's attention. If a patient develops a cough, dyspnea, fever and/or new or worsening respiratory symptoms, evaluation of interstitial lung disease should be initiated promptly. Dose reductions and spacing out dosing can make the drug much more tolerable if side events are hard to handle. Preventing and managing adverse events quickly means lower cost and better quality of life.

The future will bring additional new medications for HER2-positive disease and additional uses for currently approved agents. New antibody-drug conjugates are under investigation. Tucatinib with trastuzumab/pertuzumab is under study as first-line maintenance (HER2-CLIMB 05) and in combination with fam-trastuzumab deruxtecan (HER2CLIMB-04). Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors (palbociclib, ribociclib, and abemaciclib) which are currently used in estrogen receptor positive HER2-negative breast cancer are under study for estrogen receptor positive HER2-positive disease. One example is the PATINA study evaluating palbociclib with trastuzumab/pertuzumab/endocrine therapy as first-line maintenance.

Conclusion

The management of advanced HER2-positive breast cancer has improved rapidly over the past three years. Many new treatment options are now available, and more will be available as additional studies report conclusions. Given all the options available, shared decision making and optimization of adverse events becomes even more important. Choosing the right treatment for the right patient, and maximizing communication and adverse event management, cuts costs for all – economic costs, as well as costs to the patient in terms of quality of life.

Jane Lowe Meisel, MD is an Associate Professor of Hematology and Medical Oncology at the Winship Cancer Institute, Emory University in Atlanta, GA.

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Managed Care Considerations in the Treatment of Hereditary Angioedema: Optimizing Decision-Making Strategies for Improved Clinical and Economic Outcomes

Marc A. Riedl, MD, MS

This journal article is supported by an educational grant from BioCryst.

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Summary

Hereditary angioedema (HAE) is a rare, lifelong, disabling, and potentially life-threatening condition caused by a deficiency of C1 esterase inhibitor (C1-INH). Effective treatments are now available for managing acute attacks and preventing future attacks. Individual patient factors such as the number, severity of attacks, and other factors impact the treatment selection and management plan.

Key Points

- Early recognition and diagnosis of HAE is critical to reducing morbidity and mortality.
- An acute HAE treatment plan is necessary for every patient.
- Long-term prophylactic treatment is considered on an individual basis.
- Newer prophylactic therapies are highly effective and tolerable treatment options which reduce disease burden.
- Patient quality of life has to be considered when evaluating treatment plan efficacy.

HEREDITARY ANGIOEDEMA (HAE) IS A rare condition which can be difficult to diagnose and is frequently misdiagnosed. Angioedema is a common reason people seek care in emergency rooms. It is alarming to sufferers; however, the majority of cases are not HAE. Angioedema is the result of fluid extravasation into deep dermis and subcutaneous tissues and is non-pitting, localized, and not dependent. Diagnosis of HAE requires excluding other causes of angioedema (Exhibit 1).[1-3]

HAE is characterized by non-itching angioedema. Acute attacks of HAE can be quite severe, affecting the face, oropharynx (causing risk of asphyxiation), extremities, gastrointestinal system, and genitourinary tract. These attacks have a rapid onset from minutes to hours, increase in intensity over 24 hours, and typically resolve in two to four days without treatment. Notably, they are unresponsive to treatment with antihistamines, corticosteroids, or epinephrine, because HAE attacks are not an allergic process. Attacks typically occur unpredictably and vary in frequency. There are several known triggers of attacks (Exhibit 2) but only about 40 percent of individuals with HAE can identify the cause of an episode.[4] In most cases, a family history of HAE is identified.

The skin and abdomen are the most common locations for HAE attacks followed by the larynx.[5] With abdominal attacks, mild-to-severe pain, abdominal distension, tenderness, and vomiting occur. The symptoms can mimic other abdominal conditions, resulting in misdiagnosis and unnecessary surgery.[1] Airway angioedema can cause death. In one survey, 1.3 percent of diagnosed patients

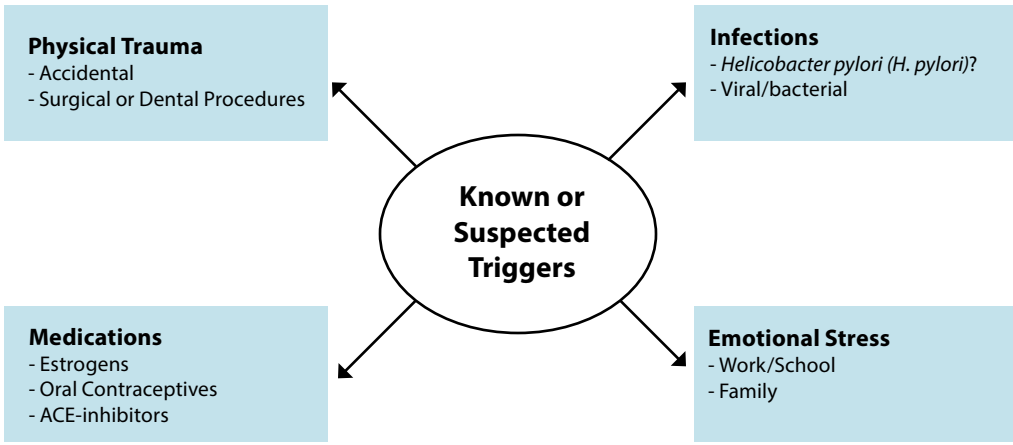
Exhibit 1: Causes of Angioedema[1-3]

- IgE-mediated:
  Foods, medicines, insect stings
- Non-IgE mediated:
  Radiocontrast media
- Chronic spontaneous urticaria/angioedema
- Physical urticaria/angioedema
- Aspirin/nonsteroidal anti-inflammatories

- Angiotensin Converting Enzyme (ACE) inhibitor-induced
- C1-INH Deficiency
  - Hereditary - Types I, II
  - Acquired
- Hereditary with normal C1-INH
  - Factor XII
  - Angiopoietin-1
  - Plasminogen
  - Kininogen
  - Myoferlin
  - HS3ST6
  - Unknown

  Idiopathic
  - Histaminergic/Mast Cell-mediated
  - Non-histaminergic

Exhibit 2: HAE Triggers[4]



died from asphyxiation and more importantly 31 percent of those undiagnosed also died.[6] Even if a patient has never had an airway attack, they need to be educated on this possibility and how to manage it.

Hereditary angioedema is associated with a significant and multifaceted disease burden.[7,8] Many contributing factors include debilitating, painful, dangerous, and unpredictable symptoms. Also challenges in diagnosis, lack of access to effective treatment, and treatment burden contribute. HAE also increases the risk of depression, anxiety, and loss of productivity. Patients can lose significant amounts of work and/or school time. Overall, HAE results in significant humanistic burden across physical and mental health domains and negatively impacts productivity.

Type 1 and Type 2 HAE are autosomal dominant diseases caused by C1-INH gene mutations which

Exhibit 3: Categories of HAE

	Type 1	Type 2	HAE-Normal C1-INH
Percent of all HAE	~ 85%	~ 15%	Rare
C4 Level	Low	Low	Normal
C1-INH antigenic level	Low	Normal	Normal
C1-INH antigenic function	Low	Low	Normal

Exhibit 4: HAE Acute Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Needs IV access • Dependent on plasma supply	• Extensive clinical experience • Relatively long half-life
Recombinant C1-INH	• Potential hypersensitivity	• Needs IV access	• No human virus risk • Scalable supply
Ecallantide	• Allergic reactions • Antibody formation	• Requires administration by a healthcare provider	• No infectious risk • Subcutaneous administration
Icatibant	• Local injection reactions		• No infectious risk • Stable at room temperature • Subcutaneous administration

lead to deficiency in or dysfunctional C1-INH.[9] C1-INH inhibits all active enzymes of the bradykinin-forming cascade. With a C1-INH deficiency, bradykinin levels increase. Bradykinin causes endothelial cell "leak" through vasodilation and increased vascular permeability.[10] C1-INHibitor functional assays are used to diagnose HAE. Exhibit 3 shows the three categories of HAE based on test results. There are rare cases of C1-INH normal HAE which can be especially difficult to diagnose using functional assays. There is significant work being done on the use of genetic mutation studies to diagnose these patients. Families of those diagnosed with HAE should be screened for the disease.

The therapeutic goals of HAE treatment are to return normalcy to life, reduce hospitalization, disability, and prevent death and excessive pain. The three treatment strategies for HAE include on-demand (to resolve angioedema symptoms as quickly as possible during an attack), short-term prophylaxis (to prevent an attack when the patient will be exposed to a known trigger), and long-term prophylaxis (to decrease the frequency and severity of ongoing attacks).[4] All patients need on-demand treatment and many will also need long-term prophylaxis. Short-term prophylaxis should be prescribed for those with known triggers. Treatment for HAE must be individualized to provide optimal care and normalize quality of life.

Since 2009 there have been dramatic advances in available treatments for HAE for both acute attack treatment and prophylaxis. All of the available agents target bradykinin production or its effects in numerous ways. Older therapies including androgens and tranexamic acid are no longer used first-line, except for the case of tranexamic acid which may be beneficial in those with C1-INH normal HAE. The newer agents have better safety data and efficacy.

Four agents are available for acute treatment, however, only one of these can be self-administered (Exhibit 4). Treatment of early symptoms of an attack, with any licensed therapy, results in milder

Exhibit 5: Prophylactic Therapies

Drug	Mechanism	Patient Age	Potential Safety Concerns	Disadvantages	Advantages
Plasma-derived nanofiltered C1-INH (intravenous)	Inactivation and consumption of C1-INH	6 years and older	• Infectious risk • Infusion reactions • Thrombosis	• Needs IV access • Dependent on plasma supply • Frequent breakthrough attacks	• Extensive clinical experience • Long half-life
Plasma-derived nanofiltered C1-INH (subcutaneous)	Inactivation and consumption of C1-INH	6 years and older	• Infectious risk • Infusion reactions • Thrombosis	• Needs IV access • Dependent on plasma supply	• Improved steady-state C1-INH levels • No IV access required
Lanadelumab	Monoclonal antibody; binds plasma kallikrein and inhibits its proteolytic activity	12 years and older	• Unknown safety in pregnancy • Anti-drug antibodies/ hypersensitivity	• Injection site reactions	• No human virus risk • Subcutaneous administration • Less frequent dosing
Berotralstat	Plasma kallikrein inhibitor	12 years and older	• Abdominal pain, vomiting, diarrhea	• Drug interactions	• Oral administration
Danocrine	Unknown	All ages	• Hepatic toxicity, elevated LDL, weight gain, hypertension	• Contraindicated in pregnancy, lactation, children, cancer	• Oral administration
Tranexamic acid	Inhibits activation of plasminogen and activity of plasmin	All ages	• Thrombosis, myalgias, abdominal pain, diarrhea	• Inferior efficacy compared to other agents • Off-label for HAE	• Oral administration

symptoms, more rapid resolution, and shorter duration of attack, compared to later treatment.[11] All acute therapies have been shown to be well-tolerated, with a minimal risk of any serious adverse events. All HAE attacks are considered for on-demand treatment and any attack affecting or potentially affecting the upper airway must be treated.[2] HAE attacks should be treated as early as possible and all patients must have sufficient medication for on-demand treatment of two attacks and always carry on-demand medication. All patients who are provided with icatibant must be taught to self-administer the medication.

Exhibit 5 provides overviews of the advantages and disadvantages of the available prophylactic treatments for HAE. All currently available prophylactic agents are associated with breakthrough attacks; therefore, an acute treatment plan is essential for every patient when on prophylactic agents. Patients may also need additional prophylaxis before surgical procedures.

Subcutaneous administration of C1-INH is a significant advancement in therapy over intravenous administration because it does not require intravenous access which can become an issue over time with patients. It is effective in reducing attacks compared to placebo.[12] Prophylactic subcutaneous C1-INH improves patient quality of life compared with on-demand stand-alone treatment.[13]

Lanadelumab is a human monoclonal antibody that targets plasma kallikrein to prevent angioedema in patients with HAE. It was approved in the United States in 2018 as the first monoclonal antibody

indicated for prophylactic treatment of HAE. In the clinical trial that led to FDA approval, subcutaneous lanadelumab for 26 weeks significantly reduced the attack rate and improved quality of life compared with placebo.[14]

Berotralstat is an oral once daily plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of HAE in adults and pediatric patients 12 years of age and older. Berotralstat demonstrated a significant reduction in the attack rate at both 110 mg (1.65 attacks per month; $p = .024$) and 150 mg (1.31 attacks per month; $p < .001$) relative to placebo (2.35 attacks per month).[15]

The treatment guidelines recommend that patients be evaluated for long-term prophylaxis at every visit.[2] Disease burden and patient preference should be taken into consideration when considering prophylaxis. A C1-Inhibitor, lanadelumab, or berotralstat are first-line long-term prophylaxis with androgens as second-line. The guidelines recommend adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize the burden of disease.

Management plans need to be individualized to lessen the burden of illness, aim to provide patients with HAE a normal quality of life, and consider treatment burden.[4] Overall, acute treatment and prophylaxis should be selected considering unique patient factors such as frequency of attacks, rapidity of attack progression, location of attacks (i.e., laryngeal), access to medical care, history of frequent hospitalization, treatment complications, and quality of life. Medication factors to consider include efficacy, safety, cost, route of administration, and patient preference/tolerability. The treatment plan needs to be assessed at least biannually and, in some cases, more often.

Quality of life is important with HAE. The disease also has an impact on quality of life in between angioedema episodes which has not always been considered by clinicians. Unpredictability of the disease is stressful, it limits educational and employment opportunities, causes disruption of social activities, and causes negative impact on family relationships. Higher frequency of attacks is associated with a higher burden of disease (physical, psychological, social). Despite advances in treatment, the burden of disease remains high.

Clinicians need to assess whether a patient's disease is being controlled, whether the patient feels they have control and can undertake life activities and are able to be adherent with their medications. There are objective HAE specific disease control and quality of life tools which clinicians can use to measure efficacy and benefit of therapy. Examples are Angioedema Control Test and Hereditary Angioedema Activity Score.[17,18] Overall studies show that those on prophylactic therapy have reduced disease burden compared to those who get on-demand treatment only.[19,20] The US HAEA Angioedema Center at the University of California San Diego has data to show that effective management of HAE reduces hospitalizations and narcotic use for painful abdominal attacks.

Conclusion

Early recognition and diagnosis of HAE is critical in reducing morbidity and mortality by allowing development of an effective management plan. An acute HAE treatment plan is necessary for every patient. Long-term prophylactic treatment is considered on an individual basis as newer therapies are highly effective and tolerable treatment options which reduce disease burden. Clinicians need to carefully consider patient quality of life when evaluating treatment plan efficacy.

Marc A. Riedl, MD, MS is a Professor of Medicine in the Division of Rheumatology, Allergy and Immunology and Clinical Director of the US HAEA Angioedema Center at the University of California in San Diego, CA.

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Recent Advances in the Management of Amyotrophic Lateral Sclerosis

Jinsy A. Andrews, MD, MSc, FAAN

This journal article is supported by educational grants from Mitsubishi Tanabe Pharma America; Amylyx Pharmaceuticals.

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http://www.namcp.org/home/education, and then click the activity title.

Summary

Although amyotrophic lateral sclerosis (ALS) is rare, the socioeconomic significance of this disease is extensive. There are now multiple treatment options which slow functional decline and improve survival.

Key Points

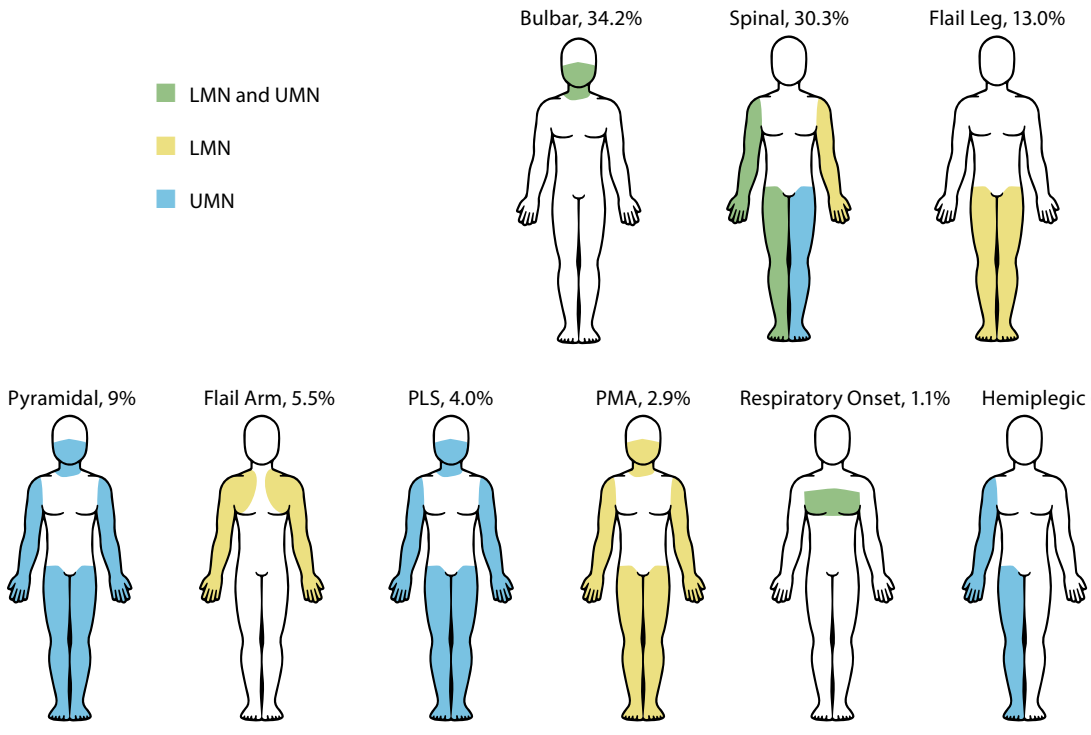
- People suspected of having ALS should be referred to a specialty center as quickly as possible.
- First steps in management are to consider all FDA-approved treatments for ALS.
- The goal of treatment is to prevent progression to another disability milestone, and loss of function of another region, as progression is related to increased healthcare utilization and costs.
- The available FDA-approved agents will be used in combination.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) was first described in 1874 and genetic mutations which lead to familial ALS were first described in 1993. The first ALS specific medication was approved in 1995. The pathology of ALS involves atrophy of muscle fibers, which are denervated as their corresponding anterior horn cells degenerate (amyotrophy) and hardening of the anterior and lateral columns of the spinal cord as motor neurons in these areas degenerate and are replaced by fibrous astrocytes (lateral sclerosis). ALS affects upper and lower motor neurons which causes muscle weakness, disability, and eventually death. Patients lose their ability to move, speak, take anything orally, and breathe unassisted.

Ninety to 95 percent of ALS cases are sporadic and have no family history or identified genetic cause. Five to 10 percent of cases are associated with family history and/or genetic mutations. In the United States (U.S.), ALS has a prevalence of 5.2 in 100,000, with an incidence of 1.7 per 100,000, reflecting short average survival.[1] There is a slightly higher incidence in men than women (1.5 to 2.1) until after age 65 when the incidence is equal. Onset can be from late teens to 90 plus years of age with the peak being between ages 55 and 75. The number of affected individuals in the U.S. is projected to increase by 34 percent by 2040, primarily because of population aging.[2] This is a fatal disease with average survival from diagnosis between three to five years although individual survival is very inconsistent due to variable phenotypes.[3]

The clinical presentation is a slow progressive and painless weakness somewhere in the body.[4] Presentation can initially be in any region of the body (bulbar, cervical, thoracic, lumbosacral regions). Exhibit 1 shows the several ways the disease can present.[4] Seventy-five to 80 percent of those affected have limb involvement first and the remainder have initial bulbar involvement (speech

Exhibit 1: The Varied Presentation of ALS[4]



PLS = primary lateral sclerosis; PMA = progressive muscular atrophy

and swallowing). Rarely can truncal weakness or respiratory weakness be the first symptom. Lower motor neuron signs of ALS include fasciculations, atrophy, and weakness whereas upper motor neuron signs are spasticity and hyperreflexia.

Diagnosis is difficult and there are no ALS specific diagnostic tests currently available. It is a clinical diagnosis based on diagnostic criteria and supported by neurophysiology testing (Exhibit 2 shows the El Escorial Criteria). Some patients are denied therapies because they have a listed diagnosis of suspected ALS even though they have ALS but do not yet meet criteria for probable or definite disease. Newer diagnostic criteria (Gold Coast) have been developed to avoid the vague terminology of the prior criteria (Exhibit 3).[5] The diagnostic delay in the U.S. is about one year after onset of symptoms; anyone suspected of ALS should be rapidly referred to a specialty center. Studies are underway to identify imaging or other biomarkers to improve diagnosis.

Once the diagnosis is made, there are algorithms to provide predictions about disease course and duration of survival.[6] The ALS Functional Rating Scale-revised (ALSFRS-R) can be used over time to measure disability progression. The ALSFRS-R examines nine domains of daily activities plus respiratory function and assigns scores from 0 (function absent) to 4 (function normal); a maximum score indicating normal function is 48. The ALSFRS-R has been validated over the past 10 years in many studies and shows test-retest reliability. The ALSFRS-R score typically declines by almost 1 point/month in ALS patients and the score tracks with disease progression milestones. Impact on the ALSFRS-R is the FDA gold standard to approve ALS therapies.

ALS has a tremendous physical, psychological, and socioeconomic impact on patients. Over time, the patient experiences step-wise decline with loss of functional capabilities (Exhibit 4). Maintaining function is important to the patient's perception of disease progression and to reducing patient and caregiver burden.

Coupled with and contributing to the severe impact on quality of life are the substantial economic costs of ALS, which can be direct, indirect and personal, as well as societal.[7] Annual total direct costs of ALS in U.S. were estimated at $54,000 to $64,000 in 2014 – 2015 and are substantially more today.[8-9] Direct costs include medications, hospitalizations, outpatient visits, and durable medical equipment. As the disease progresses from diagnosis to noninvasive ventilation

Exhibit 2: Revised El Escorial Criteria for ALS

Definite ALS

- Upper and lower motor neuron signs in three regions.

Probable ALS

- Upper and lower motor neuron signs in two regions.

Laboratory Supported ALS

- Upper and lower motor neuron sign in one region or upper motor neuron one or more regions with electromyography evidence of acute denervation in two or more limbs.

Possible ALS

- Upper and lower motor neuron sign in one region.

Suspected ALS

- Upper motor neuron sign only in one or more region or lower motor neuron sign only in one or more region.

Exhibit 3: Gold Coast Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis[5]

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function,

   AND

2. The presence of upper and lower motor neuron dysfunction in at least ONE body region[‡], with: upper and lower motor neuron dysfunction noted in the same body region if only one region is involved, or lower motor neuron dysfunction in at least TWO body regions,

   AND

3. Investigations[§] excluding other disease processes.
   a. Increased deep tendon reflexes, including the presence of a reflex in a clinically weak and wasted muscle, or spread to adjacent muscles.
   b. Presence of pathological reflexes, including Hoffman sign, Babinski sign, crossed adductor reflex, or snout reflex.
   c. Increase in velocity- dependent tone (spasticity).
   d. Slowed, poorly coordinated voluntary movement, not attributable to weakness of lower motor neuron origin or Parkinsonian features.
   e. Evidence of chronic neurogenic change, defined by large motor unit potentials of increased duration and/or increased amplitude (with polyphasia), and motor unit instability regarded as supportive but not obligatory evidence.
   f. Evidence of ongoing denervation, including fibrillation potentials or positive sharp waves, or fasciculation potentials.

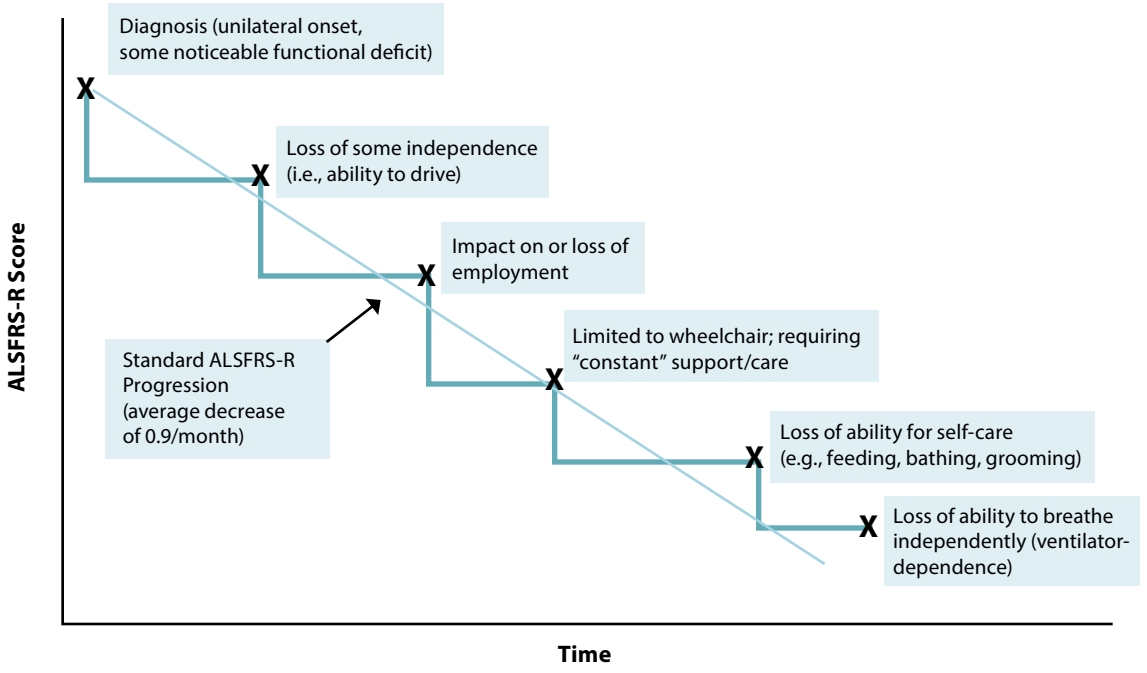
[‡] Body regions are defined as bulbar, cervical, thoracic and lumbosacral. To be classified as an involved region with respect to lower motor neuron involvement, there must be abnormalities in TWO limb muscles innervated by different roots and nerves, or ONE bulbar muscle, or one thoracic muscle, either by clinical examination or by electromyography (EMG).

[§] The appropriate investigations depend on the clinical presentation, and may include nerve conduction studies and needle EMG, MRI or other imaging, biofluid studies, or other modalities as clinically necessary.

to hospice care, costs increase.[10] Indirect costs of ALS, including loss of employment for the patient and caregiver, are substantial; one estimate put costs at $15,000 annually but this is likely a significant underestimation.[8] Home and vehicle modifications and hiring of in-home caregivers not covered by insurance are some of the other indirect costs.

The Institute of Clinical and Economic Review (ICER) published a cost-effectiveness analysis of ALS medications in 2022 and concluded that despite possible net health benefit of these agents they were not cost effective at prices used in the analysis.[11] The ALS community (researchers, patients, advocacy organizations) had many issues with the

Exhibit 4: Disability Progression from the Patient Perspective



ICER review. Quality adjusted life year (QALY) is discriminatory to people living with disability according to the National Council on Disability. ICER used Equal Value Life Years Gained (evLYG) as an alternative to QALY to avoid discrimination but this measure does not adequately address or consider quality of life that is valued by ALS patients; it uses data from those without the disease to make inferences on quality of life and care. ICER also utilized cost of care data that was not from the U.S. The ALS community's stance was that a review of therapies should be stopped if there are no adequate sets of U.S. data to produce an informed analysis. The ICER review failed to recognize the many ways ALS presents and develops. ALS is a heterogeneous disease. Some patients will maintain function for many years whereas others will rapidly deteriorate. Lastly, the review did not include considerations for cost of caregiving, which ALS requires as it progresses to an advanced disease stage.

Advances in the understanding of underlying biological processes in ALS, including the causative genetic mutations, and of the influence of environmental factors have increased the understanding of ALS disease pathophysiology.[12] The consequent identification of pathogenic targets such as gene mutations means that the introduction of effective therapies has become a realistic prospect. The pathophysiology of ALS is thought to involve glutamate-induced excitotoxicity, structural abnormalities of mitochondria, autophagy, neuroinflammation and disruption of axonal transport mechanisms.[12] Non-neuronal cells, including astrocytes and microglia, also play a role in neurodegeneration in ALS via the secretion of neurotoxic mediators and the modulation of glutamate receptor expression. Sixteen different genetic mutations have been found associated with ALS; many of these mutations affect proteins that are involved in gene expression and regulation via the regulation of transcription, microRNA processing, and RNA maturation and splicing.

The goal of currently available treatment is to prevent progression of the disease to other regions and delay time to disability milestones. Treatments are pharmacologic and non-pharmacologic, which is briefly discussed later. Four currently available therapies approved by the FDA for ALS are riluzole, edaravone, sodium phenylbutyrate/taurursodiol (PBT), and tofersen.

Riluzole was the first FDA-approved disease-modifying therapy for ALS (1995). It is a benzothiazole given orally that blocks the release of glutamate and modulates sodium channels which are neuroprotective. Compared with placebo, riluzole prolongs median tracheostomy-free survival by two to three months in patients younger than 75 years of age with definite or probable ALS who have had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent.[13,14] A retrospective review of riluzole evaluated whether the benefit of riluzole occurs in the earlier or later stages of the disease and found riluzole primarily prolonged survival in the last clinical stage of ALS.[15] This was a retrospective study and this finding needs to be confirmed in a prospective study. This study could not determine treatment effects at Stage 1 (patients came in as Stage 2 or later per eligibility criteria of probable or definite ALS and could have symptoms for up to 5 years). The ALS stage at which benefit occurs is important for counseling patients before starting treatment. The thinking in the clinical community is that earlier treatment may have a bigger impact with riluzole. A meta-analysis of population studies that compared riluzole versus placebo found significant differences in median survival between the two groups, ranging from six to 19 months.[16] This is longer than the two- to three-month survival benefit observed in the pivotal clinical trials of riluzole.

Edaravone was approved by the FDA in 2017 to slow the functional decline in patients with ALS. In people who showed rapid progression (some degree of impairment in each of the ALSFRS-R domains, had an FVC ≥ 80 percent of expected value, were within two years of symptom onset, and had a further decline of –1 to –4 ALSFRS-R points during a 12-week observation period), edaravone slowed the rate of disease progression, as measured by a decrease in ALSFRS-R score, by 33 percent at six months compared to the rate of disease progression for patients in the placebo group.[17] Additional studies are ongoing to further define benefit. This agent was initially given as a once daily intravenous infusion on a complicated cycle; because of difficulties with administration, the uptake of this agent was limited until an oral formulation was approved in 2022. The annual cost of the oral formulation is approximately $177,000.

The sodium phenylbutyrate/taurursodiol (PBT) combination targets mitochondrial dysfunction and endoplasmic reticular stress. While taurursodiol improves the production of mitochondria energy, sodium phenylbutyrate improves endoplasmic reticulum stress through the upregulation of chaperone proteins. This combination appears to act by blocking cell-death pathways in mitochondria and in the endoplasmic reticulum. Sodium phenylbutyrate is a chemical chaperone that helps proteins maintain their normal conformation, preventing aggregation that may lead to cell death. PBT, which reduced functional decline on the ALSFRS-R by 25 percent over 24 weeks compared to placebo was FDA approved in September 2022. In a modified intention-to-treat analysis, the mean rate of change in the ALSFRS-R score was -1.24 points per month with the active drug and -1.66 points per month with placebo (difference, 0.42 points per month; $p = 0.03$).[18] Trial participants had definite ALS and an onset of symptoms within the previous 18 months and were on background ALS therapies (edaravone, riluzole). A long-term survival analysis of this trial found the median overall survival was 25.0 months among participants originally randomized to PBT and 18.5 months among those originally randomized to placebo (hazard ratio, 0.56; $p = .023$).[19] Initiation of PBT treatment at baseline resulted in a 6.5-month longer median survival as compared with placebo. When the groups that initially received PBT and continued was compared to those who received placebo and crossed over to PBT, the best survival was in those who started the therapy earlier in the disease process. This combination is priced at $158,000 per year. Overall, this combination produces both functional and survival benefits.

The newest agent is tofersen, an antisense oligonucleotide that targets superoxide dismutase 1 (SOD1) mRNA to reduce the synthesis of SOD1 protein in those with this mutation (SOD1-ALS); it was approved in April 2023. Preventing the build-up of SOD1 protein may help preserve motor neuron function. One to two percent of people with ALS have SOD1 mutations.

In the Phase III trial used to conditionally approve tofersen, it led to greater reductions in concentrations of SOD1 in the cerebral spinal fluid and of neurofilament light chains in plasma than placebo.[20] In the faster-progression subgroup (primary analysis), the change to week 28 in the ALSFRS-R score was -6.98 with tofersen and -8.14 with placebo (difference, 1.2 points; $p = 0.97$). A total of 95 participants (88%) entered the open-label extension. At 52 weeks, the change in the ALSFRS-R score was -6.0 in the early-start cohort and -9.5 in the delayed-start cohort (difference, 3.5 points; 95% CI, 0.4 to 6.7). This intrathecally infused therapy is given every 28 days after three loading doses 14

days apart. Lumbar puncture-related adverse events were common. Serious adverse events (myelitis, radiculitis, papilledema, and increased intracranial pressure, and aseptic meningitis) have occurred. It is FDA approved for the treatment of adults with SOD1 ALS and this indication is approved under accelerated approval based on the reduction in plasma neurofilament light chain.[21] Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). Tofersen will launch with a list price of $184,990 per year after initial loading doses.

A combination of dextromethorphan and quinidine (DMQ) is an FDA-approved treatment for pseudobulbar affect (PBA), involuntary emotional expression (laughter or crying) not congruent with mood. About 50 percent of those with ALS have PBA. Because patients receiving this agent reported other improvements beyond PBA symptoms, a small randomized, blinded, crossover clinical trial was done to determine whether it enhanced speech, swallowing, and salivation (all bulbar functions) in patients with ALS, and it did show improvements. A subsequent Phase II, multicenter, double-blind, randomized crossover trial was designed to evaluate DMQ treatment on bulbar functions in patients with ALS.[22] The primary endpoint was a reduction in the self-report Center for Neurologic Study Bulbar Function Scale (CNS-BFS) score. Each of the individual domains of bulbar function responded to treatment. Similarly, the bulbar component of the ALSFS-R improved with active treatment (p = 0.003), although the medication did not affect the motor and respiratory components of this scale.

The earlier the FDA-approved treatments are initiated the more they may be beneficial. Independence and quality of life mean different things to different people living with ALS and delaying another disability milestone is meaningful to most patients. Approved treatments are anticipated to be used in combination. The mechanisms of each of these are applicable to all types of people living with ALS, except tofersen which is only appropriate for those few with SOD1 ALS.

For managed care, applying stringent eligibility criteria for ALS medications is inaccurate and not in alignment with FDA label indication for access to medications. Some plans restrict these medications to only those patients who meet the study inclusion criteria but due to disease heterogeneity with ALS all those with ALS should have access to these medications. Diagnosis of SOD1 mutation for tofersen access is the only reasonable restriction. Combination therapy should not be restricted because of the differing mechanisms of actions. Delays related to coverage hurdles can also delay the start of medication, which may put the patient on a pathway of faster progression.

Multidisciplinary teams are important because ALS affects so many functions and care by these teams has been shown to improve survival and quality of life. Multidisciplinary teams will have an ALS neurologist, and at least some of the following specialists: pulmonologist, gastroenterologist, physiatrist, psychiatrist, social worker, occupational therapist, physical therapist, speech therapist, psychologist, respiratory therapist, genetic counselor, palliative care specialist, specialized nurse, dietician, and dentist.

Care for those living with ALS includes rehabilitative care (upper and lower extremity support and assistive devices), ventilation support, nutritional support, and symptom management. Ventilation support usually begins with non-invasive ventilation (NIV). NIV is initiated early as the lung muscles begin to fail to modify the disease; many use it mostly at night and have relative independence during the day to perform activities of daily living. NIV has been shown to improve survival and quality of life in ALS.[23,24] All patients should be seen by a nutrition therapist for strategies to maintain weight because hypermetabolism is a major component of ALS.[25] The goal is to maintain weight via oral intake as long as possible but at some point most patients with ALS will need to decide on a feeding tube (another disability milestone).

Because many different treatments are under investigation, the future of ALS treatment is going to be increasingly complicated. Treatments targeting additional gene mutations in ALS, mechanisms associated with motor neuron degeneration, nerve and muscle communication, muscle response to diminished nerve input, neuroprotection of nerve cells, delivering protective factors to the motor neurons, and the support cells surrounding the motor neurons (glial cells) are all under investigation. There are also numerous gene and cell directed therapies under investigation. The Accelerating Access to Critical Therapies for ALS (ACT for ALS) bill is making $100,000,000 available each fiscal year from 2022–2026 to build new pathways to fund early access to ALS investigational therapies, accelerate ALS and neurodegenerative disease therapy development through public/private partnership, and increase research on and development of interventions for rare neurodegenerative diseases through a new FDA research grants program.

Conclusion

People suspected of having ALS should be referred to a specialty center as quickly as possible. The first steps in management are to consider all FDA-approved treatments for ALS. The goal of treatment is to prevent progression to the next disability milestone or loss of function of another region as progression is related to increased healthcare utilization and costs. Treatments such as riluzole, edaravone and PBT are anticipated to be used in combination. The first gene targeting therapy, tofersen, will also likely be used with the other agents in appropriate patients.

Jinsy A. Andrews, MD, MSc, FAAN is Co-Chair of the Northeastern ALS (NEALS) Consortium and an Associate Professor of Neurology and Director of Neuromuscular Clinical Trials at Columbia University Irving Medical Center in New York, NY.

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Managed Care Considerations in the Treatment and Management of Acute Myeloid Leukemia: Optimizing Decision-Making Strategies for Improved Clinical and Economic Outcomes

Nicholas Short, MD

This journal article is supported by educational grants from Jazz Pharmaceuticals; AbbVie.

For a CME/CEU version of this article, please go to
http://www.namcp.org/home/education, and then click the activity title.

Summary

The management of acute myeloid leukemia (AML) has changed dramatically with the addition of many new agents since 2017. Intensive chemotherapy regimens with or without a stem-cell transplant remain the most effective option for those who can tolerate aggressive therapy. For those who cannot, a combination of oral agents can effectively be used.

Key Points

- Intensive chemotherapy remains standard of care for patients less than 60 years of age.
- Hypomethylating agents in combination with venetoclax is the standard of care for older unfit patients with AML.
- Appropriate therapy for patients 60 to 74 years of age who appear fit is controversial.
- Despite new agents for relapsed/refractory AML, outcomes remain poor and stem-cell transplant is the goal for all patients.

ACUTE MYELOID LEUKEMIA (AML) ACCOUNTS for 1 percent of all cancer cases in the United States and is primarily a disease of older adults with a median age at diagnosis of 68 years of age.[1] Two-thirds of those with AML are aged 60 years or older and one-third are aged 75 years or older at diagnosis. Because many patients are aged 75 and older, the treatment that they can tolerate is not as aggressive as the regimens chosen for younger patients. As a result, those older than aged 75 account for a disproportionate number of deaths due to AML.

Historical outcomes of AML are poor. In the 1970s, median survival was 2.7 months in those less than 60 years of age and 0.9 months in those over 60 years of age. Almost no one survived with the disease for five years; the five-year survival rate was 3 percent in those less than 60 years of age and 0 percent in those older.[2] With advancements in treatment, through 2000 to 2009, the median survival improved to 22.8 months and 7.4 months, respectively.[2] The overall five-year survival rate for AML is now over 28 percent.[3]

AML is subdivided into many diverse types based on chromosomal alterations, genetic mutations, and cytogenetic findings which all impact prognosis, disease biology and phenotype, response to therapy, therapy selection, and risk of subsequent relapse. Exhibit 1 shows examples of some genetic mutations and their impact on survival.[4] Risk stratification is undertaken based on an individual's findings using the European LeukemiaNet (ELN) guidelines and placing them in favorable-, intermediate-, or adverse-risk categories.[5]

Patient-related factors that impact AML outcomes include advanced age, inferior performance status, and comorbidities which lead to poor therapy tolerance. Prior cytotoxic chemotherapy, radiation, or antecedent hematologic disorder (e.g., myelodysplastic

Exhibit 1: Genetic Mutations in AML[4]

Mutation	Frequency	Impact on Prognosis
FLT3	20 to 25% (ITD) 5 to 10% (TKD)	↓ **survival** (*FLT3*-ITD), especially if high allelic burden No clear impact on survival with *FLT3*-TKD
NPM1	~ 30%	↑ **survival** (in absence of *FLT3*-ITD)
CEBPA	~ 10%	↑ **survival** if in bZIP region
KIT	~ 10%	↓ **survival** in core-binding factor leukemias
DNMT3A	~ 20%	No clear impact on survival
IDH1/2	5 to 15% (*IDH1*) 10 to 20% (*IDH2*)	No clear impact on survival
NRAS	~ 15%	No clear impact on survival
TET2	5 to 20%	No clear impact on survival
ASXL1	5 to 15%	↓ **survival**
RUNX1	5 to 20%	↓ **survival**
TP53	5 to 20%	↓ **survival**

syndromes [MDS], myeloproliferative neoplasm [MPN]) are associated with poor-risk features. Treated secondary AML (ts-AML) is a very poor-risk subgroup. These are patients who have AML arising from MDS/MPN previously exposed to hypomethylating agents (HMA) and have outcomes inferior to secondary AML without prior HMA exposure. Complete response rates with standard therapies for ts-AML are only 25 to 30 percent and the median overall survival (OS) is less than six months (similar to TP53-mutated AML, another poor-risk subgroup).[6]

The goal of AML treatment is measurable residual disease (MRD) negativity by sensitive techniques. Those who achieve MRD negativity have a better five-year OS and disease-free survival (DFS) compared to someone with MRD positivity, irrespective of age, time of assessment, method, or AML subtype.[7]

Historically, intensive chemotherapy was the only effective treatment for AML. With intensive chemotherapy, the five-year OS is approximately 40 percent in those less than 60 and 20 percent in those over 60.[8,9] In many cases, therapy has moved away from intensive chemotherapy in the oldest patients. For most patients with favorable-risk disease, the treatment will be induction and consolidation chemotherapy but dosing and composition of the treatment regimen will vary by patient factors. For those with adverse risk, induction chemotherapy and an allogeneic hematopoietic stem-cell transplant (HSCT), if possible, based on patient factors, is the treatment of choice. Those with intermediate risk may get induction chemotherapy with either consolidation chemotherapy or HSCT.

In the past, treatment options for patients unfit for intensive chemotherapy were best supportive care (including hydroxyurea), low-dose cytarabine, or HMA (azacitidine or decitabine). Since 2017 there has been unprecedented growth in the number of medications available for the treatment of AML including venetoclax for those unfit for chemotherapy (Exhibit 2). Some of the new medications are targeted at specific mutations and others are specifically studied in relapsed/refractory disease.

The availability of venetoclax has dramatically changed the treatment of AML in those unable to tolerate chemotherapy. Venetoclax is an oral B cell lymphoma two (BCL2) inhibitor which selectively binds and inhibits BCL2, a pro-apoptotic protein, leading to the initiation of apoptosis in AML. In combination with HMA, it produces a very high rate of response (50% to 60%) and significantly improves OS compared to HMA alone.[10] Venetoclax plus azacitidine or decitabine is the National Comprehensive Cancer Network (NCCN) Guideline preferred regimen for induction in those who are not candidates for intensive remission induction chemotherapy.[11] NPM1 and IDH2 mutations are markers for excellent response to venetoclax and resistance to venetoclax is commonly associated with expansion or acquisition of TP53 or signaling mutations including K/NRAS and FLT3-ITD.[12]

Exhibit 2: New Therapies Approved for AML 2017 – 2022

Drug	Class/Mechanism	Primary Indication
Midostaurin (Rydapt®)	FLT3 inhibitor	FLT3+, new AML
Gemtuzumab Ozogamicin (Mylotarg®)	CD33 antibody-drug conjugate	CD33+, new AML
Daunorubicin-cytarabine liposome (Vyxeos®)	Cytotoxic chemotherapy	New secondary AML
Enasidenib (Idhifa®)	IDH2 inhibitor	IDH2+ rel/refr AML
Venetoclax (Venclexta®)	BCL2 inhibitor	New, elderly AML (combined with azacitidine, decitabine, or cytarabine)
Gilteritinib (Xospata®)	FLT3 inhibitor	FLT3+ rel/refr AML
Glasdegib (Daurimso®)	SMO inhibitor	New, elderly AML (combined with cytarabine)
Ivosidenib (Tibsovo®)	IDH1 inhibitor	IDH1+ AML (New or rel/refr)
Oral Azacitidine (Onureg®)	Hypomethylating agent	Maintenance in CR1
Pemigatinib (Pemazyre®)	FGFR 1, 2 and 3 inhibitor	FGFR1 rearrangement rel/refr myeloid or lymphoid cancer
Olutasidenib (Rexlidhia®)	IDH1 inhibitor	IDH1+ rel/refr AML

CR1 = complete response one; FLT3 = MS-like tyrosine kinase; rel/refr = relapsed/refractory; BCL = B-cell lymphoma/leukemia; IDH = isocitrate dehydrogenase; SMO = smoothened; FGFR = fibroblast growth factor receptor

Many centers also use venetoclax in combination with intensive chemotherapy in younger fit patients even though this is not an FDA-approved indication based on two trials showing survival benefit.[13,14] Venetoclax essentially primes leukemia cells to die easier from chemotherapy.

Another newer agent is glasdegib, an oral smoothened inhibitor which inhibits the Hedgehog pathway, an option for older patients with newly diagnosed AML who are unsuitable for intensive chemotherapy. Although this agent did modestly improve survival in combination with low-dose cytarabine compared to low-dose cytarabine alone, it is rarely used because venetoclax has proven to be a better agent.[15]

Six of the newer therapies target common mutations – FMS-like tyrosine kinase 3 (FLT3) mutation, isocitrate dehydrogenase 1 or 2 (IDH1, IDH2) mutation, and fibroblast growth factor receptor (FGFR) 1, 2, or 3 rearrangements. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation. FLT3 ITD mutations occur in 20 to 25 percent of AML cases and result in poor prognosis and high

Exhibit 3: Challenges of Treating Older Adults with AML[18]

Clinical factors
• Decreased performance status
• Higher incidence of comorbidities
• Decreased organ function and bone marrow reserve
• Higher risk of myelosuppression-related complications (e.g., infections or bleeding)
• Need for dose reductions, delays or interruptions
Factors associated with acute myeloid leukemia
• Higher incidence of adverse-risk cytomolecular features (e.g., TP53 mutation or poor-risk cytogenetics)
• Lower incidence of favorable-risk cytomolecular features (e.g., core-binding factor AML or NPM1 mutation)
• Higher incidence of secondary acute myeloid leukemia from a preceding hematological disorder (e.g., myelodysplastic syndromes)
Social factors
• Inadequate caregiver or social support
• Difficulties in travelling to a tertiary care center
Other factors
• Perception of a minimal benefit to anti-leukemia therapy

rates of relapse after treatment and FLT3 TDK mutations occur in 5 to 10 percent of cases.[16] The presence of a FLT3 mutation is an indication for incorporation of FLT3 inhibitors with induction and consolidation chemotherapy in fit patients and HSCT if the patient achieves remission/complete response one (CR1). Midostaurin has been shown to improve OS in newly diagnosed FLT3-mutated AML.[17] The decision whether to proceed to HSCT in first remission is based on cytogenetic-molecular risk stratification and patient fitness.

Oral azacitidine is now available to use as maintenance therapy after completion of first remission. Many centers use venetoclax in combination with azacitidine and, in those with FLT3 mutations, FLT3 inhibitors for maintenance even though these are not FDA approved for maintenance therapy.

There are numerous challenges of treating older people with AML (Exhibit 3).[18] They have increased treatment-related toxicity and mortality, lower response rates, and less durable responses. Clinical, disease, and social factors all contribute. Intensive chemotherapy is associated with early death rates of 10 to 25 percent even in highly selected patients. While intensive chemotherapy may be reserved for older fit patients, "fitness" is challenging to define. Multiple assessment tools are available but these are rarely used clinically. Despite these models, many "fit" patients still have significant morbidity/mortality with intensive chemotherapy. Clinicians must consider whether risks associated with intensive chemotherapy in older patients, regardless of perceived fitness, are advisable. Based on the available evidence, the MD Anderson Cancer Center approach is to prefer a lower-intensity venetoclax-based regimen for most patients 60 years of age and older, regardless of perceived fitness. Intensive chemotherapy should be considered in some cases (e.g., exceptionally fit patients 60 to 64 years of age, reasonably fit patients 60 to 74 years of age with core-binding factor AML). Patients up to 78 years of age with intermediate- or adverse-risk disease are referred for HSCT in CR1. Their frontline approach is not altered according to HSCT eligibility.

After initial treatment, many patients will have a disease relapse or develop treatment refractory disease. Outcomes are poor for patients with relapsed/refractory AML (R/R AML). The response rates with chemotherapy are only 20 to 30 percent with a median OS less than six months and a long-term survival of about 10 percent. Predictors of survival after first relapse are age, cytogenetics, relapse-free interval, and prior HSCT. Cure of R/R AML is exceptionally rare without HSCT. R/R AML often differs from the original AML clone so genomic analysis at relapse is imperative.

Several of the newer FDA-approved agents are treatment options for R/R AML which improve median OS to around nine months. Gilteritinib is a

next generation, more specific FLT3 inhibitor than midostaurin and improves overall survival (OS) in the relapsed/refractory AML patient population compared to chemotherapy alone.[19] Enasidenib is an oral, selective inhibitor of mutant IDH2 and ivosidenib and olutasidenib target IDH1. Twenty to 30 percent of patients with AML have an IDH1 or IDH2 mutation.[20,21] Although IDH inhibitors demonstrate efficacy as monotherapy, recent trials have shown that they produce higher response rates in combination with HMA. Current trials of IDH inhibitors include combination with standard induction chemotherapy as maintenance therapy, and in combination with venetoclax-based regimens. Pemigatinib is the newest targeted agent. It is an inhibitor of FGFR 1, 2 and 3 and is FDA approved for FGFR1 rearrangement relapsed or refractory myeloid or lymphoid cancer. A study in newly diagnosed AML is currently under way.

If the patient with R/R AML is not eligible for a targeted agent, other treatment options include intensive chemotherapy, HMA, or low-dose azacitidine with or without venetoclax (off label), or gemtuzumab ozogamicin. If remission is achieved with a targeted agent or another treatment option, a HSCT should occur as soon as possible.

Conclusion

Outcomes of patients with AML are improving due to increased understanding of cyto-molecular features that impact prognosis and inform decision for HSCT in CR1 and the rapid expansion of effective therapeutic options. Intensive chemotherapy remains standard of care for patients less than 60 years of age. Ongoing studies evaluating the addition of venetoclax to intensive chemotherapy are showing promising data. An HMA in combination with venetoclax is standard of care for older unfit patients with AML. Appropriate therapy for patients 60 to 74 years of age who appear fit is controversial. Despite new agents for R/R AML, outcomes remain poor, and HSCT is the goal for all patients.

Nicholas Short, MD is an Assistant Professor in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, TX.

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Best Practices in the Treatment and Management of Cystic Fibrosis: Managed Care Perspectives on the Role of New Therapies

Gary M. Owens, MD

This journal article is supported by an educational grant from Vertex Pharmaceuticals.

For a CME/CEU version of this article, please go to
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Summary

Cystic fibrosis (CF) is a progressive, genetic disease that affects the lungs, pancreas, and other organs. The underlying genetic mutations which cause this disease are known and can now be targeted with oral therapies. While expensive in terms of acquisition costs, these agents decrease the symptoms and complications of the disease.

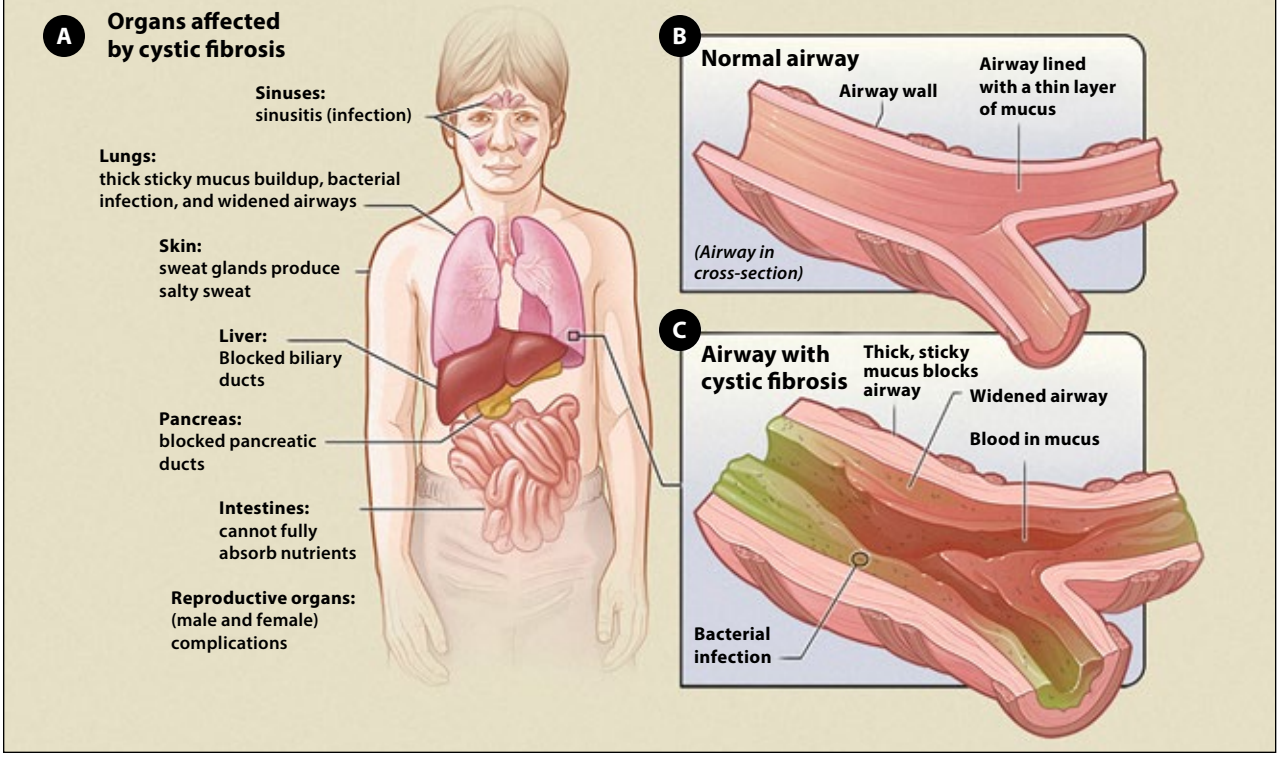
Key Points

- CFTR modulators have dramatically changed the treatment of CF and are changing outcomes.
- These therapies are available for most patients but selection depends on the genetic mutations present.
- Additional therapies are on the horizon.

CYSTIC FIBROSIS (CF), A SINGLE-GENE DISEASE with autosomal recessive inheritance, is caused by a mutation in the CF gene aptly named the cystic fibrosis transmembrane conductance regulator (CFTR) protein.[1] CFTR protein forms a chloride channel that regulates the flow of salt and fluids in and out of the cells in various parts of the body. Mutations in CFTR disrupt chloride secretion, sodium reabsorption, and water transport, leading to mucus hyper-concentration and decreased mucociliary clearance. Sticky, thick mucus builds up in organs which in turn leads to persistent lung infections, destruction of the pancreas, and complications in other organs. Persistent and frequent lung infections can result in the development of severe bronchiectasis and, eventually, respiratory failure.[2]

CF is the most common autosomal recessive disease in Caucasians. Among Caucasians, CF occurs in approximately one in 3,000 to 4,000 live births.[3] Approximately one in 25 to 30 Caucasians are carriers of a pathogenic mutation of the CFTR gene. In other races and ethnicities CF occurs less commonly, including approximately one in 4,000 to 10,000 Latin Americans, one in 15,000 to 20,000 African Americans, and even less commonly in Asian Americans. In the United States, approximately 1,000 individuals are diagnosed with CF each year and there are approximately 40,000 people living with CF. Prior to the widespread use of newborn screening (NBS), individuals with CF were diagnosed either after presenting symptomatically, or via family history. Epidemiological changes have occurred both in the incidence of CF, which seems to be decreasing in most countries, and in the survival of CF patients, which has greatly improved in recent decades.[4] In most countries with well-established CF care, adult patients now outnumber children, and life expectancy is expected to increase further with newer treatments, narrowing the survival gap with the general population.[4]

Exhibit 1: Impact on Multiple Organs[3]



CF affects many parts of the body (Exhibit 1).[5] The earliest manifestations of CF are gastrointestinal and nutritional disorders. Destruction of acinar pancreatic tissue, pancreatic duct obstruction, and lack of enzymatic activity lead to malabsorption of fats and proteins and failure to thrive in infants.[6] Respiratory manifestations are uncommon in the newborn period, but older infants may present with persistent coughing, recurrent wheezing, tachypnea, and frequent lung infections.[7] As the lung disease progresses, the patient with CF may experience shortness of breath and exercise intolerance.

The diagnosis of CF requires clinical symptoms consistent with CF in at least one organ system and evidence of CFTR dysfunction. This evidence is usually based on abnormal results from a sweat chloride test or the presence of mutations in the CFTR gene. Currently, most cases are diagnosed at birth with NBS which is performed in all 50 states and the District of Columbia.

All people have two copies of the CFTR gene, and there must be mutations in both copies to cause CF. More than 1,700 mutations of the CFTR gene have been identified. Although some are common, others are rare and found in only a few people. There are six classes of CFTR mutations – production, processing, gating, conduction, quantity, and stability – which lead to different changes in the CFTR protein or its function (Exhibit 2).[8,9] The most common CFTR mutation, present in approximately 80 percent of people with CF, is F508del. Different classes of mutations – depending on the extent of deficiency of CFTR protein quantity or function – lead to variable phenotypes, For example, people with CF who have some residual CFTR function (Classes 4, 5 and 6) tend to have milder or later onset of symptoms.

The primary goals of CF treatment include the following:

- maintenance of lung function as near to normal as possible by improving CTFR function.
- control respiratory infection.
- clear airways of mucus.
- maintain adequate growth in children.
- manage complications.

Pancreatic enzyme supplements and multivitamins (including fat-soluble vitamins) are the primary nutritional interventions. Mucolytics, inhaled hypertonic saline, inhaled mannitol, bronchodilators, and manual and assisted chest therapy are the primary therapies for clearing mucus. High-dose ibuprofen can be used as an anti-inflammatory to slow lung function decline. Agents

Exhibit 2: CTFR Mutations

	Class I	Class II	Class III	Class IV	Class V	Class VI
Percentage of Patients	22	88	6	6	5	?
Description	No functional CFTR created.	CFTR protein created, but misfolds, keeping it from moving to cell surface.	CFTR protein created and moves to the cell surface, but channel gate does not open properly.	CFTR protein created and moves to the cell surface, but channel function is faulty.	CTFR protein is normal but insufficient quantity produced.	CFTR protein normal but degrades rapidly.
Type	**Production**	**Processing**	**Gating**	**Conduction**	**Quantity**	**Stability**
Mutation examples	G542X	F508del	G551D	D1152H	3849+10kb C→T	4326delTC
	W1282X	N1303K	S549N	R347P	2789+5G→A	
	R553X	I507del		R117H		

to treat associated conditions or complications such as insulin for diabetes, antibiotics for infection, and bisphosphonates for osteoporosis may also be necessary. Specific CF targeted therapies are now available to manage this disease and help to maintain lung function and reduce complications of the disease.

CTFR modulators which are either correctors or potentiators increase CFTR function. Correctors increase the cellular processing and delivery of CFTR proteins to the cell surface and potentiators increase the flow of ions. Ivacaftor is a potentiator that binds to the defective protein at the cell surface and opens the chloride channel (holds the gate open) so that chloride can flow through, thus, regulating the amount of fluids at the surface of the cell. Ivacaftor is FDA approved in patients aged one month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. Lumacaftor is a corrector that helps the F508del-CFTR protein form the right shape, so it can traffic to the cell surface, and stay there longer. With lumacaftor only, about one-third of the CFTR protein reaches the cell surface, and those proteins do not open enough to allow chloride to pass through the cell membrane. Tezacaftor, another corrector, acts in the same way as lumacaftor.

A corrector is used in combination with a potentiator – ivacaftor/lumacaftor or ivacaftor/tezacaftor – to hold the gate open on the CFTR protein so enough chloride can then flow to reduce the manifestations of CF. The difference between the correctors is that the tezacaftor/ivacaftor combination has been shown to cause fewer adverse events, such as chest tightness, and drug interactions, than lumacaftor/ivacaftor. In addition to providing another treatment option for people ages six and older with two copies of the F508del mutation, this combination is also approved for people ages six and older with a single copy of one of 154 specified mutations.

Elexacaftor/tezacaftor/ivacaftor is a triple combination that combines the next-generation corrector elexacaftor with tezacaftor/ivacaftor. Like lumacaftor and tezacaftor, elexacaftor also helps the F508del-CFTR protein form the right shape so that it can traffic to the cell surface. Because elexacaftor corrects an additional flaw in the formation of the F508del-CFTR protein, including it with tezacaftor/ivacaftor helps the CFTR protein perform better than other modulators for an even greater number of people with CF. The triple combo has been approved for people with CF ages two and older who have at least one copy of the F508del mutation or at least one copy of 177 specified mutations.

Medication costs of CF have increased dramatically since 2012 with the first approval of CTFR targeted therapy. The annual cost of each of these therapies is approximately $300,000 per person. In an analysis using 2010 to 2016 claims data for privately insured CF patients, average total medical spending adjusted for inflation nearly doubled from roughly $67,000 per patient in 2010

and 2011 to approximately $131,000 per patient in 2016.[10] Virtually all of the growth in pharmaceutical spending was accounted for by spending on the CTFR targeting agents; inflation-adjusted spending on other medications increased by 1.3 percent per year. The annual growth rate in pharmaceutical spending rose by 33.1 percent during 2014 to 2016, the years during which lumacaftor/ivacaftor was introduced. Costs increased again when the triple combination elexacaftor/tezacaftor/ivacaftor was introduced in 2019. According to one analysis, uptake of this combination was rapid, and the total cost of care increased despite reductions in hospitalizations and nonpharmacy costs. Twelve months after FDA approval, 68 percent of Blue Cross North Carolina members with CF were using elexacaftor/tezacaftor/ivacaftor.[11] Of these, 33 had switched from a different CFTR modulator and 44 were naïve to CFTR modulator therapy. The average total cost of care increased by 52 percent ($p < 0.00001$). Overall, pharmacy costs increased $6.8 million, facilities costs decreased by $0.8 million, and professional costs decreased by $0.3 million. Hospitalizations decreased from an average of 7.7 (± 7.2) to 3.9 (± 5.5) ($p < 0.00001$). The sum and average number of *Pseudomonas aeruginosa* infections were numerically lower, but the results did not meet statistical significance. Use of other supportive medications was numerically lower, but no statistically significant differences were observed.

A 2020 Institute for Clinical and Economic Review (ICER) review found the evidence of clinical effectiveness showed a high impact on the disease but the cost of the clinical outcomes was high. The independent appraisal committee unanimously concluded that the triple combination delivers substantial benefits for patients, family members, and society.[12] Nonetheless, analyses suggest that the price set by the manufacturer would need to be deeply discounted to align fairly with these benefits and ensure that they are not outweighed by the negative health effects for others resulting from increasing healthcare costs.[12]

Balancing the improved outcomes in CF with CTFR modulators with the need to manage cost is an ongoing challenge for payers. Restrictive payer management strategies may have had unintended negative outcomes on patients and providers who care for CF patients. Payers must consider a patient-centered approach that considers the impact of CF on day-to-day activities, family dynamics and the impact of CF on quality of life. Payers should facilitate early referral to expert centers to accurately diagnose and initiate treatment, develop programs to improve quality of life and medication adherence, and work collaboratively with multiple healthcare providers, including primary care, in order to help optimize patient outcomes.

Payers need to coordinate patient care with the CF physician and the rest of the care team. The CF physician is responsible for staying up-to-date with the latest CF care guidelines, trends in patient outcomes, and new therapies. Collaboration with other healthcare professionals is essential, including the patient's primary care doctor. Payer programs should include case management to help facilitate this communication/collaboration as navigating the system can be complex for both the patient and providers. CF specialized nurses have a critical role in care coordination for payers. They provide medical care plan coordination, facilitate communication between the patient and the other members of the CF care team, provide health information or direct the patient to resources to help manage this complex disease, coordinate psychological, social, and financial concerns for patients and families, and educate others about CF.

Another important CF team member is the pharmacist. Pharmacists play a key role helping patients and caregivers learn about the benefits, adverse events, and proper dosing of CF medications. They also help prevent or manage drug interactions. Another role is to work with the patient and caregiver to be adherent with therapy. With high acquisition costs of CFTR modulator therapies, payers want patients to be adherent with their medications in order to achieve the best outcomes. In CF, there is some room for improved adherence. One analysis, using 2017 and 2018 claims data, found the highest proportion of days covered (PDC) was 0.92 with tezacaftor/ivacaftor while PDC values for both lumacaftor/ivacaftor and ivacaftor were 0.84.[13] Patients had medication to cover 92 percent and 84 percent of therapy days.

The management of CF-related costs is going to be more complicated in the future. Numerous therapies which are not just CFTR modulators are under investigation. Another triple combination of vanzacaftor/tezacaftor/deutivacaftor is currently in Phase III trials. Various gene therapies are in early preclinical and Phase I human trials.

Conclusion

The evolution in the CF treatment with CFTR modulators has revolutionized treatment approaches and outcomes. These therapies are available for most patients and selection depends on the genetic mutations present. Additional therapies are on the horizon which will further complicate treatment decisions and cost controls.

Gary M. Owens, MD is President of Gary Owens and Associates in Ocean View, DE.

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Evolving Considerations in the Treatment and Management of Multiple Sclerosis: Implementing Expert Switching and Sequencing Strategies

Benjamin Greenberg, MD, MHS

This journal article is supported by educational grants from Biogen; Sanofi; Novartis Pharmaceuticals Corporation.

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

There have been many changes over the last 20 years in treating those with multiple sclerosis and these changes have been very impactful for those affected. Selecting an appropriate treatment requires consideration of many disease and patient factors. Additional medications are on the horizon, so treatment will continue to become more complicated.

Key Points

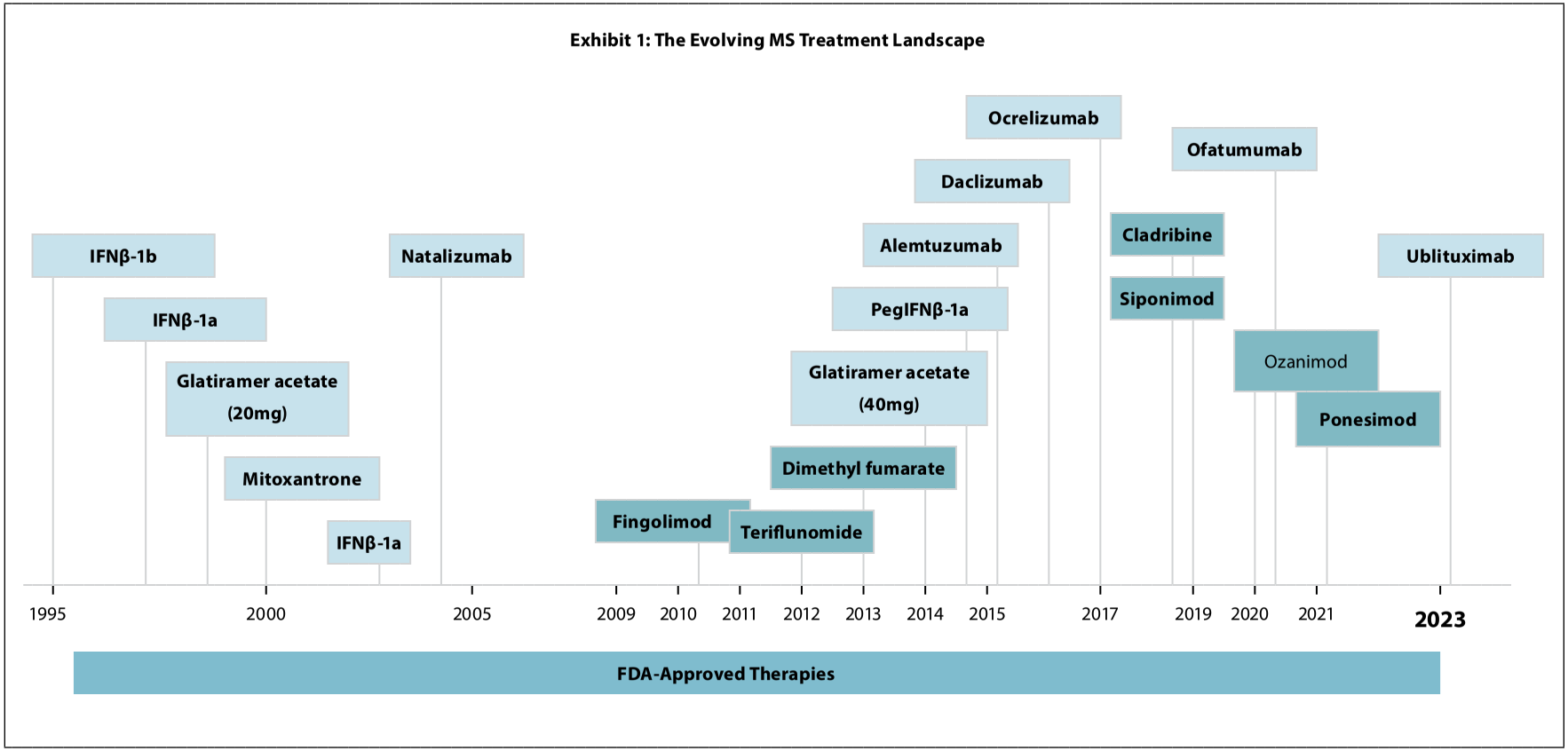
- Early accurate diagnosis is critical in getting patients access to available therapies.
- Individualized treatments selected by shared decision making are critical to achieve adherence and the best outcomes.
- Multiple novel therapies are coming in the next few years.

MULTIPLE SCLEROSIS (MS) IS A PROGRESSIVE immune disease with neurodegeneration early in the disease process which is mediated by adaptive and innate immune system. Characterized by inflammatory plaques or scars, in the deep white matter of the brain and spinal cord, it is the most common cause of non-traumatic neurologic disability in young adults. For many years, the ability to walk has been how clinicians defined disability in MS. Now we know that multidimensional disability (fatigue, depression, cognitive dysfunction) starts early during the disease long before walking is affected.

In MS, early diagnosis and treatment as soon as possible are keys to prevent irreversible nervous system damage and to preserve as much function as possible. The currently available treatments are effective in relapsing remitting MS (RRMS) but not as effective in progressive disease and do not restore damaged tissue. Another reason for early treatment is that symptoms and relapses correlate poorly with the ongoing inflammation and resultant irreversible tissue destruction in early MS. The diagnostic criteria for MS have evolved over time to be more sensitive and include objective findings from an MRI as a measure of tissue damage and inflammation in the brain. In addition to MRI findings, there are also blood tests which can rule out common MS mimics and help confirm the diagnosis. MS can now be diagnosed at the time of the first attack of symptoms rather than waiting for a second attack to occur.

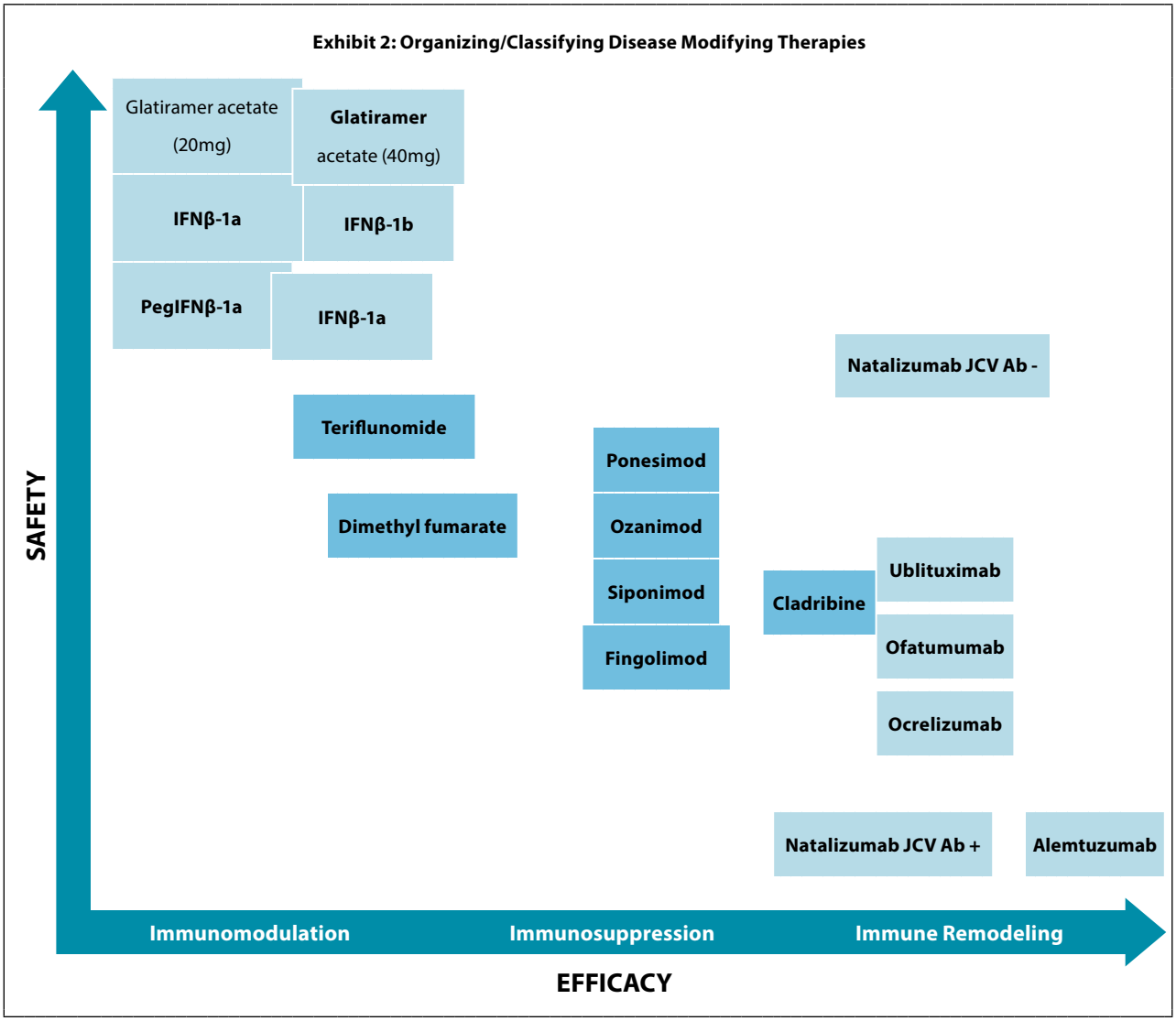
Exhibit 1 shows the evolving treatment landscape for this disease. These 20 different agents span several different mechanisms of action, type of administration (infusion, self-injection, oral), and potential for serious adverse events. In general, the agents can be divided into those that work by immunomodulation, immunosuppression, or immune remodeling. The agents which are immune modulators are safer in general than those which cause immune suppression and especially immune remodeling (Exhibit 2). The more aggressive agents which cause immune remodeling are the most effective at reducing the annual relapse rate and

Exhibit 1: The Evolving MS Treatment Landscape



IFN = interferon
Peg = pegylated

Exhibit 2: Organizing/Classifying Disease Modifying Therapies



JCV = John Cunningham virus; AB = antibody

reducing disability progression.[1,2] It is important to note that data on efficacy and safety are primarily from placebo-controlled trials with different trial designs and different populations over 25 years. The people who enrolled in the original trials for interferon are vastly different from those enrolled in contemporary trials. Over time the placebo annualized relapse rates in trials has significantly declined from 1.27 in a 1993 interferon trial to 0.36 in a 2012 dimethyl fumarate trial.[3] The reason for this decline is an improvement in diagnostic criteria which has led to earlier diagnosis.

A better outcome measure to use instead of annualized relapse rate is no evidence of disease activity (NEDA). Annualized relapse rate change is required for FDA approval but in the clinic clinicians care if the patient has disease activity. NEDA is defined as no relapses, no progression on disability scale, no recent changes in brain MRI, and normal brain atrophy. In untreated MS, the rate of brain atrophy is four times normal age-related atrophy. Exhibit 3 shows NEDA rates from some clinical trials.[4-8] Again although these data are not always from active medication comparison trials, the NEDA rates follow with the prior data on the immune-remodeling agents being more effective. Long-term data are showing evidence of efficacy out to 10 years with all the agents.[9,10]

Clinicians now have highly effective disease-modifying therapies (DMT) which can put patients into remission as measured by NEDA and prevent long-term disability. The trick is finding the right medication for the right patient. Currently, there is no good predictor of which agent a patient will

Exhibit 3: No Evidence of Disease Activity in Clinical Trials

- Interferon Beta 1a 27% at 2 years
- Teriflunomide 18% to 24% at 2 years
- Dimethyl Fumarate 23% to 28% at 2 years
- Cladribine 48% at 4 years
- Fingolimod 33% at 2 years
- Ocrelizumab 48% at 2 years
- Natalizumab 55% at 4 years
- Alemtuzumab 68% at 2 years

respond to so finding the right medication can be a trial-and-error process.

There are also safety concerns with each agent primarily because of effects on the immune system. For example, the most efficacious but also least safe agent is alemtuzumab. This agent is given as five days of infusion followed by three days of infusion 12 months later. An additional three days of infusion can be given on a yearly basis. Because this agent dramatically remodels the immune system, about 48 percent of those who receive it will develop a secondary autoimmune disease with thyroid disease being most common.[11] There are also questions about potential increased risk of thyroid cancer, melanoma, and lymphoproliferative disorders with this agent. Because of adverse event risk, this agent is only available through a Risk Evaluation and Mitigation Strategy (REMS) program and patients have to commit to five years of monthly laboratory monitoring even when they only receive the first two rounds of therapy.

There are numerous agents under investigation for managing MS. A big area currently lacking is for an agent or agents to repair damage which has already occurred. Other areas of interest are additional ways to suppress the immune system and how to develop immune tolerance so as not to incur the risk of immune suppression.

The newest class of agents closest to market are the Bruton's tyrosine kinase (BTK) inhibitors. BTK itself is important in the maturation of B cells which are overactive in MS. Four BTK inhibitors are already FDA approved for treating B-cell lymphomas and chronic lymphocytic leukemia (CLL). In addition to effects on B cells, BTK inhibitors shift the signaling of myeloid cells from inflammatory cytokine production to anti-inflammatory cytokines which may lead to MS damage repair in the nervous system.

At least four BTK inhibitors are currently under investigation. Phase II trials of evobrutinib and tolebrutinib showed a reduction in the number of new brain lesions compared to placebo and dimethyl fumarate, in the case of evobrutinib.[12,13] Both of these agents have moved to Phase III trials. Other BTK inhibitors in Phase III trials include fenebrutinib and remibrutinib and the BTK inhibitor trials are in relapsing, primary-progressive, and secondary-progressive MS. Liver function abnormalities are the most significant adverse events of this class; some trials with evobrutinib and tolebrutinib have been partially on hold by the FDA because of this adverse event.[14] One or more of these agents will likely be coming to market in 2024 or later. Whatever therapy is chosen, adhering to that DMT is critical for treatment efficacy and cost-effective care. Worse adherence can lead to relapses, increase in disability, relapse-associated hospitalizations and emergency department visits, and higher medical costs. Patients who do not adhere to therapy have worse overall quality of life compared to those who are adherent. Reasons for nonadherence to medication can vary, but the most reported include forgetfulness, injection-site pain, and adverse events.[15]

Seventy-five to 90 percent of patients with MS prefer having an active role in treatment decisions (shared decision making). Choice of therapy should be individualized to the patient based on aggressiveness of disease, reproductive considerations, comorbid conditions, and patient risk tolerance. There is a significant connection between shared decision making and higher treatment adherence rates.[16] For the oral MS therapies especially, patients must have buy-in in order to take them daily for years to maintain remission. In addition to an effective therapy that promotes adherence, there needs to be an efficacy monitoring plan and an action plan for change of therapy if it is not working.

Delays in starting therapy which can result from managed care policies matter to patients because it impacts the development of long-term disability. A one- to two-year delay in starting therapy results in worse outcomes over time; some clinicians believe if you let the fire of the disease burn too long in the beginning, you will never get it under control. The medications work when started after a delay but never as well as they would if started early in the disease process.

Forcing patients to step through certain therapies before moving on to more expensive therapies is not good practice. Based on prognostic factors, clinicians can predict which patients are likely to be

disabled at 10 years and these patients need the most aggressive therapy up front rather than letting the disease ravage their nervous system while trying out various less effective therapies.[17]

Although there are no studies among individuals with MS, systematic reviews in other diseases show that prior authorization and other coverage restrictions are detrimental to medication adherence and worsen clinical outcomes. A growing body of evidence consistently indicates that cost-sharing can have a negative effect on DMT adherence. Among commercially insured patients with MS, those facing high cost-sharing amounts were 12.7 percent less likely to initiate a DMT in the two years following initial diagnosis relative to those without cost-sharing.[18] There are no studies that quantify the effects of DMT cost-sharing on MS-related outcomes.

Conclusion

Multiple sclerosis is a common, potentially disabling condition that is highly treatable. Early accurate diagnosis is critical to get patients access to available therapies. Individualized treatments selected by shared decision making are critical to achieve adherence and best outcomes. Multiple novel therapies are under development and the treatment algorithm is going to become even more complicated.

Benjamin Greenberg, MD, MHS is a distinguished teaching Professor and Vice Chairman of Clinical and Translational Research in the Department of Neurology at the University of Texas Southwestern in Dallas, TX.

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Best Practices in the Treatment and Management of Melanoma: Expert Strategies on Evolving Combinations for Optimized Patient Outcomes

Hussein A. Tawbi, MD, PhD

This journal article is supported by an educational grant from Bristol Myers Squibb.

For a CME/CEU version of this article, please go to
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Summary

Prior to 2011 there were no therapeutic options that significantly improved survival with advanced melanoma. There are now 13 targeted and immunotherapy options. The numerous treatment options have led to tremendous improvement in overall survival (OS).

Key Points

- The use of immunotherapy is the current standard for first-line treatment in the metastatic, adjuvant, and neoadjuvant setting.
- Targeted therapy is the second-line choice in those with BRAF-mutated disease.
- Triplet therapy is an option for selected patients.

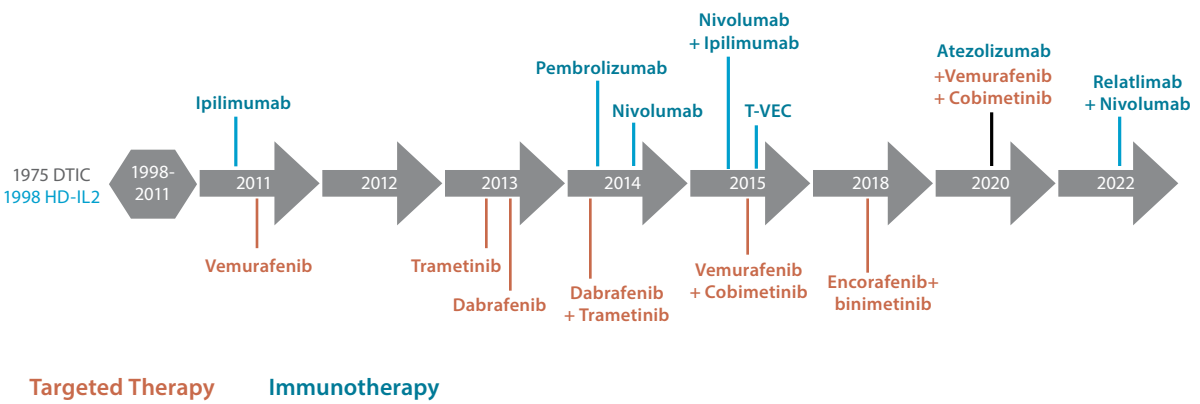
FOR 2023, THE AMERICAN CANCER SOCIETY estimates there will be 97,610 newly diagnosed melanomas (about 58,120 in men and 39,490 in women) and 7,990 people are expected to die of melanoma (about 5,420 men and 2,570 women).[1] Prior to 2011, no therapy improved survival in advanced melanoma. Thirteen targeted and immunotherapy options have been approved since 2011 for managing Stage IV, metastatic melanoma (Exhibit 1). Prior to 2011, the five-year OS for Stage IV disease was less than 5 percent and median survival was seven months. Today with these advances, the five-year OS is greater than 50 percent and median survival is over six years. For a newly diagnosed patient with metastatic melanoma, it is now possible to cure them about 50 percent of the time, even with brain metastases.

The benefits with interleukin two (IL-2) shown in the late 1990s provided the proof that advanced melanoma could be cured, at least in some patients (approximately 15%). This proved that melanoma is an immunogenic cancer and thus susceptible to attack from an activated immune system. Unfortunately, few patients with advanced disease are healthy enough to tolerate IL-2 but there are still a few centers in the United States (U.S.) that offer this option.

Ipilimumab was the first checkpoint inhibitor studied in melanoma and completely changed the treatment landscape by showing an improvement in survival. Because it is better tolerated than IL-2, ipilimumab increased the number of patients who could be treated with survival and curative intent. Ipilimumab monotherapy resulted in a median OS of 11.4 months and became the standard of care for advanced melanoma in 2011.[2]

The combination of ipilimumab with nivolumab, a second checkpoint inhibitor targeting programmed death one (PD-1), was shown to be better than either alone. OS at 6.5 years was 49 percent in the

Exhibit 1: Approved Agents for Stage IV Melanoma



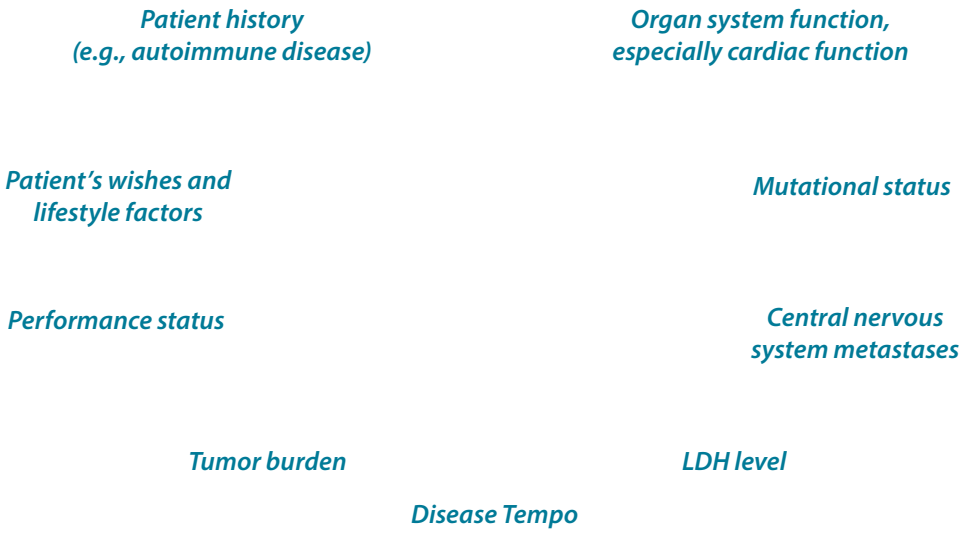
nivolumab/ipilimumab group and 42 percent in the nivolumab group, as compared with 23 percent in the ipilimumab group.[3] This trial was not designed to show a difference between the combination and nivolumab monotherapy. A higher percentage of patients who received the combination were alive and treatment-free at 6.5 years than with nivolumab or ipilimumab monotherapy (77% versus 69% versus 43%). This trial reinforced the idea that completeness of response in advanced melanoma matters in terms of long-term survival which was also seen in the IL-2 trials. Those with a complete response (CR) and partial response (PR) have the best long-term survival. These findings allowed clinicians to be bold enough to talk to patients about a potential cure in advanced disease. Dual checkpoint inhibitor therapy does cause a higher rate of immune-related adverse events compared with monotherapy.

The newest immunotherapy combination is targeting lymphocyte-activation gene 3 (LAG-3) in combination with PD-1 inhibition. LAG-3 and PD-1 are distinct inhibitory immune checkpoints that contribute to T-cell exhaustion. A fixed dose combination of relatlimab and nivolumab is FDA approved for first-line treatment of unresectable or metastatic melanoma. The median progression-free survival (PFS) was 10.1 months with relatlimab/nivolumab as compared with 4.6 months with nivolumab (hazard ratio for progression or death, 0.75; p = 0.006 by the log-rank test).[4] PFS at 12 months was 47.7 percent with relatlimab/nivolumab as compared with 36.0 percent with nivolumab. PFS across key subgroups favored relatlimab/nivolumab over nivolumab. Response rates with this combination were the same whether the patient had BRAF-mutated or wild-type tumors and LAG3 levels did not impact response. Grade 3 or 4 treatment-related adverse events occurred in 18.9 percent of patients in the relatlimab/nivolumab group and in 9.7 percent of patients in the nivolumab group. In practice, the adverse event rates of relatlimab/nivolumab compared to nivolumab are very similar. Long-term survival data with this particular combination are not yet available. Data on the benefits of relatlimab/nivolumab and ipilimumab/nivolumab make it difficult to justify treating patients with PD-1 monotherapy.

BRAF (v-Raf murine sarcoma viral oncogene homolog B) mutation, primarily V600, is present in approximately 50 percent of melanomas and leads to increased cell proliferation and survival. Targeted therapy includes BRAF and MEK (mitogen-activated protein kinase) inhibitor combinations which are better than either alone. Dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib are the three combinations approved in the U.S. Targeted therapy for BRAF-mutated tumors provides a high response rate (65% to 70%).[5-7] There are now five-year data with the various combinations indicating a 20 percent long-term survival.[8,9] The best survival (55%) is in those patients with normal LDH levels and less than three sites of disease. The three combinations appear to have similar efficacy; however, it is with adverse events that they differ. Vemurafenib/cobimetinib primarily causes skin toxicity, dabrafenib/trametinib causes fevers, and encorafenib/binimetinib is known for more gastrointestinal adverse events and increased liver function tests.

It has been a major debate for over 10 years which strategy – targeted therapy or immunotherapy – to use first-line in the patient with BRAF mutation. A

Exhibit 2: Patient Characteristics which Impact Treatment Decisions



sequencing trial published in early 2023 appears to have resolved the dilemma. This trial randomized patients with treatment-naïve BRAF V600-mutated metastatic melanoma to either combination nivolumab/ipilimumab (arm A) or dabrafenib/trametinib (arm B) in step 1, and at disease progression patients were enrolled in step 2 to receive the alternate therapy, dabrafenib/trametinib (arm C) or nivolumab/ipilimumab (arm D).[10] The two-year OS for those starting on arm A was 71.8 percent and arm B was 51.5 percent which is a 20 percent difference in survival. Step 1 PFS also favored arm A (p = .054). Objective response rates were arm A: 46.0 percent; arm B: 43.0 percent; arm C: 47.8 percent; and arm D: 29.6 percent. Median duration of response was not reached for arm A and was 12.7 months for arm B (p < .001). This trial concluded that combination nivolumab/ipilimumab followed by BRAF- and MEK-inhibitor therapy, if necessary, should be the preferred treatment sequence for a large majority of patients.

Another option instead of sequencing immunotherapy and targeted therapy is upfront combination of both approaches. Targeted therapy has an earlier impact but resistance develops quickly, whereas immunotherapy takes longer to start working but provides longer lasting efficacy. The hope of using both approaches simultaneously is that there will be early tumor response and a higher survival rate long-term. IMspire150 was a trial studying an initial cycle of vemurafenib/cobimetinib followed by atezolizumab, a programmed death ligand one (PD-L1) inhibitor, or placebo in combination with vemurafenib/cobimetinib. At a median follow-up of 18.9 months, PFS was significantly prolonged with atezolizumab/vemurafenib/cobimetinib versus placebo/vemurafenib/cobimetinib (15.1 versus 10.6 months; p = 0·025).[11] With 29-month follow-up, median OS was 39.0 months in the atezolizumab group versus 25.8 months in the control group (HR 0.84; p=0.14).[12] Final survival data are not yet available. Although FDA approved, triplet therapy is not currently often used. One place in therapy for triplet therapy may be in those with central nervous system metastases who are symptomatic and receiving corticosteroids based on results of a Phase II trial with the triplet.[13]

Currently first-line therapy for advanced melanoma is either nivolumab/ipilimumab or nivolumab/relatlimab for most patients. Treatment selection does depend on several patient specific factors (Exhibit 2). If the patient has progression on first-line therapy, there are no therapies specifically FDA approved for second-line use. There is convincing evidence as previously discussed that BRAF/MEK inhibition should be used after immunotherapy for BRAF-mutated melanoma. If BRAF-wild type disease was initially treated with single agent PD-1 immunotherapy, many clinicians will switch to combination PD-1/ipilimumab but there are limited data to support this approach.[14] Another approach that is under study is pembrolizumab plus lenvatinib,

a tyrosine kinase inhibitor. Better insights into mechanisms of resistance are needed to determine the best selection of second-line therapy.

Patients with earlier stage disease may also receive immunotherapy or targeted therapy. For those with surgically resected Stage III and high-risk Stage II disease, there is a significant risk of recurrence. Approximately 35 percent of patients with resected Stage III disease recur within two years. Adjuvant immunotherapy or targeted therapy for BRAF mutation are options which have been shown to reduce recurrence after surgical resection but about one-third of patients who receive adjuvant therapy would never have progressed and are thus overtreated. Patient selection for adjuvant therapy is still being debated. Neoadjuvant dual immunotherapy is very effective; this results in robust tumor shrinkage before surgery.[15] Low-dose ipilimumab/nivolumab for two doses is used before surgery. There is a significant advantage of neoadjuvant compared to adjuvant dual immunotherapy (20% difference in relapse-free survival with nivolumab/relatlimab).[16] The best choice of regimen for neoadjuvant use is still to be decided.

Stage 2B and C patients with resected disease also have a high risk of recurrence. The use of adjuvant immunotherapy (pembrolizumab for 1 year) reduces risk of recurrence by almost 35 percent. The impact is on both local and distant recurrence. Again, as with Stage III disease, a significant proportion of people with this stage disease would be overtreated with adjuvant therapy. The patient needs to be involved in the decision whether to use adjuvant or neoadjuvant immunotherapy.

Conclusion

The use of immunotherapy is the current standard for first-line treatment in the metastatic, adjuvant, and neoadjuvant setting. Targeted therapy is considered in select patient populations including as second-line and adjuvant therapy in those with BRAF-mutated disease. Treatment selection should consider tumor burden, LDH level, brain metastases, and patient overall health. Triplet therapy is still finding its place in therapy. Ongoing and further analyses of recently reported clinical trials will help move the field forward.

Hussein A. Tawbi, MD, PhD is Professor and Deputy Chair, Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, and is Co-Director of the MD Anderson Brain Metastasis Clinic in Houston TX.

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Evolving Considerations in the Management of Chronic Lymphocytic Leukemia: Optimizing Clinical and Economic Outcomes with BTK Inhibitors

John N. Allan, MD

This journal article is supported by educational grants from AstraZeneca; AbbVie; Merck Sharp & Dohme LLC.

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Summary

Chronic lymphocytic leukemia (CLL) affects primarily older people. Oral targeted therapies which change B cell signaling are now the preferred first-line treatment. Patients will receive these agents for long durations that will require cost management.

Key Points

- Oral targeted therapy is the main treatment for CLL.
- BTK inhibitors have demonstrated long-term efficacy and safety data.
- Later generation agents are better tolerated.
- Additional BTK inhibitors are on the horizon.

CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL lymphocytic leukemia (CLL/SLL) is a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23.[1] A diagnosis of CLL requires a clonal B cell count of $5x10^9$/L or more and SLL is restricted to cases with a less than $5x10^9$/L cell count but with documented nodal, splenic, or extramedullary involvement. SLL accounts for about 15 percent of cases. Hereafter only CLL is used to refer to both since they are treated identically. Many patients are identified based on a routine blood draw which shows a high lymphocyte count. Molecular tests predict which patients need to be treated immediately and those who can be monitored.

CLL accounts for 1.2 percent of all cancers diagnosed in the United States (U.S.) annually. The American Cancer Society's estimates for 2023 are 18,740 new cases of CLL and 4,490 deaths from CLL.[2] The five-year relative survival rate with CLL is 88 percent and there are about 200,000 people living with CLL in the U.S.[3]

B cell receptor signaling drives CLL cell survival thus various targeted treatments have been developed which alter this signaling. Targeted treatment options include oral Bruton tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib), an oral B cell lymphoma 2 inhibitor (venetoclax), and injectable anti-CD20 monoclonal antibodies (e.g., rituximab, obinutuzumab). First-line CLL treatment has shifted away from chemo-immunotherapy (CIT)-based approaches, which combine chemotherapy and anti-CD20 agents to oral targeted therapy, because of survival advantages and fewer short- and long-term adverse events. Oral targeted therapy does not cure CLL but can control it for many years; patients are typically given BTK inhibitors until intolerance or disease progression occurs whereas venetoclax is used for a limited duration.

Ibrutinib, which was the first BTK inhibitor, had been the most commonly used first-line therapy for CLL and improves overall survival (OS) over chemotherapy and CIT in both older and younger patients.[4-6] The National Comprehensive Cancer Network Guidelines now recommend acalabrutinib and zanubrutinib, second generation agents, over ibrutinib (Exhibit 1).[7] Ibrutinib was moved from

Exhibit 1: NCCN Recommended First-Line Regimens[7]

Type	Preferred First-Line
CLL with del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab Venetoclax + obinutuzumab Zanubrutinib
CLL without del(17p)/TP53 mutation	Acalabrutinib ± obinutuzumab (category 1) Venetoclax+ obinutuzumab (category 1) Zanubrutinib (category 1)

preferred regimens to other recommended regimens in the guidelines based on toxicity profile compared to the other two BTK inhibitors. A comparison trial of acalabrutinib versus ibrutinib (Elevate RR) found the two agents noninferior with a median progression-free survival (PFS) of 38.4 months in both arms.[8] All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% versus 16.0%; $p = .02$) and median overall survival (OS) was not reached in either arm. In patients who are already taking ibrutinib with no intolerance, ibrutinib can be continued until disease progression.

Zanubrutinib was FDA-approved for CLL in April 2023 after being approved in 2019 for several other indications. In the Alpine study, zanubrutinib was compared to ibrutinib in relapsed or recurrent CLL. At a median follow-up of 29.6 months, zanubrutinib was found to be superior to ibrutinib with respect to PFS (hazard ratio for disease progression or death, 0.65; $p = 0.002$).[9] At 24 months, PFS rates were 78.4 percent in the zanubrutinib group and 65.9 percent in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer PFS than those who received ibrutinib (hazard ratio for disease progression or death, 0.53). PFS across other major prognostic subgroups consistently favored zanubrutinib. The safety profile of zanubrutinib was better than that of ibrutinib, with fewer adverse events leading to treatment discontinuation and fewer cardiac events, including fewer cardiac events leading to treatment discontinuation or death. A lower rate of atrial fibrillation/flutter was observed with zanubrutinib (2.5% versus 10.1%; $p = .0014$) and major bleeding rates were also lower (2.9% versus 3.9%), as were adverse events leading to treatment discontinuation (7.8% versus 13.0%, respectively) or death (3.9% versus 5.8%). Neutropenia occurred more often with zanubrutinib (28.4% versus 21.7%).

CLL B cell clones change over the course of the disease based on time, treatment pressures, and underlying biology resulting in treatment resistance mutations.[10] A significant portion of patients treated with a BTK inhibitor eventually experience treatment failure due the development of resistance or intolerance. Ibrutinib, zanubrutinib and acalabrutinib are all irreversible, covalent BTK inhibitors which bind to the C481 site on BTK.[11] Reversible, non-covalent BTK inhibitors are the next evolution of CLL therapy. They exert their inhibition of BTK by different mechanisms to covalent BTKi. They do not act by binding to the C481 site on BTK, and therefore offer a potential alternative therapeutic option to patients with B-cell malignancies, including those who have developed acquired resistance due to BTK C481 mutations following prior therapy with a covalent BTKi. Pirtobrutinib is the first highly selective, non-covalent, reversible BTK inhibitor to be approved by the FDA; it blocks the ATP binding site of BTK. Selectivity for BTK also impacts the adverse event profile.

Pirtobrutinib was approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including another BTK inhibitor in January 2023. It is also being studied in CLL and it appears, based on available data, that it will become a treatment option for relapsed/refractory CLL, especially with covalent BTK inhibitor resistance. In a Phase I/II study in 121 patients with CLL treated with a previous covalent BTK inhibitor (median previous lines of treatment 4), the overall response rate (ORR) with pirtobrutinib was 62 percent.[12] The ORR was similar in CLL patients with previous covalent BTK inhibitor resistance (67%), covalent BTK inhibitor intolerance (52%), BTK C481-mutation (71%) and BTK wild-type (66%) disease. Fatigue, constipation, and nausea were the most common adverse events. Atrial fibrillation, hypertension, and bruising (common adverse events with less specific BTK inhibitors) occurred at low

rates. Several other noncovalent BTK inhibitors are under investigation for CLL and other B-cell malignancies.

The main drivers of cost for CLL patients are infusions, outpatient visits, hospitalizations, and medication costs. Adoption of targeted agents has dramatically increased the cost of CLL management. In one analysis, the annual cost of CLL management was projected to increase 590 percent between 2011 and 2025.[13] The increase in cost is due to high medication prices, prolonged treatment duration, and increased number of patients living longer because of medication efficacy. Although CLL is an incurable disease, patients can live a long time with oral therapy. For example, with BTK inhibitors, a patient may be on this therapy for six or seven years before developing resistance or disease progression. The wholesale acquisition price of the BTK inhibitors is $14,000 to $16,000 annually. Patients may have a $900 per month out-of-pocket cost. The newer, more specific agents are modestly less expensive than ibrutinib.

Managing adverse events with targeted therapy may also contribute to costs. In one study, ibrutinib treated patients had significantly higher all-cause and CLL-related inpatient costs than CIT (bendamustine/rituximab) patients as well as all-cause outpatient pharmacy prescriptions costs, while CIT patients had significantly higher per member per month outpatient medical costs.[14] In another study of Medicare data, mean all-cause monthly cost of CLL increased significantly based on the number of adverse events a patient had ($5,144 with 1 to 2 versus $10,077 with ≥ 6).[15] In this analysis, patients receiving targeted therapy (ibrutinib) were more likely to have multiple adverse events than those getting CIT. A reason for this difference is CIT is used short-term whereas targeted therapy is given until disease progression or intolerance. Additionally, patients continue to age while taking this long-term therapy and so are more vulnerable to adverse events. An analysis of adverse events with newer, more specific BTK inhibitors which do not cause as many adverse events is not available.

Fixed duration therapies like venetoclax or CIT compared to continuous BTK inhibitor therapy has similar costs in year one of treatment but decline in years two and three whereas the cost of the BTK inhibitor continues.[16] One approach currently being developed is to combine fixed duration BTK inhibitor and venetoclax to try to limit medication exposure and costs while also maximizing outcomes. This approach may become the first-line standard of care in appropriate patients.

Conclusion

The management of CLL has moved to oral targeted therapies instead of CIT as first-line therapy. BTK inhibitors have long-term efficacy and later generation agents are replacing ibrutinib as preferred therapy because of an improved safety profile. Additional BTK inhibitors are on the horizon which will further complicate managing costs in CLL.

John N. Allan, MD is an Assistant Professor of Medicine in the Division Hematology and Medical Oncology at Weill Cornell Medicine in New York, NY.

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Expert Approaches to the Treatment and Management of Psoriasis

Paul S. Yamauchi, MD, PhD

This journal article is supported by educational grants from Arcutis Biotherapeutics; Bristol Myers Squibb.

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Summary

Treatment of psoriasis focuses on reducing skin and joint manifestations of the disease and reducing the impact of various comorbidities. There are now many different agents for treating psoriasis. Among these agents, biologic agents are the most effective in managing moderate-to-severe disease.

Key Points

- Primary goals of treatment include clearing the skin, reducing signs and symptoms of joint pain, minimizing adverse events, addressing comorbidities, and enhancing patient quality of life.
- In addition to other factors, patient preference and disease severity should be considered when selecting therapy.
- Dermatologists should screen for joint involvement in their psoriasis patients and collaborate with rheumatologists to adequately manage both skin and joint involvement over the long-term.

PSORIASIS IS A CHRONIC RELAPSING immune-mediated inflammatory disease.[1] It affects multiple parts of the body. Overall, psoriasis causes significant clinical, social, emotional, and economic burden and has multiple associated comorbidities related to systemic inflammation.[1,2] Up to 30 percent of patients with psoriasis develop psoriatic arthritis (PsA), usually 10 to 15 years after onset of psoriasis, which can lead to significant joint damage and pain. In addition to PsA, other comorbidities include cardiovascular disease, obesity, metabolic syndrome, type 2 diabetes, depression, anxiety, among others.

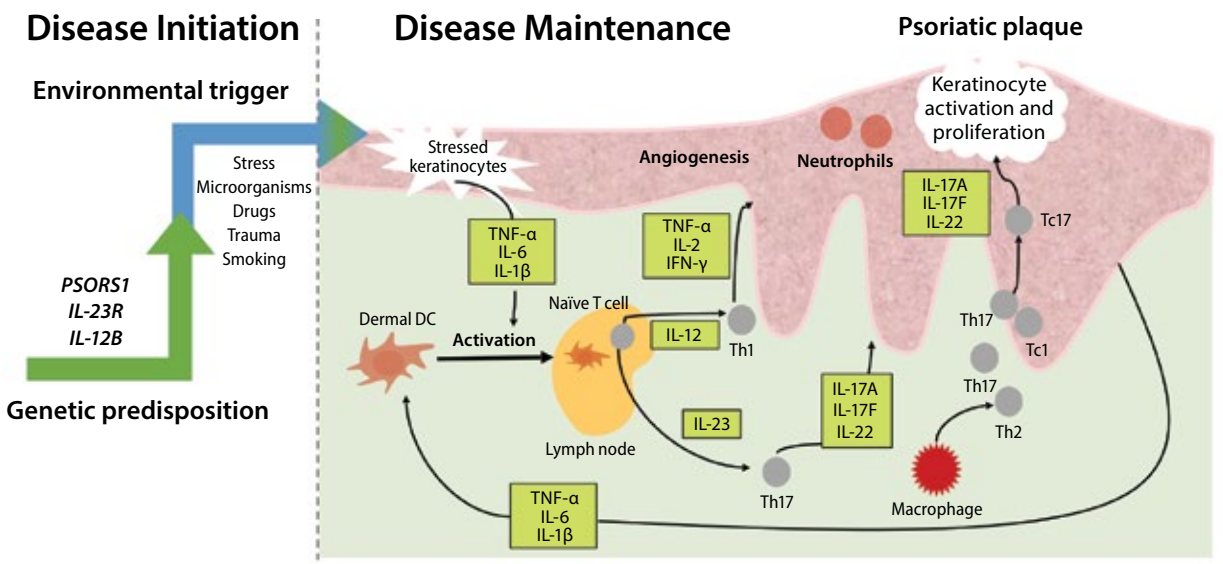
Psoriasis has a bimodal age of onset with the first peak in the second to third decade of life and second peak incidence after 50 years of age. Onset at less than 15 years of age may indicate more severe, resistant disease. Up to one-third of patients report a family history and several genetic markers have been identified.

Psoriasis is thought to be triggered by an event such as stress, infection, or medication in a genetically susceptible individual. The inflammatory process is perpetuated by tumor necrosis factor (TNF) and various interleukins (IL) including 1beta, 2, 6, 12, 17A, 17F, 22, 23 (Exhibit 1).[3,4] TNF and IL-12, IL-17, and IL-23 are all targeted by currently approved biologics.

There are several types of psoriasis – plaque, guttae, inverse, pustular, and erythrodermic. Plaque psoriasis represents about 80 percent of the cases and is characterized by erythema, induration (thickness), and desquamation (scaling). The differential diagnosis for plaque psoriasis includes atopic dermatitis, a drug-related eruption, and tinea corporis. Palmar plantar psoriasis can be especially debilitating because of the functional impact on hands and feet.

The estimated prevalence of PsA in psoriasis patients is up to 30 percent. Earlier age of onset of PsA is associated with poorer prognosis. The frequency

Exhibit 1: Immunopathogenesis of Chronic Plaque Psoriasis[3,4]



DC=dendritic cell; PSORS1=psoriasis susceptibiity 1; IL=interleukin; TNF=tumor necrosis factor.

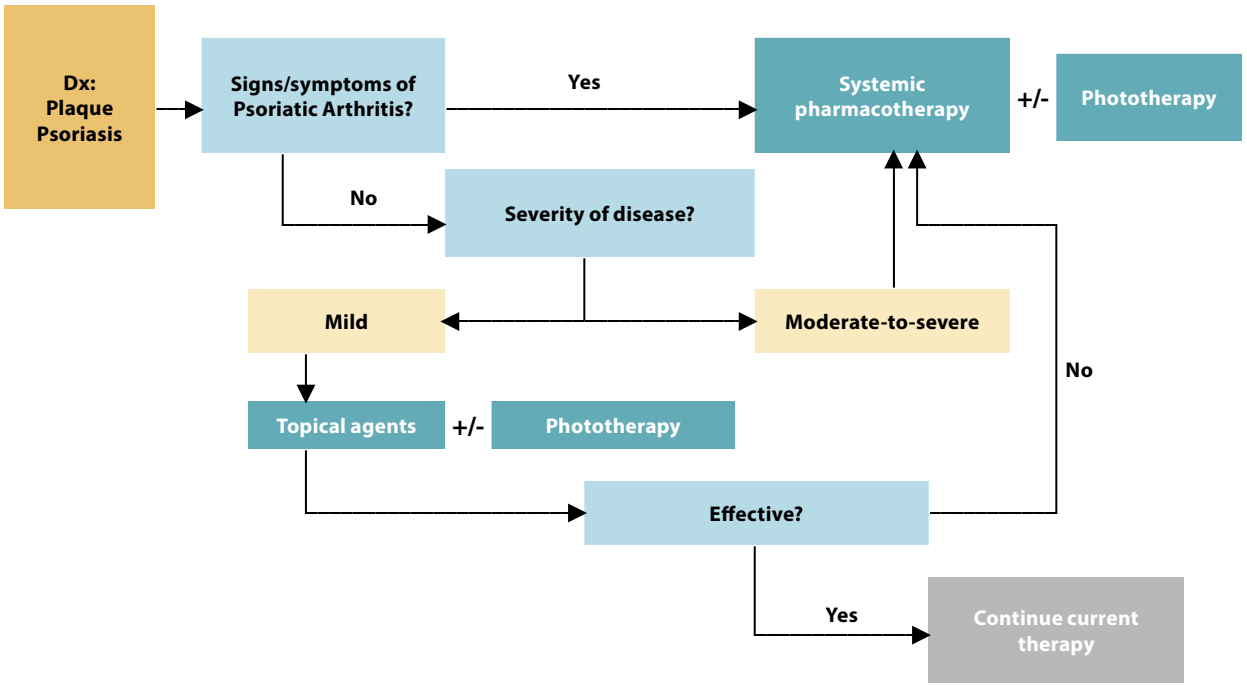
of PsA increases with disease severity and duration and occurs equally in men and women. Psoriasis precedes arthritis in 75 percent of cases typically within 10 years after appearance of skin lesions. In 15 percent of cases, psoriasis and arthritis begin at the same time and arthritis precedes psoriasis in 10 percent of cases. All patients with psoriasis should be screened for PsA.

The severity of psoriasis is assessed based on body surface area (BSA) affected. Mild is considered 1 percent to 3 percent BSA affected, moderate 3 percent to 10 percent, and severe more than 10 percent. Location also determines severity. Patients may have scalp, hands, feet, groin, and skin folds affected which are less than 10 percent of BSA but they have significant disability. The Psoriasis Area Severity Index (PASI) is used in clinical trials to assess medication efficacy. The PASI score is composed of scores for erythema, induration, scaling, and surface area in each body region. A PASI score over 12 (out of 72) is considered moderate-to-severe disease. Clinical trial endpoints can range from PASI 50 to PASI 100 which indicates 50 to 100 percent improvement in the score. Investigator or physician global assessment (IGA/PGA) score change and itching assessments are also used in clinical trials.

Treatment goals in psoriasis are to clear the skin of lesions, minimize adverse events, enhance patient quality of life, and address comorbidities especially PsA.[5] Patients should be involved in treatment decision making and their preferences considered when selecting therapy.[5,6] Mild psoriasis can be managed with topical agents but moderate-to-severe disease requires phototherapy, systemic agents, oral small molecules, or biologics to achieve control (Exhibit 2).[7-10] Six classes of biologics are available for use in psoriasis with some of them also being approved for PsA. If a patient has PsA, an agent studied in this condition and FDA approved should be selected. Other considerations in selecting therapy include cost and insurance coverage, adverse events of the various treatment options, potential for immune suppression, and contraindications.

Three new agents came to market in 2022. Topical tapinarof cream, an aryl hydrocarbon receptor agonist, is indicated for the topical treatment of plaque psoriasis in adults. The aryl hydrocarbon receptor is highly expressed among epithelial and immune system cells of the skin and plays a role in regulating skin barrier function and immune response. In the two trials with this agent, 36 percent and 40 percent of patients achieved clear or almost clear skin by PGA compared with 6 percent with vehicle placebo and 36.1 percent and 47.6 percent achieved PASI 75 compared to 10.2 percent and 6.9 percent.[11] The patient's skin also stayed clear for three to five months after stopping therapy in one of the clinical trials.[11] The most common adverse

Exhibit 2: Use Disease Severity to Guide Treatment Selection[7-10]



reactions with this agent are folliculitis, contact dermatitis, and pruritus.

Topical roflumilast, a selective phosphodiesterase 4 (PDE4) inhibitor, is indicated for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.[12] Roflumilast was already FDA approved as an oral agent for reducing exacerbations in COPD. PDE4 inhibition increases cyclic AMP in the skin and reduces production of inflammatory cytokines. Roflumilast cream administered once daily to affected areas of psoriasis was superior to vehicle cream in leading to a state of clear or almost clear skin at eight weeks in two trials in people with up to 20 percent affected BSA.[13] In these two trials, statistically significantly greater percentages of roflumilast-treated patients than vehicle-treated patients had IGA success (clear or almost clear status plus ≥ 2-grade improvement from baseline) at week eight (trial 1: 42.4% versus 6.1%; trial 2: 37.5% versus 6.9%; $p < .001$ for both). Of nine secondary end points, statistically significant differences favoring roflumilast versus vehicle were observed for eight in trial 1 and nine in trial 2, including intertriginous IGA success (71.2% versus 13.8%; 68.1% versus 18.5; $p < .001$ for both), 75 percent reduction in PASI score (41.6% versus 7.6%; 39.0% versus 5.3%; $p < .001$ for both), and reduction of itching. The incidence of treatment-emergent adverse events was similar between roflumilast and vehicle in both trials. With up to 64 weeks of use, the rate of application site pain (1%) and discontinuations related to adverse events (1%) remained low.

Deucravacitinib is a first-in-class, oral, selective tyrosine kinase 2 (TYK2) inhibitor which inhibits signaling of IL-23, IL-12 and Type 1 interferon, key cytokines involved in the pathogenesis of multiple immune-mediated diseases. It was FDA approved for use in moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy but it is also being studied in PsA, lupus and inflammatory bowel disease.[14,15] In a Phase III trial, deucravacitinib was superior to placebo and apremilast across multiple efficacy end points and was well tolerated in moderate-to-severe plaque psoriasis. (PASI 75 – 58.4% versus placebo 9.4 and 12.7%, apremilast 40.2 and 35.1%).[16]

Exhibit 3 notes which agents are approved to treat both psoriasis and PsA and compares the PASI 75, 90, and 100 rates from the various trials used for FDA approval of the biologics, apremilast, and deucravacitinib. Although the rates shown are not from head-to-head trials, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab appear to be the most effective for skin

Exhibit 3: Biologic and Oral Agents Approved for Psoriasis and Psoriatic Arthritis

Type	Generic Name	Psoriasis and/or Psoriatic Arthritis	Psoriasis Efficacy* PASI75	PASI90	PASI100
TNF-alpha Inhibitor	Etanercept	PsO and PsA	49	22	-
	Adalimumab	PsO and PsA	71	45	-
	Infliximab	PsO and PsA	76	45	-
	Certolizumab pegol	PsO and PsA	77	49	-
IL-12/23 Inhibitor	Ustekinumab	PsO and PsA	69	43	-
IL-17A Inhibitor	Secukinumab	PsO and PsA	79	56	29
	Ixekizumab	PsO and PsA	90	71	40
IL-17 Receptor Inhibitor	Brodalumab	PsO	85	70	42
IL-23 Inhibitor	Guselkumab	PsO and PsA	91	72	42
	Tildrakizumab	PsO	64	35	22
	Risankizumab	PsO	89	75	43
PDE4 Inhibitor (oral)	Apremilast	PsO and PsA	33	-	-
Tyk2 Inhibitor (oral)	Deucravacitinib	PsO	58.4	-	-

*Data not from head-to-head trials, and trials also of different length.
Note: JAK inhibitors are FDA approved for psoriatic arthritis but not psoriasis and are not included in table.

clearing. A Cochrane systemic review concluded that the biologics infliximab, bimekizumab, ixekizumab, and risankizumab were the most effective treatments for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of high-certainty evidence.[17] The highly effective agents are more effective than TNF inhibitors or ustekinumab in the available head-to-head trials.[18-24] In one comparison between two of the highly effective agents for psoriasis, ixekizumab and guselkumab were found to be noninferior to each other at 24 weeks.[25] Guselkumab showed superior long-term efficacy based on PASI 90 at week 48 when compared with secukinumab for treating moderate-to-severe psoriasis (84% versus 70%) with similar rates of adverse events.[26] Ixekizumab and secukinumab have also been shown to be more effective than adalimumab for PsA.[27,28]

An additional new agent, spesolimab, has been FDA approved as the first agent for treating generalized pustular psoriasis (GPP) flares. With GPP, also known as von Zumbusch psoriasis, pustules often cover large areas of the body and typically patients present with fever, shivers, intense itching, a rapid pulse, fatigue, headache, nausea, muscle weakness, and joint pain. It can be precipitated by systemic steroids or acute withdrawal of systemic agents for psoriasis and can be a medical emergency. People with GPP tend to have sudden flares that last for a few weeks, followed by spontaneous remission where their skin partly or completely clears. Spesolimab, an interleukin-36 receptor antagonist, is administered as a single 900 mg dose by intravenous infusion over 90 minutes.[29] If flare symptoms persist, an additional intravenous 900 mg dose one week after the initial dose can be given. In a Phase II randomized trial, spesolimab resulted in a higher incidence of lesion clearance at one week than placebo (54% versus 6%) but was associated with infections and systemic drug reactions.[30]

Several additional agents are under investigation for treating psoriasis. The closest to market is bimekizumab which selectively neutralizes the function of IL-17A and IL-17F. In trials it produced better results than adalimumab, secukinumab, and ustekinumab.[31-33] Approximately 60 percent of patients achieve PASI 100 with this agent. Like other IL-17 inhibitors, bimekizumab increases the risk for oral candida infections. It is currently under FDA review.[34]

Conclusion

Multiple treatment options are now available. The primary goals of treatment include clearing the skin, reducing signs and symptoms of joint pain, minimizing adverse events, addressing comorbidities, and enhancing patient quality of life. In addition to other factors, patient preference and disease severity should be considered when selecting therapy. Dermatologists should screen for joint involvement in their psoriasis patients and collaborate with rheumatologists to adequately manage both skin and joint involvement over the long-term.

Paul S. Yamauchi, MD, PhD is a dermatologist in private practice and Medical Director at both the Dermatology Institute and Skin Care Center and Clinical Science Institute in Santa Monica, CA and a Clinical Assistant Professor of Medicine in the Division of Dermatology at the David Geffen School of Medicine at UCLA John Wayne Cancer Institute in Los Angeles, CA.

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Optimizing LDL-C Reduction in Lipid Management: What Managed Care Needs to Know about Reducing Major CV Risks with New and Emerging Therapies

Michael Miller, MD, FACC, FAHA

This journal article is supported by an educational grant from Novartis Pharmaceuticals Corporation.

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Summary

Lipid management requires both lifestyle changes and medications in the majority of those with elevated values. Selected patients without evidence of atherosclerotic disease should receive statins for primary prevention based on a risk assessment and risk/benefit discussions. Everyone who already has evidence of atherosclerotic disease should receive a statin for event prevention and may require additional therapy to further reduce risk.

Key Points

- Lifestyle changes are the backbone of LDL-C reduction for both primary and secondary prevention.
- Primary prevention with statins is indicated for selected patients based on risk assessment and patient discussion.
- Secondary prevention should include statins for all those who can tolerate them.
- If LDL-C is still above goal on maximally tolerated statin therapy, ezetimibe addition should be considered.
- If still above goal on statin/ezetimibe, addition of a PSCK9 inhibitor should be considered.

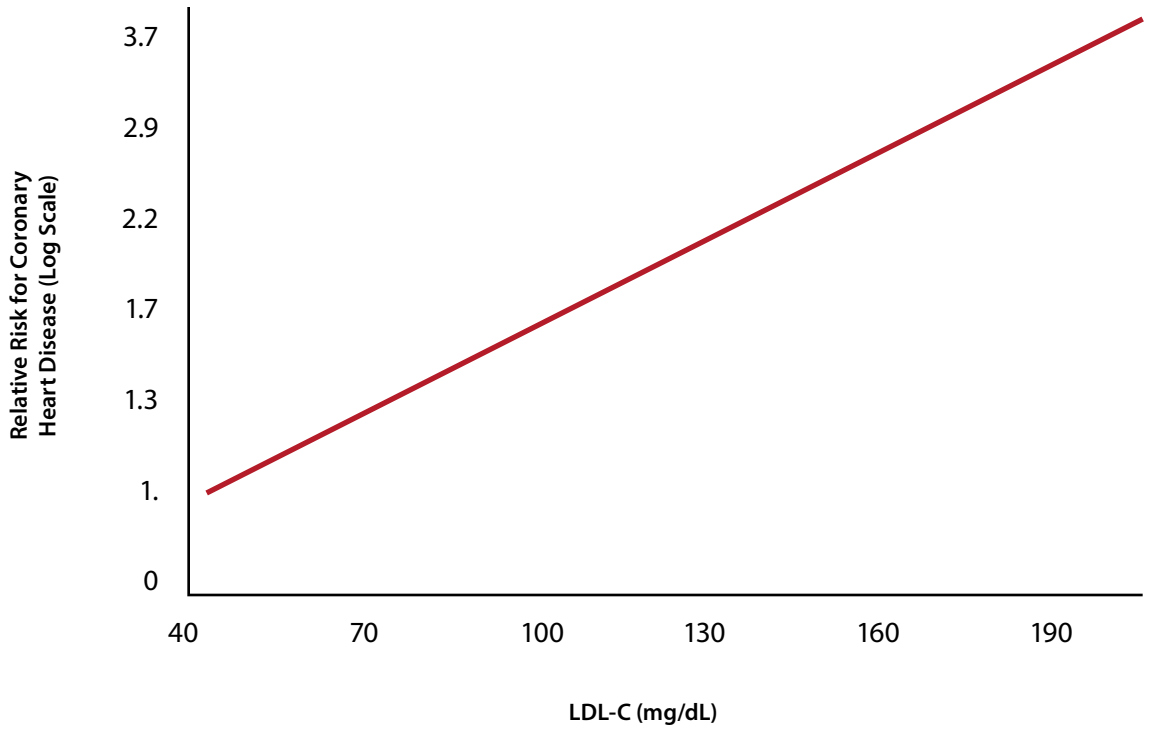
THERE ARE AN ESTIMATED 16 MILLION people with coronary artery disease in the United States and heart disease is still the number one killer of Americans.[1] Lipids are a significant risk factor for atherosclerotic cardiovascular disease (ASCVD) with a log-linear relationship between low density lipoprotein cholesterol (LDL-C) levels and relative heart disease risk (Exhibit 1).[2,3]

There are huge benefits of early, aggressive lipid-lowering strategies that target absolute LDL-C reduction in patients who are at elevated risk for – or already have – ASCVD. Keeping LDL-C levels low throughout life reduces the risk of ASCVD. There is even a benefit to beginning LDL-C lowering later in life. Data suggest that for every 30 mg/dL change in LDL-C, the relative risk for ASCVD is changed in proportion by about 30 percent.

An LDL-C level of 40 mg/dL is where there is no risk for ASCVD; humans are born with LDL-C levels of around 30 mg/dL and lucky people with familial hypobetalipoproteinemia have life-long LDL-C levels of around 50 mg/dL. LDL-C of 50 to 60 mg/dL carries a minimal risk of developing ASCVD; anything above this level significantly increases risk.[4] Those with familial combined hyperlipidemia (FCH) and familial hypercholesterolemia (FH) have LDL-C levels of 200 or more.

Key populations of interest for targeting lipid values are those who already have clinical ASCVD (secondary prevention) and those at the highest risk of developing ASCVD (primary prevention).[5] Clinical ASCVD consists of acute coronary syndrome (ACS), those with a history of myocardial infarction, stable or unstable angina or coronary other arterial

Exhibit 1: Relationship Between LDL-C Levels and Relative Heart Disease Risk[2,3]



revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm – all of atherosclerotic origin.[5] Primary severe hypercholesterolemia (LDL-C 190 mg/dl or higher) and diabetes are example of risk factors for developing ASCVD which would indicate a need for primary prevention.

Lifestyle interventions to lower LDL-C are important in anyone with elevated LDL-C even if on medication. A patient taking a statin is negating some of the benefit of that medication if they routinely eat saturated fats. Exhibit 2 shows the benefits of various lifestyle interventions.[6-11] Realistically, with combined dietary changes you can get 20 percent to 25 percent lowering with some individuals obtaining more benefit with strict adherence.

For those people who already have clinical ASCVD, high intensity statin therapy is recommended for most (Exhibit 3).[5] Very high-risk in the algorithm refers to those with a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (age 65 years or older, heterozygous FH, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), diabetes mellitus, hypertension, chronic kidney disease, current smoking, and persistently elevated LDL-C of ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe, and heart failure). The goal in secondary prevention is to drive LDL-C to less than 70 mg/dL or as low as possible. Atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 mg to 40 mg are high intensity regimens which will typically produce a greater than 50 percent reduction in LDL-C. If the patient is tolerating the statin, LDL-C levels below 30 mg/dL have not been shown to cause untoward cognitive or muscle adverse events – several years ago, clinicians would back off statin dosing if these low levels were achieved. In the secondary prevention setting, high-intensity statins have been shown to reduce major cardiovascular events.[12]

Primary prevention is taking healthy people who have risk factors and giving them statins to prevent the development of ASCVD and reduce risk of negative outcomes such as myocardial infarction. Because this is a lengthy process, it can be difficult to prove benefit; many of the primary prevention trials were only five years in length and required very large patient populations. Benefits of primary prevention have been shown with statins for higher risk patients.[5,13] Exhibit 4 shows the guideline recommendations for primary prevention.[5] The goal with primary

Exhibit 2: Lifestyle Interventions to Lower LDL-Cholesterol[6-11]

Dietary Modification	Recommendation	≈ LDL-C Reduction
Saturated fat	< 7% calories	8% to 10%
Dietary cholesterol	< 200 mg/day	3% to 5%
Plant stanols/sterols	Up to 2 grams per day	6% to 10%
Viscous dietary fiber	5 to 10 grams per day	3% to 5%
Soy protein	20 to 30 grams per day	5% to 7%
Almonds	> 10 grams per day	1% per 10 grams
Weight reduction	Lose 10 lbs. (4.5 kg)	5% to 8%
Total		**30% to 45%**

prevention is LDL-C less than 100 mg/dL.

For primary prevention candidates with diabetes, there are diabetes specific risk enhancers which should be considered when deciding between moderate- and high-intensity statin doses. These include long duration (≥ 10 years for type 2 or ≥ 20 years for type 1), albuminuria (≥ 30 mcg of albumin/creatinine), estimated glomerular filtration rate < 60 mL/min/1.73m^2, retinopathy, neuropathy, and ankle-brachial index (ABI) < 0.9. Primary prevention in those with diabetes does have a significant impact on outcomes.[14]

Patients may be concerned that statins can cause diabetes. They do raise glucose on average 2 to 5 mg/dL but there is no evidence that they promote the diabetes disease process. They actually improve micro and macrovascular disease. Statins may tip someone with prediabetes over the line to glucose levels that are considered diabetic but that patient was already on the path to developing diabetes.

Risk enhancers for those with intermediate ASCVD risk include family history of premature ASCVD, persistently elevated LDL-cholesterol (≥ 140 mg/dL), chronic kidney disease, metabolic syndrome, history of preeclampsia or premature menopause, inflammatory diseases (e.g., rheumatoid arthritis, psoriasis, HIV), South Asian ancestry, persistently elevated triglycerides (≥ 175 mg/dL), highly specific C reactive protein (hs-CRP) ≥ 2.0 mg/l, lipoprotein a (Lp_a) > 50 mg/dL, apolipoprotein B ≥ 130 mg/dL, or ABI < 0.9.

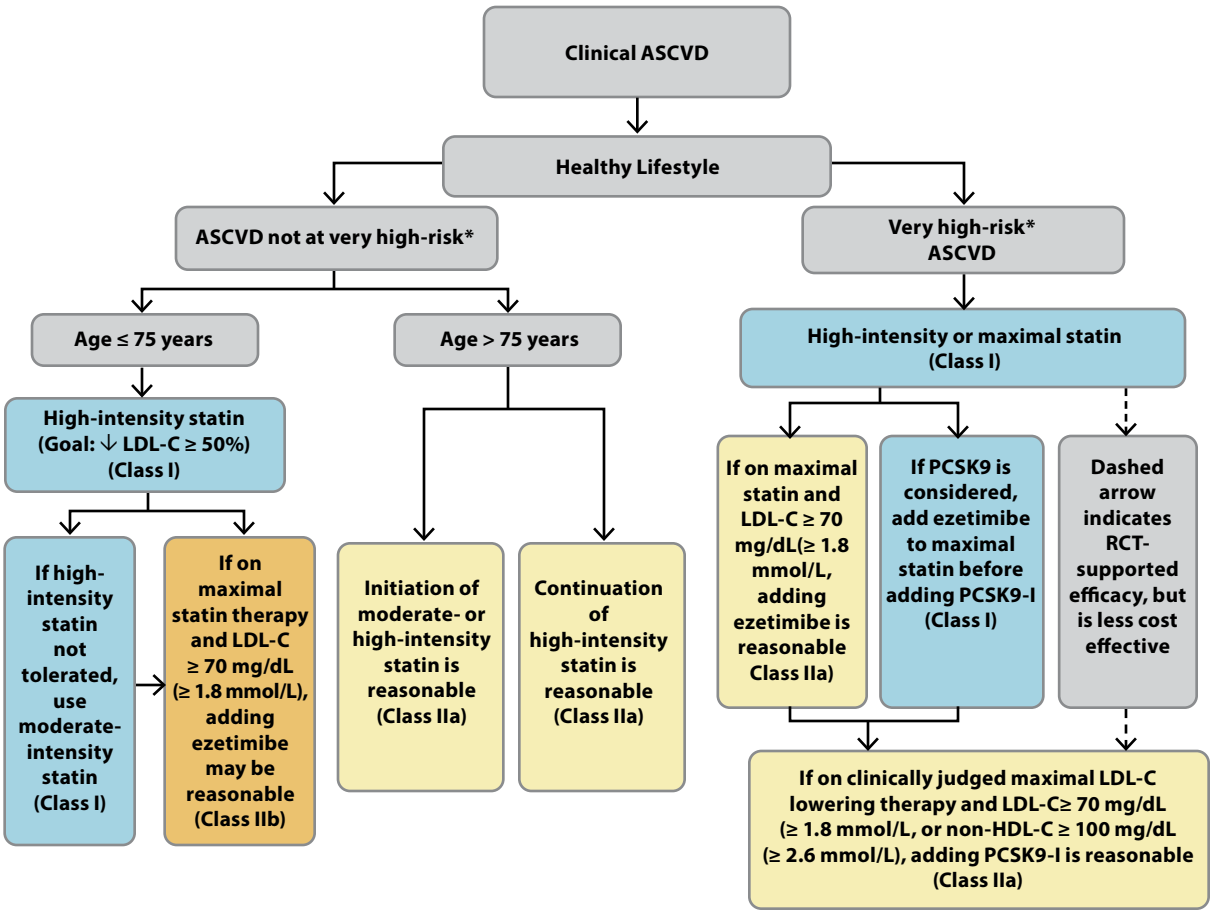
In deciding to prescribe a statin, especially in those with borderline and intermediate risk, shared decision making is very important for several reasons. It strengthens the clinician-patient relationship, increases patient engagement and medication adherence, heightens patient satisfaction, and acknowledges that each case is unique, and that the patient's preference matters.[15]

There is still significant underuse of statins in high-risk groups. This has been shown in those with confirmed ASCVD, LDL-C > 190 mg/dL, and diabetes. In one study, about one-third of those who qualified were not receiving lipid-lowering therapy.[16] Persistence is also an issue with about 50 percent of those who started on a statin stopping within one year. Importantly, stopping a statin increases the risk of cardiovascular disease. There are also gender and racial gaps in care. In one study, women with ASCVD were less likely to be prescribed statins or prescribed high-intensity statins than men.[17] African Americans are less likely to receive statins and less likely to receive appropriate statin dosing compared to Caucasians.[18] African American patients initiating statin therapy are less likely to achieve LDL-C goal, even after controlling for adherence differences and other factors.[19]

Despite high-intensity statin use and achieving goal LDL-C, patients still have residual risk. In major trials that showed reduced risk of events with high-intensity versus standard dosing, people still had events even when at goal LDL-C levels.[20-22] Thus, they may need additional LDL-C lowering. Non-statin lipid lowering agents are added to statin therapy in some patients both to reach LDL-C goals and to reduce residual risk. They may also be used in those who are statin intolerant.

Ezetimibe, bempedoic acid, and proprotein convertase subtilisin/kexin type 9 (PCSK9) agents are the major non-statin lipid lowering agents. The

Exhibit 3: Guideline Recommendations for Secondary Prevention[5]



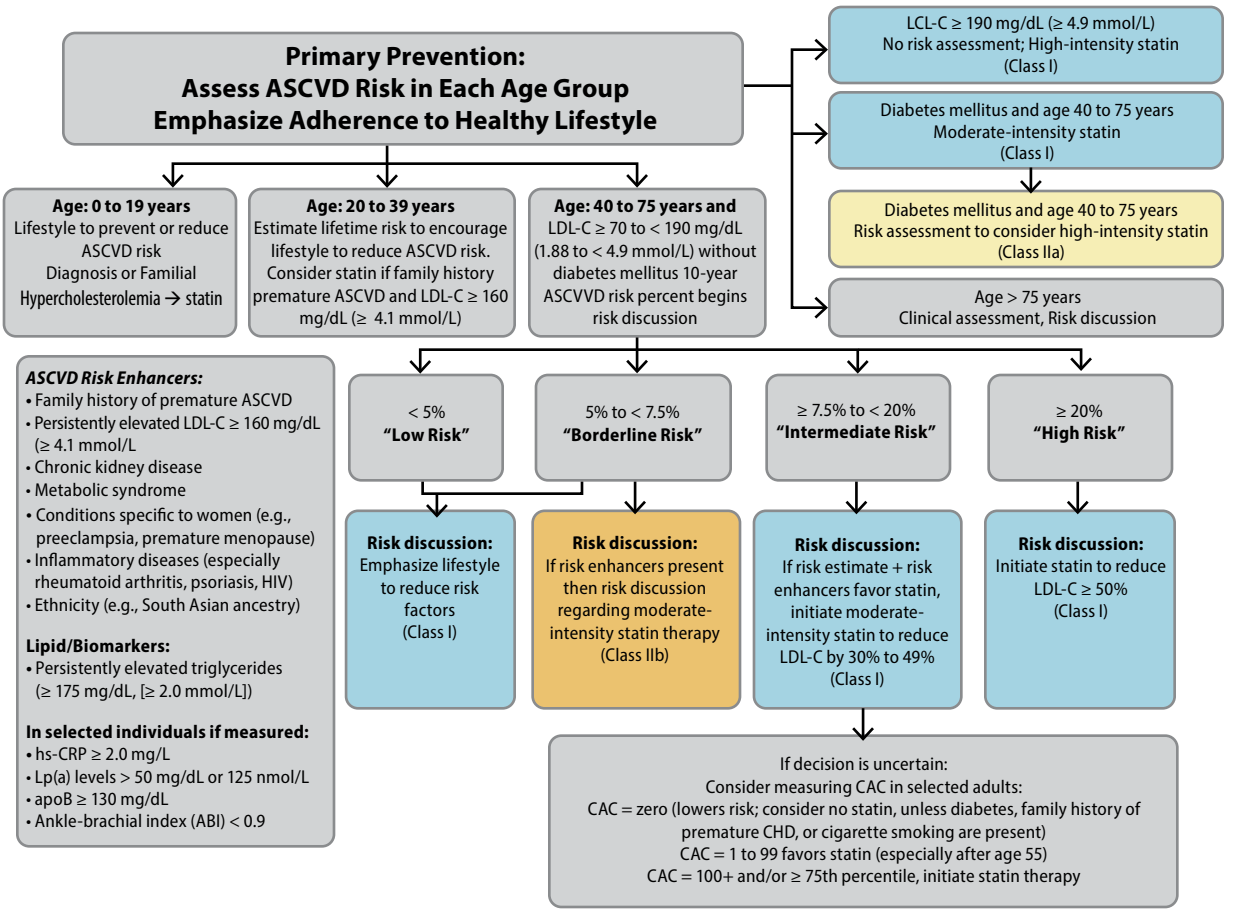
* Very high-risk is defined in text

clinical guidelines recommend that in very high-risk ASCVD, clinicians should use an LDL-C threshold of 70 mg/dL to consider addition of non-statins to statin therapy.[5] Ezetimibe is usually the first agent added to statins. In combination with a statin, it has been shown to reduce residual risk.[23] In patients at very high risk whose LDL-C level remains ≥ 70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable.[5] Based on approved indications, bempedoic acid (with or without ezetimibe) is an option to add to diet and maximally tolerated statin therapy to lower LDL-C in patients with heterozygous FH and those with established clinical ASCVD. It is not yet included in the clinical guidelines.

Alirocumab, evolocumab, and inclisiran are the three available agents that target PCSK9. PCSK9 promotes the degradation of the LDL receptor and prevents it from recycling to the cell membrane. PCSK9 inhibitors alirocumab and evolocumab are injectable monoclonal antibodies that bind to PCSK9 and prevent association between the LDL receptor and PCSK9 which results in LDL-C lowering. On a background of statin therapy in patients with acute coronary syndrome, addition of a PCSK9 inhibitor reduced LDL-C an additional 50 percent to 60 percent and reduced events.[24,25]

Inclisiran is the most recently approved PCSK9 targeting agent. It is a small interfering RNA (siRNA) that prevents intracellular translation of PCSK9 messenger RNA to protein which reduces hepatic synthesis of PCSK9. This injectable is given as two doses a year, after an initial dose and a second dose at three months. Inclisiran reduced LDL-C 52 percent in patients with ASCVD or an ASCVD disease risk equivalent with elevated LDL-C despite maximal tolerated statin therapy.[26] Outcome data with this agent are not yet available. It is FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH or ASCVD, who require additional lowering of LDL-C.

Exhibit 4: Primary Prevention Guidelines[5]



The PCSK9 targeting agents are expensive but the cost of managing a heart attack, bypass surgery, cardiac rehab, and other interventions for ASCVD are also very costly. The costs of these agents range from $5,400 to $6,950 per year. The wholesale price of alirocumab and evolocumab were reduced by their respective manufacturers in 2018/2019. The Institute for Clinical and Economic review found alirocumab and evolocumab would be cost effective at the $100,000 per quality-of-life year at the current prices.[27] Multiple barriers exist for appropriate use of the PCSK9 inhibitors in patients with documented ASCVD or FH with inadequately controlled LDL-C despite standard therapies. Among these barriers, high payer rejection rates and inadequate prior authorization documentation by providers hinder optimal use of these agents.[28] Clinicians are seeing only about 20 percent of high-risk patients who are appropriate candidates being approved by insurance initially. With prior authorization, the rate increases to about 40 percent. Two other barriers are tiered placement and out-of-pocket patient costs. One analysis of Medicare Part D plans found that, in 2020, only one-third of Part D beneficiaries had access to a preferred option across the PCSK9 inhibitors class, despite the decreases in list price.[29] This analysis also found out-of-pocket costs of greater than $100 per month. The PCSK9 agents are not for all patients but they are vital for many high-risk patients. The prior authorization procedures need to be streamlined and access for appropriate patients improved.

Conclusion

Atherosclerosis burden increases with a rising in LDL-C level. Lifestyle changes including dietary changes, weight reduction, and exercise are the backbone of LDL-C reduction for both primary and secondary prevention. Primary prevention with statins is indicated for selected patients based on risk assessment and discussion with the patient. Secondary prevention should include statins for all who can tolerate them. In patients above the LDL-C

goal on maximally tolerated statin therapy, ezetimibe should be considered. If still above the LDL-C threshold on statin/ezetimibe, addition of a PSCK9 agent, priced now within a cost-effectiveness range, should be considered.

Michael Miller, MD, FACC, FAHA is a cardiologist and Chief of Medicine at the CMJC VA Medical Center and Vice Chair of Medicine at the Hospital of the University of Pennsylvania in Philadelphia, PA.

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Novel Approaches to Treating and Managing Menopause: Expanding Options to Improve Outcomes

Genevieve Neal-Perry, MD, PhD

This journal article is supported by an educational grant from Astellas.

For a CME/CEU version of this article, please go to http://www.namcp.org/home/education, and then click the activity title.

Summary

Every woman experiences menopause but many will have this stage of their life significantly impacted by various symptoms. Vasomotor symptoms can be managed with various non-pharmacologic and pharmacologic therapies. The first in a new class of agents has recently come onto the market.

Key Points

- Vasomotor symptoms (VMS) often severely impacts physical, psychosocial, sexual, and overall well-being.
- Hormone replacement therapy is the most clinically effective in managing VMS.
- Non-hormonal options result in 50 to 65 percent reduction in VMS.
- The clinical endpoint of any VMS treatment is patient satisfaction with symptom relief and their ability to tolerate potential risks.
- A new agent to target VMS has recently been FDA approved.

MENOPAUSE IS A RETROSPECTIVE DIAGNOSIS defined as at least 12 consecutive months of no menses and the amenorrhea does not result from surgery. In the United States (U.S.), the median age of menopause is 51 with a typical range between 46 and 52 years. Reproductive senescence is complex and there is emerging evidence in human and non-human models suggesting that in addition to ovarian factors, neuroendocrine factors independently contribute to the menopausal transition.

There are seven stages of reproductive aging (Exhibit 1). The road to menopause starts in the early transition stage where there is more than seven days variability in menses schedule but less than 60 days of amenorrhea. The median age of early transition is 47 and this is the most variable stage which can be less than one year to over 10 years. Late transition is an episode of over 60 days of amenorrhea and typically lasts two years. The early post-menopause phase starts with the last menses but of course cannot be identified until 12 months later. Numerous factors affect the timing of the menopause (Exhibit 2).

Typical symptoms of menopausal transition include menstrual irregularity (90% of women), hot flashes and/or night sweats (80%), insomnia (45%), mood changes and/or depression (30%), cognitive changes (45%), musculoskeletal pain and achiness (50%), diminished libido (60%), and dyspareunia (20%).[1] Insomnia may be related to hot flashes and/or night sweats but not always.

Hot flashes, hot flushes, and night sweats, also known as vasomotor symptoms (VMS), are episodes lasting one to five minutes characterized by rapid and exaggerated heat dissipation consisting of profuse sweating, peripheral vasodilation, and feeling of intense heat primarily involving the head and upper body (unlike exercise). VMS can be accompanied by perspiration, chills, anxiety, and occasionally

Exhibit 1: Reproductive Aging Staging System

- **Reproductive years include three stages:**
  - Early (starts at menarche)
  - Peak
  - Late
- **Menopausal transition includes two stages:**
  - Early
  - Late
- **Post-menopause includes two stages:**
  - Early (starts at final menstrual period)
  - Late

Exhibit 2: What Affects the Timing of Menopause?

- Family genes
- Autoimmune disorder
- Smoking
- Chemotherapy or radiation therapy
- Industrial exposures
- Pelvic surgery or removal of one or both ovaries
- Genetic defects (< 1%)
  - Turner syndrome
  - Fragile X
  - Galactosemia

heart palpitations. Late perimenopause and early menopause stages are when VMS are most likely to be present. Seventy-five percent of women report hot flashes within two years of the final menstrual cycle and 25 percent remain symptomatic for five years or more.[2] Ten percent still report symptoms 11 to 12 years later and 2.2 percent of 70-year-olds report symptoms.[3]

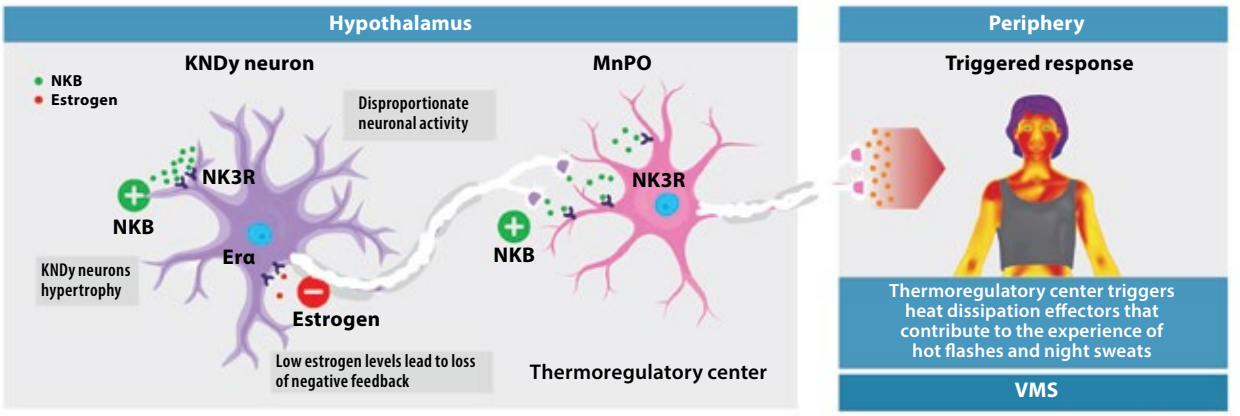
VMS is related to reduced estrogen levels, but peripheral estrogen levels do not predict severity of symptoms. VMS can be mild (sensation of heat without sweating), moderate (with sweating but able to function), or severe (cannot continue regular activities). Moderate-to-severe VMS is considered seven to eight episodes per day or 50 to 60 per week. VMS, particularly when moderate-to-severe, adversely affects health and quality of life.[1,4] VMS often severely impacts physical, psychosocial, sexual, and overall well-being.

There are genetic variants which increase and decrease severity of VMS and the associations are not limited to variations in sex-steroid metabolism genes.[5] Serotonergic and tachykinin receptor 3 genes have been shown to have impact.[6]African American women may start having hot flashes even before perimenopausal transition. Compared with women of other racial/ethnic groups, African American women reported the longest total VMS duration (median, 10.1 years).[4] Other modifiers of duration of VMS include higher body mass index, pre/perimenopausal symptom onset, younger age at the time of first VMS symptom, ever smoker and ever passive smoke.[4] Shorter duration of VMS is associated with postmenopausal onset of VMS, higher social economic status, and Asian ethnicity. No effect of alcohol intake and physical activity has been found.

VMS is a brain-driven phenomena where menopause modifies the Thermoneutral Zone which is regulated by the hypothalamus.[7-8] Kisspeptin/neurokinin B (NKB)/dynorphin [KNDy] neurons are located in the hypothalamus and project into the part of the brain responsible for heat sensing and to neurons that make luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Exhibit 3 shows a model of the current understanding of VMS.[9] With declining estrogen levels, NK3 receptor-mediated activation is unopposed. Unopposed NKB signaling increases neuronal activity, leading to hypertrophy of the KNDy neuron and alters the activity on the thermoregulatory center. The thermoregulatory center triggers heat dissipation effectors. Vasodilation in the skin causes heat loss, which is experienced as hot flashes, sweating, and chills.

There are non-pharmacologic and pharmacologic options for managing VMS. Non-pharmacological treatments are good options for all women experiencing these symptoms. Behavior modifications including paced breathing, relaxation techniques, and biofeedback can help women manage VMS. Lifestyle modifications including wearing layered light-weight clothing; avoiding hot drinks, spicy foods, alcohol, and caffeine if these prompt VMS; and keeping the environment cool with air conditioning or fans can also be helpful. Smoking cessation is also helpful. In studies of medications, even the placebo effect can be as high as 50 percent. In a meta-analysis of randomized controlled medication trials for moderate-to-severe VMS, substantial and consistent placebo effects were seen. This analysis found a reduction of 5.44 times per day in frequency and 0.36 in severity was observed as a placebo effect.[10] In addition to behavioral and lifestyle changes, patients may be interested in herbals, acupuncture, and other

Exhibit 3: Pathophysiology of VMS: Dysregulation of Hypothalamic Thermoregulatory Activity[9]



Erα = estrogen receptor alpha; KNDy = kisspeptin-neurokinin B-dynorphin; MnPO = median preoptic nucleus; NK3R = neurokinin 3 receptors; NKB = neurokinin B; VMS = vasomotor symptoms

alternative therapies but studies show little or no impact beyond the placebo response.

Hormone therapy using estrogens with or without progesterone is well known to improve frequency and severity of VMS from diaries and objectively recorded hot flashes, night sweats, wakening after sleep onset, and life interference. However, for many years there has been controversy about the use of hormone replacement therapy (HRT). The Women's Health Initiative published in 2002 generated much of the controversy.[11] This was a large randomized clinical trial examining the proposed benefits and risks of HRT (cardioprotective, hip fracture, stroke, breast and colon cancer, thromboembolism). The study was stopped early because of an increased incidence of heart disease, breast cancer, stroke, and pulmonary embolism in women with an intact uterus using estrogen and progesterone. There were benefits seen for colon cancer and hip fracture in this group. In women without a uterus who only received estrogen, there was increased risk of stroke and thromboembolic events. This group had reduced risk of coronary heart disease, breast cancer, colon cancer, and hip fracture. Publicity about this trial led to dramatic reductions in HRT use and many women being afraid of HRT. Further analysis of this trial found that the increased risk came from using HRT in the older age group (70 to 79) compared to younger age group (50 to 59). The average age in this trial was 63 years.

This controversy has led to changes in how and when HRT is used. HRT is only intended for treatment of VMS for the shortest period possible and at a low estrogen dose which adequately reduces symptoms. Patients are no longer told that HRT is being prescribed for heart disease or osteoporosis prevention and age matters when therapy is started and stopped. The clinical endpoint of HRT is patient satisfaction with symptom relief and ability to tolerate potential risks. The most bothersome symptoms should be targeted. Once started, HRT doses should be adjusted for symptom control with the patient as the arbiter of 'adequate relief.' Many women choose partial symptom control to avoid perceived risk of HRT.

The American Association of Clinical Endocrinologists, the American College of Endocrinology, and the North American Menopause Society recommendations for VMS management are the use of natural estrogen and progesterone and non-oral forms of estrogen.[12-14] Benefits may exceed risks for the majority of symptomatic post-menopausal women who are under age 60 or under 10 years since the onset of menopause. Consideration for extended use of estrogen can be given in continuing in women without a uterus who remain symptomatic. Clinicians should evaluate the risks, benefits, and alternatives to HRT periodically.

Clinicians, with patient input, can choose from transdermal, oral, or vaginal HRT products. Non-oral dosage forms allow for lower estrogen dose, have lower risk of thromboembolism and less impact on lipids. Other considerations are convenience, cost, and physiological similarity to endogenous hormones. Estradiol and micronized progesterone are the most physiologically similar.

Various non-hormonal agents have been used to manage VMS in those who cannot or are not willing

Exhibit 4: Non-Hormonal Treatments for VMS

Drug	Dose	Percentage Reduction[A]
Venlafaxine	37.5 to 150mg	Up to 61%
Desvenlafaxine	50 to 100mg	Up to 64%
Paroxetine mesylate[B]	7.5mg	Up to 60%
Fluoxetine	20 to 40mg	Up to 50%
Citalopram	10 to 30mg	Up to 50%
Escitalopram	10 to 20mg	Up to 60%
Gabapentin	Up to 2,700mg	Up to 68%
Clonidine	0.1 to 0.4mg	Up to 26%
Fezolinetant[B]	45mg	Up to 65%

[A] Raw value, not placebo subtracted
[B] FDA approved for VMS

to use HRT (Exhibit 4). This includes serotonin norepinephrine reuptake inhibitors (SNRIs, venlafaxine, desvenlafaxine), selective serotonin reuptake inhibitors (SSRIs, paroxetine, fluoxetine, citalopram, escitalopram), gabapentin, clonidine, and a new NK3 receptor antagonist (fezolinetant). Few of the non-hormonal agents have been directly compared to HRT or each other. Venlafaxine has been compared to gabapentin and clonidine in women with breast cancer and escitalopram has been compared to estradiol in women with both depression and VMS.[15-19]

Fezolinetant is the newest agent for managing VMS. It is a neurokinin 3 (NK3) receptor antagonist that blocks NKB binding on the KNDy neuron to modulate neuronal activity in the thermoregulatory center. It is indicated for the treatment of moderate-to-severe VMS due to menopause and was FDA approved in May 2023.[20] In a double-blind, placebo-controlled, 12-week Phase III trial with a 40W active treatment extension (NCT04003142; SKYLIGHT 2), women aged 40 to 65 years with a minimum average of seven moderate-to-severe VMS per day were randomized to 12 weeks of a once-daily placebo, fezolinetant 30 mg, or fezolinetant 45 mg.[21] Completers were rerandomized to fezolinetant 30 or 45 mg for 40 additional weeks. Both fezolinetant doses statistically and significantly reduced VMS frequency and severity at weeks four and 12 versus placebo. For VMS frequency at week 12, the 30 mg resulted in a -1.86 ($p < .001$) reduction and 45 mg, a -2.53 ($p < .001$) reduction. For VMS severity at week 12, the 30 mg dose reduced severity -0.16 ($p < .05$) and 45 mg, -0.29 ($p < .001$). The approved dose is 45 mg once daily. Improvement in VMS frequency and severity was observed by week one and maintained through week 52. Serious TEAEs were infrequent; these were reported by 2 percent, 1 percent, and 0 percent of those receiving fezolinetant 30 mg, fezolinetant 45 mg, and placebo, respectively. Elevated liver function tests were the most common serious adverse event. Abdominal pain was the most common adverse event. The study population was predominately white women with a body mass index less than 38 and mean age of 54. At this time, fezolinetant has only been compared to placebo and has a monthly cost of approximately $550 without insurance coverage. Fezolinetant is a highly specific agent for VMS which is an option for those who are unable to take HRT or for whom HRT or other non-hormonal agents have not controlled their VMS. Several other agents targeting KNDy neurons are under investigation.

Overall, the non-hormonal options do not increase risk for hormone-responsive cancers or coronary heart disease but they also do not improve urogenital symptoms of menopause or protect bone health. The adverse event profile of the older agents frequently contributes to patient discontinuing treatment. Not enough is yet known about the tolerance with fezolinetant.

Clinicians should consider certain patient factors in selecting between hormonal and non-hormonal therapies. For example, obese women have a higher

risk of venous thromboembolism and thus may be better candidates for non-hormonal options.[22] In women with hormonal mediated breast cancer or high-risk for breast cancer, estrogen is not an option so non-hormonal therapy is chosen. Paroxetine does interact with tamoxifen, so another agent should be chosen for those patients taking tamoxifen. Gabapentin is an excellent choice for those who also have chronic pain or sleep dysfunction. For HRT, non-oral estrogens have less impact on triglycerides which may benefit those with elevated or borderline levels. In people who are post-bariatric surgery, intestinal absorption may be compromised thus non-oral HRT should be prescribed. For women with dermatologic diseases or skin sensitivity, transdermal options should be avoided.

If therapy does not improve VMS, other causes for these symptoms beyond menopause should be considered. Autonomic dysfunction from central nervous system tumors, spinal cord injury, and multiple sclerosis can cause similar symptoms. Hyperthyroidism, carcinoid syndrome, pheochromocytoma, serotonin syndrome, and mastocytosis can all lead to vasodilatory flushing.

There are several barriers to optimal VMS management. These include health system barriers such as insurance issues (limited approved medications, large co-pays) and provider barriers including fear of litigation related to HRT adverse events, lack of menopause training, provider discomfort with HRT, and lack of appreciation of VMS impact on women's lives. Patient barriers include fear of hormone therapy, fear of adverse events from non-hormonals, reticence to take antidepressant medications because of stigma, and internet-based disinformation.

Conclusion

VMS can have a major impact on a women's quality of life but there are effective non-pharmacologic and pharmacologic treatments. HRT is the most clinically effective in managing VMS. Non-hormonal options result in 50 to 60 percent reduction in VMS compared with a placebo response rate of up to 50 percent. The clinical endpoint of any VMS treatment is patient satisfaction with symptom relief and ability to tolerate potential risks. The place in therapy for the newest agent which targets the underlying physiology of VMS in a new way is yet to be determined but will likely be in those who are unable to take HRT or for whom other therapies have not controlled their VMS.

Genevieve Neal-Perry, MD, PhD is the Robert A. Ross Distinguished Professor and Chair of Obstetrics and Gynecology at the University of North Carolina School of Medicine, in Chapel Hill, NC.

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NAMCP Introduces the Organization for Objective Review and Clinical Assessment (OORCA)

iRhythm – Zio Device Review

IMAGINE A MEETING BETWEEN A MEDICAL director at a payer organization and a professional representative from industry during which the seller conveys messaging and claims about its respective product using sales and marketing information and clinical studies where applicable. At the conclusion of the meeting, the medical director is left to assume that the presented claims and associated messaging are credible and objective without the time or their own health and economics/outcomes expertise to affirm those claims.

In 2021, the medical leadership of the Value Based Care Council (VBCC) of the National Association of Managed Care Physicians (NAMCP) uncovered an unmet need and requested that an objective third party be created whereby the value propositions of products, such as pharmaceuticals and medical devices, could be assessed for both credibility and objectivity based on the evidence. The goal was to supply the marketplace with an objective entity that would help bridge the trust chasm between manufacturers and payers/customers by providing such an assessment. This assessment is not an endorsement of a product, but affirmation of the viability of a manufacturer's product claims. This is distinctly different from other assessment frameworks as this process does not measure the value of a product and has nothing to do with price. The VBCC agreed that function is up to payer organizations to determine for their respective membership. Thus, the purpose of the Organization for Objective Review and Clinical Assessment

(OORCA) is to provide affirmation from an objective third party about a product's value proposition and its supporting body of evidence that will be helpful when payers evaluate a product.

Once created, OORCA was charged with conducting an initial assessment to pressure test the infrastructure, methodology, and processes, with the VBCC reviewing and providing input/feedback for improvement along the way. Over the last two years, OORCA's approach was refined based upon this feedback and now utilizes the Value Proposition Customer Engagement Short Form* (previously developed and approved by the VBCC) for the submission of manufacturer information for assessment.

The assessment is predicated upon evidence and information submitted by the manufacturer with a methodology/process and established criteria to review four domains of claims: efficacy, safety, economic, and other patient outcomes or product attributes. Once the evaluation is completed, a final report is generated. OORCA's inaugural assessment was conducted for iRhythm on its value proposition for the Zio device. The report's summary page for that assessment is at the end of this article. The goal of NAMCP is to have OORCA available for manufacturer request submissions by the end of 2023/early 2024. If a company has interest in an assessment, it can reach out to NAMCP directly at *(see below).

About iRhythm Technologies, Inc.

iRhythm is a leading digital healthcare company that creates trusted solutions that detect, predict, and prevent disease. Combining wearable biosensors and cloud-based data analytics with powerful proprietary algorithms, iRhythm distills data from millions of heartbeats into clinically actionable information. Through a relentless focus on patient care, iRhythm's vision is to deliver better data, better insights, and better health for all. To learn more about iRhythm, including its portfolio of Zio products and services, please visit irhythmtech.com.

*** Value Proposition Customer Engagement Short Form can be found under the Councils/VBCC tab of the NAMCP website, www.namcp.org.**

Organization for Objective Review and Clinical Assessment (OORCA)

Objective Review and Clinical Assessment of Manufacturer's Value Proposition*

iRhythm's value proposition for the Zio XT cardiac monitor was assessed for credibility and objectivity based on available evidence submitted as of April 25, 2023.

Efficacy Claims

Although there are no traditional large, pivotal, label-enabling, Phase III trials that support the efficacy and FDA clearance of the Zio XT cardiac monitor, multiple studies published since 2013 have shown the clinical utility of the device to detect arrhythmias effectively, as outlined in #8a of the full report. The value proposition for the Zio XT device is credible and objective based on available evidence as it relates to:

- Diagnostic yield, including compared with other alternatives (e.g., Holter monitor)
- Analyzable wear time
- Detection of many types of arrhythmias
- Lower likelihood for retesting compared with other monitor types
- Improved clinical outcomes
- Decreased time to diagnosis

Safety Claims

No specific safety claims were made.

Other Claims About Patient Outcomes or Product Attributes

Patient compliance was shown in multiple studies to be high, as demonstrated by long median and mean wear times. Published studies have reported that patients preferred the Zio XT over the Holter monitor and found the device comfortable to wear (Barrett et al. 2014; Reed et al. 2018). Thus, claims about patient compliance and preference are credible and objective.

Economic Claims

The Dossier states that Zio XT reduces healthcare costs; however, the only referenced study in the Dossier that supports cost savings is Kaura et al (2019). Authors reported that an economic model demonstrated that Zio XT would result in more strokes avoided compared with Holter monitoring, which was associated with direct medical cost savings. Since the Dossier was developed, two additional studies have shown that Zio XT is associated with lower HCRU and costs (Waalen et al. 2020; Reynolds et al. 2023). Despite limited evidence for cost savings, iRhythm is the only manufacturer of cardiac monitors that have conducted and published real-world comparative economic and outcome data to support the value proposition of the Zio XT monitor. The economic claims for Zio XT are credible and objective. That said, additional research would be helpful to further elucidate the economic impact and cost-effectiveness of Zio XT compared to other modalities in monitoring and screening for arrhythmias.

*** The full report can be found under the VBCC tab of the NAMCP website, www.namcp.org.**

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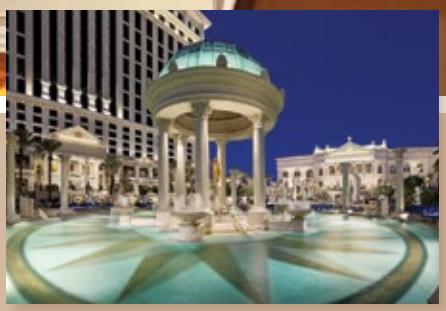

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