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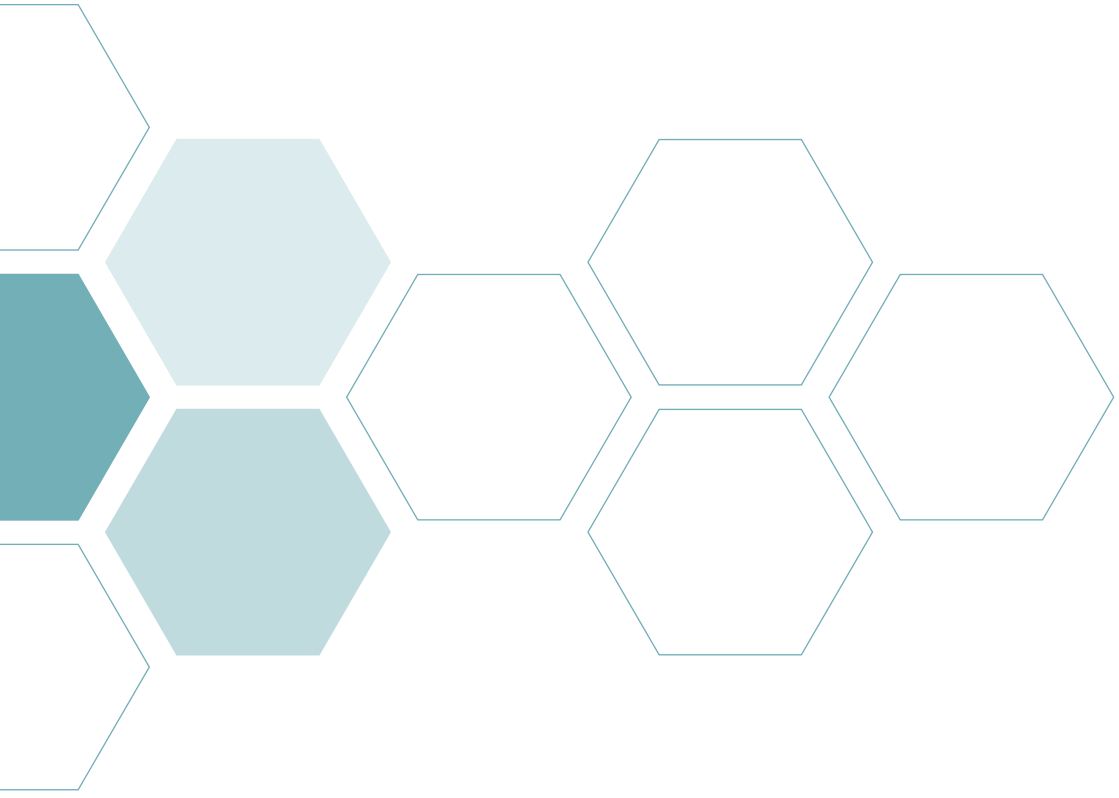
Educating Medical Directors of Employers, Health Plans and Provider Systems



FEATURED ARTICLES INCLUDE:

Patient-Focused Treatment Decisions in HER2-Positive Advanced Breast Cancer: A Closer Look at the Role of New and Emerging Therapies

Treating Chronic Inflammatory Demyelinating Polyradiculoneuropathy with Immunoglobulin: Managed Care Considerations in an Evolving Treatment Paradigm

New Developments in the Treatment and Management of Psoriasis: Key Considerations for Improving Outcomes

Editorial Review Board

When adult patients with obstructive sleep apnea (OSA) or narcolepsy are struggling with excessive daytime sleepiness (EDS),

ONCE-DAILY SUNOSI

is the first and only WPA proven to improve wakefulness through **9 HOURS**[1,2]*†

*As seen at week 12.

†The 75 mg dose did not show a statistically significant improvement for patients with narcolepsy-associated EDS.

WPA=wake-promoting agent.

SUNOSI® (solriamfetol) CIV
75, 150 mg tablets

Eligible patients may get started on SUNOSI with savings cards, samples, and/or free vouchers.

Visit SUNOSIhcp.com or contact your Jazz Account Manager to learn more

INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adults with excessive daytime sleepiness (EDS) associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use:

SUNOSI is not indicated to treat the underlying obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI. SUNOSI is not a substitute for these modalities, and the treatment of the underlying airway obstruction should be continued.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion. Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment could be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders, as SUNOSI has not been evaluated in these patients.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Observe SUNOSI patients for the possible emergence or exacerbation of psychiatric symptoms. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5%) reported more frequently with the use of SUNOSI than placebo in either narcolepsy or OSA were headache, nausea, decreased appetite, anxiety, and insomnia.

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

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders.* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. SUNOSI (solriamfetol) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc.

Jazz Pharmaceuticals

SUNOSI® (solriamfetol) tablets, for oral use, CIV
BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the Full Prescribing Information for complete product information.
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SUNOSI is indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA).

Limitations of Use

SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities.

DOSAGE AND ADMINISTRATION

Important Considerations Prior to Initiating Treatment

Prior to initiating treatment with SUNOSI, ensure blood pressure is adequately controlled.

General Administration Instructions

Administer SUNOSI orally upon awakening with or without food. Avoid taking SUNOSI within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.

SUNOSI 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.

CONTRAINDICATIONS

SUNOSI is contraindicated in patients receiving concomitant treatment with monoamine oxidase (MAO) inhibitors, or within 14 days following discontinuation of monoamine oxidase inhibitor, because of the risk of hypertensive reaction.

WARNINGS AND PRECAUTIONS

Blood Pressure and Heart Rate Increases

SUNOSI increases systolic blood pressure, diastolic blood pressure, and heart rate in a dose-dependent fashion.

Epidemiological data show that chronic elevations in blood pressure increase the risk of major adverse cardiovascular events (MACE), including stroke, heart attack, and cardiovascular death. The magnitude of the increase in absolute risk is dependent on the increase in blood pressure and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high body mass index (BMI).

Assess blood pressure and control hypertension before initiating treatment with SUNOSI. Monitor blood pressure regularly during treatment and treat new-onset hypertension and exacerbations of pre-existing hypertension. Exercise caution when treating patients at higher risk of MACE, particularly patients with known cardiovascular and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Use caution with other drugs that increase blood pressure and heart rate.

Periodically reassess the need for continued treatment with SUNOSI. If a patient experiences increases in blood pressure or heart rate that cannot be managed with dose reduction of SUNOSI or other appropriate medical intervention, consider discontinuation of SUNOSI.

Patients with moderate or severe renal impairment may be at a higher risk of increases in blood pressure and heart rate because of the prolonged half-life of SUNOSI.

Psychiatric Symptoms

Psychiatric adverse reactions have been observed in clinical trials with SUNOSI, including anxiety, insomnia, and irritability.

SUNOSI has not been evaluated in patients with psychosis or bipolar disorders. Exercise caution when treating patients with SUNOSI who have a history of psychosis or bipolar disorders.

Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of SUNOSI.

Patients treated with SUNOSI should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of SUNOSI, consider dose reduction or discontinuation of SUNOSI.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Blood Pressure and Heart Rate Increases
- Psychiatric Symptoms

Clinical Trials Experience

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

The safety of SUNOSI has been evaluated in 930 patients (ages 18 to 75 years) with narcolepsy or OSA. Among these patients, 396 were treated with SUNOSI in the 12-week placebo-controlled trials at doses of 37.5 mg (OSA only), 75 mg, and 150 mg once daily. Information provided below is based on the pooled 12-week placebo-controlled studies in patients with narcolepsy or OSA.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥ 5% and greater than placebo) reported more frequently with the use of SUNOSI than placebo in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, anxiety, and insomnia.

Table 1 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the narcolepsy population.

Table 1: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy (75 mg and 150 mg)

	Narcolepsy	
System Organ Class	**Placebo** N = 108 (%)	**SUNOSI** N = 161 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	9
Psychiatric Disorders		
Insomnia*	4	5
Anxiety*	1	6
Nervous System Disorders		
Headache*	7	16
Cardiac Disorders		
Palpitations	1	2
Gastrointestinal Disorders		
Nausea*	4	7
Dry mouth	2	4
Constipation	1	3

*"Insomnia" includes insomnia, initial insomnia, middle insomnia, and terminal insomnia. "Anxiety" includes anxiety, nervousness, and panic attack. "Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Table 2 presents the adverse reactions that occurred at a rate of ≥ 2% and more frequently in SUNOSI-treated patients than in placebo-treated patients in the OSA population.

Table 2: Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in OSA (37.5 mg, 75 mg, and 150 mg)

	OSA	
System Organ Class	**Placebo** N = 118 (%)	**SUNOSI** N = 235 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	1	6
Psychiatric Disorders		
Anxiety*	1	4
Irritability	0	3
Nervous System Disorders		
Dizziness	1	2
Cardiac Disorders		
Palpitations	0	3
Gastrointestinal Disorders		
Nausea*	6	8
Diarrhea	1	4
Abdominal pain*	2	3
Dry mouth	2	3
General Disorders and Administration Site Conditions		
Feeling jittery	0	3
Chest discomfort	0	2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	0	2

*"Anxiety" includes anxiety, nervousness, and panic attack. "Nausea" includes nausea and vomiting. "Abdominal pain" includes abdominal pain, abdominal pain upper, and abdominal discomfort.

Other Adverse Reactions Observed During the Premarketing Evaluation of SUNOSI

Other adverse reactions of < 2% incidence but greater than placebo are shown below. The following list does not include adverse reactions: 1) already listed in previous tables or elsewhere in the labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, or 4) which were not considered to have clinically significant implications.

Narcolepsy population:

Psychiatric disorders: agitation, bruxism, irritability

Respiratory, thoracic and mediastinal disorders: cough

Skin and subcutaneous tissue disorders: hyperhidrosis

General disorders and administration site conditions: feeling jittery, thirst, chest discomfort, chest pain

Investigations: weight decreased

OSA population

Psychiatric disorders: bruxism, restlessness

Nervous system disorders: disturbances in attention, tremor

Respiratory, thoracic and mediastinal disorders: cough, dyspnea

Gastrointestinal disorders: constipation, vomiting

Investigations: weight decreased

Dose-Dependent Adverse Reactions

In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg daily of SUNOSI to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth (Table 3).

Table 3: Dose-Dependent Adverse Reactions ≥ 2% in Patients Treated with SUNOSI and Greater than Placebo in Pooled 12-Week Placebo-Controlled Clinical Trials in Narcolepsy and OSA

	Placebo N = 226 (%)	**SUNOSI 37.5 mg** N = 58* (%)	**SUNOSI 75 mg** N = 120 (%)	**SUNOSI 150 mg** N = 218 (%)
Headache**	8	7	9	13
Nausea**	5	7	5	9
Decreased appetite	1	2	7	8
Anxiety	1	2	3	7
Dry mouth	2	2	3	4
Diarrhea	2	2	4	5

*In OSA only.

**"Headache" includes headache, tension headache, and head discomfort. "Nausea" includes nausea and vomiting.

Adverse Reactions Resulting in Discontinuation of Treatment

In the 12-week placebo-controlled clinical trials, 11 of the 396 patients (3%) who received SUNOSI discontinued because of an adverse reaction compared to 1 of the 226 patients (< 1%) who received placebo. The adverse reactions resulting in discontinuation that occurred in more than one SUNOSI-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).

Increases in Blood Pressure and Heart Rate

SUNOSI's effects on blood pressure and heart rate are summarized below. Table 4 shows maximum mean changes in blood pressure and heart rate recorded at sessions where the Maintenance of Wakefulness Test (MWT) was administered. Table 5 summarizes 24-hour ambulatory blood pressure monitoring (ABPM) and ambulatory heart rate monitoring performed in the outpatient setting.

Table 4: Maximal Mean Changes in Blood Pressure and Heart Rate Assessed at MWT Sessions from Baseline through Week 12: Mean (95% CI)*

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n	52		51	49	53
	SBP	3.5 (0.7, 6.4)	-	3.1 (0.1, 6.0)	4.9 (1.7, 8.2)	6.8 (3.2, 10.3)
	n	23		47	49	53
	DBP	1.8 (-1.8, 5.5)	-	2.2 (0.2, 4.1)	4.2 (2.0, 6.5)	4.2 (1.5, 6.9)
	n	48		26	49	53
	HR	2.3 (-0.1, 4.7)	-	3.7 (0.4, 6.9)	4.9 (2.3, 7.6)	6.5 (3.9, 9.0)
OSA *STUDY 2*	n	35	17	54	103	35
	SBP	1.7 (-1.4, 4.9)	4.6 (-1.1, 10.2)	3.8 (1.2, 6.4)	2.4 (0.4, 4.4)	4.5 (1.1, 7.9)
	n	99	17	17	107	91
	DBP	1.4 (-0.1, 2.9)	1.9 (-2.3, 6.0)	3.2 (-0.9, 7.3)	1.8 (0.4, 3.2)	3.3 (1.8, 4.8)
	n	106	17	51	102	91
	HR	1.7 (0.1, 3.3)	1.9 (-1.9, 5.7)	3.3 (0.6, 6.0)	2.9 (1.4, 4.4)	4.5 (3.0, 6.0)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*For study weeks 1, 4, and 12, SBP, DBP, and HR were assessed pre-dose and every 1-2 hours for 10 hours after test drug administration. For all time points at all visits, the mean change from baseline was calculated, by indication and dose, for all patients with a valid assessment. The table shows, by indication and dose, the mean changes from baseline for the week and time point with the maximal change in SBP, DBP, and HR.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 5: Blood Pressure and Heart Rate by 24-hour Ambulatory Monitoring: Mean Change (95% CI) from Baseline at Week 8

		Placebo	SUNOSI 37.5 mg	SUNOSI 75 mg	SUNOSI 150 mg	SUNOSI 300 mg**
Narcolepsy *STUDY 1*	n*	46		44	44	40
	SBP	-0.4 (-3.1, 2.4)	-	1.6 (-0.4, 3.5)	-0.5 (-2.1, 1.1)	2.4 (0.5, 4.3)
	DBP	-0.2 (-1.9, 1.6)	-	1.0 (-0.4, 2.5)	0.8 (-0.4, 2.0)	3.0 (1.4, 4.5)
	HR	0.0 (-1.9, 2.0)	-	0.2 (-2.1, 2.4)	1.0 (-1.2, 3.2)	4.8 (2.3, 7.2)
OSA *STUDY 2*	n*	92	43	49	96	84
	SBP	-0.2 (-1.8, 1.4)	1.8 (-1.1, 4.6)	2.6 (0.02, 5.3)	-0.2 (-2.0, 1.6)	2.8 (-0.1, 5.8)
	DBP	0.2 (-0.9, 1.3)	1.4 (-0.4, 3.2)	1.5 (-0.04, 3.1)	-0.1 (-1.1, 1.0)	2.4 (0.5, 4.4)
	HR	-0.4 (-1.7, 0.9)	0.4 (-1.4, 2.2)	1.0 (-0.9, 2.81)	1.7 (0.5, 2.9)	1.6 (0.3, 2.9)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

*Number of patients who had at least 50% valid ABPM readings.

**The maximum recommended daily dose is 150 mg. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

DRUG INTERACTIONS

Monoamine Oxidase (MAO) Inhibitors

Do not administer SUNOSI concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAO inhibitors and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

Drugs that Increase Blood Pressure and/or Heart Rate

Concomitant use of SUNOSI with other drugs that increase blood pressure and/or heart rate has not been evaluated, and such combinations should be used with caution.

Dopaminergic Drugs

Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with SUNOSI. Interactions with dopaminergic drugs have not been evaluated with SUNOSI. Use caution when concomitantly administering dopaminergic drugs with SUNOSI.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to SUNOSI during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.

Risk Summary

Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproductive studies, oral administration of solriamfetol during organogenesis caused maternal and fetal toxicities in rats and rabbits at doses ≥ 4 and 5 times and was teratogenic at doses 19 and ≥ 5 times, respectively, the maximum recommended human dose (MRHD) of 150 mg based on mg/m^2 body surface area. Oral administration of solriamfetol to pregnant rats during pregnancy and lactation at doses ≥ 7 times the MRHD based on mg/m^2 body surface area resulted in maternal toxicity and adverse effects on fertility, growth, and development in offspring *(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 risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Solriamfetol was administered orally to pregnant rats during the period of organogenesis at 15, 67, and 295 mg/kg/day, which are approximately 1, 4, and 19 times the MRHD based on mg/m^2 body surface area. Solriamfetol at ≥ 4 times the MRHD caused maternal toxicity that included hyperactivity, significant decreases in body weight, weight gain, and food consumption. Fetal toxicity at these maternally toxic doses included increased incidence of early resorption and post-implantation loss, and decreased fetal weight.

Solriamfetol was teratogenic at 19 times the MRHD; it increased the incidence of fetal malformations that included severe sternebrae mal-alignment, hindlimb rotation, bent limb bones, and situs inversus. This dose was also maternally toxic. The no-adverse-effect level for malformation is 4 times and for maternal and embryofetal toxicity is approximately 1 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rabbits during the period of organogenesis at 17, 38, and 76 mg/kg/day, which are approximately 2, 5, and 10 times the MRHD based on mg/m^2 body surface area. Solriamfetol at 10 times the MRHD caused maternal toxicity of body weight loss and decreased food consumption. Solriamfetol was teratogenic at ≥ 5 times the MRHD, it caused fetal skeletal malformation (slight-to-moderate sternebrae mal-alignment) and decreased fetal weight. The no-adverse-effect level for malformation and fetal toxicity is approximately 2 times and for maternal toxicity is approximately 5 times the MRHD based on mg/m^2 body surface area.

Solriamfetol was administered orally to pregnant rats during the period of organogenesis from gestation day 7 through lactation day 20 post-partum, at 35, 110, and 350 mg/kg/day, which are approximately 2, 7, and 22 times the MRHD based on mg/m^2 body surface area. At ≥ 7 times the MRHD, solriamfetol caused maternal toxicity that included decreased body weight gain, decreased food consumption, and hyperpnea. At these maternally toxic doses, fetal toxicity included increased incidence of stillbirth, postnatal pup mortality, and decreased pup weight. Developmental toxicity in offspring after lactation day 20 included decreased body weight, decreased weight gain, and delayed sexual maturation. Mating and fertility of offspring were decreased at maternal doses 22 times the MRHD without affecting learning and memory. The no-adverse-effect level for maternal and developmental toxicity is approximately 2 times the MRHD based on mg/m^2 body surface area.

LACTATION

Risk Summary

There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.

Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUNOSI and any potential adverse effects on the breastfed child from SUNOSI or from the underlying maternal condition.

Clinical Considerations

Monitor breastfed infants for adverse reactions, such as agitation, insomnia, anorexia and reduced weight gain.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of SUNOSI in pediatric patients have not been conducted.

Geriatric Use

Of the total number of patients in the narcolepsy and OSA clinical studies treated with SUNOSI, 13% (123/930) were 65 years of age or over.

No clinically meaningful differences in safety or effectiveness were observed between elderly and younger patients.

Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

Renal Impairment

Dosage adjustment is not required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m^2). Dosage adjustment is recommended for patients with moderate to severe renal impairment (eGFR 15-59 mL/min/1.73 m^2). SUNOSI is not recommended for patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

SUNOSI contains solriamfetol, a Schedule IV controlled substance.

Abuse

SUNOSI has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of SUNOSI 300 mg, 600 mg, and 1200 mg (two, four, and eight times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals experienced with the recreational use of stimulants. Results from this clinical study demonstrated that SUNOSI produced Drug Liking scores similar to or lower than phentermine. In this crossover study, elevated mood was reported by 2.4% of placebo-treated subjects, 8 to 24% of SUNOSI-treated subjects, and 10 to 18% of phentermine-treated subjects. A 'feeling of relaxation' was reported in 5% of placebo-treated subjects, 5 to 19% of SUNOSI-treated subjects and 15 to 20% of phentermine-treated subjects.

Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (e.g., methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of SUNOSI (e.g., incrementation of doses, drug-seeking behavior).

Dependence

In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of SUNOSI were evaluated following at least 6 months of SUNOSI use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of SUNOSI were also evaluated during the two-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of SUNOSI resulted in a consistent pattern of adverse events in individual subjects that was suggestive of physical dependence or withdrawal.

OVERDOSAGE

A specific reversal agent for SUNOSI is not available. Hemodialysis removed approximately 21% of a 75 mg dose in end stage renal disease patients. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring.

Consult with a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

PATIENT COUNSELING INFORMATION

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

Potential for Abuse and Dependence

Advise patients that SUNOSI is a federally controlled substance because it has the potential to be abused. Advise patients to keep their medication in a secure place and to dispose of unused SUNOSI as recommended in the Medication Guide.

Primary OSA Therapy Use

Inform patients that SUNOSI is not indicated to treat the airway obstruction in OSA and they should use a primary OSA therapy, such as CPAP, as prescribed to treat the underlying obstruction. SUNOSI is not a substitute for primary OSA therapy.

Blood Pressure and Heart Rate Increases

Instruct patients that SUNOSI can cause elevations of their blood pressure and pulse rate and that they should be monitored for such effects.

Psychiatric Symptoms

Instruct patients to contact their healthcare provider if they experience, anxiety, insomnia, irritability, agitation, or signs of psychosis or bipolar disorders.

Lactation

Monitor breastfed infants for adverse reactions such as agitation, insomnia, anorexia, and reduced weight gain.

For more information, visit www.SUNOSI.com

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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
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

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

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

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Patient-Focused Treatment Decisions in HER2-Positive Advanced Breast Cancer: A Closer Look at the Role of New and Emerging Therapies

Sara A. Hurvitz, MD, FACP

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

Summary

It is an exciting time to be treating HER2-positive metastatic breast cancer. Three new treatments have been FDA-approved in the past year. Previously, this type of breast cancer was associated with the worst long-term outcomes and now has some of the best outcomes.

Key Points

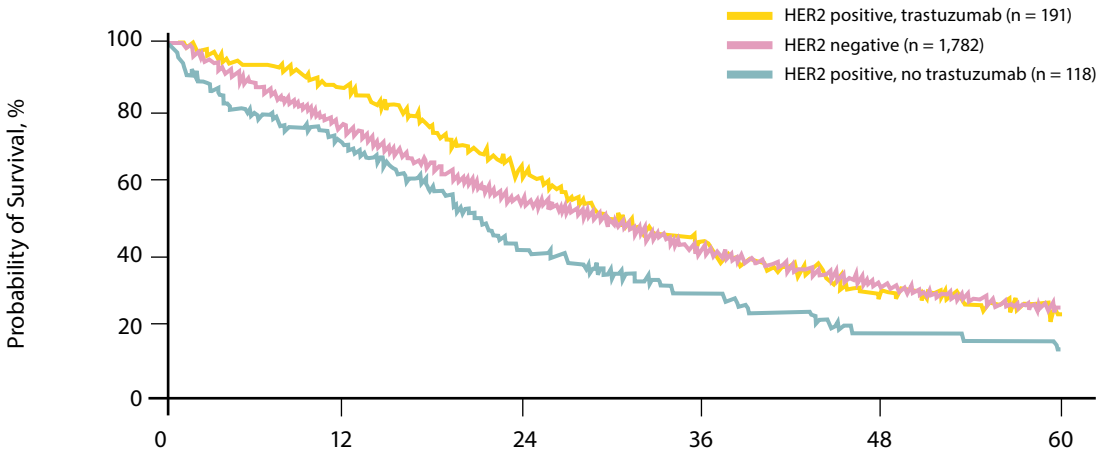
- First-line therapy is the triple combination of pertuzumab, trastuzumab and docetaxel or paclitaxel.
- Second-line therapy is ado-trastuzumab emtansine.
- There are many options for third-line and beyond therapy.
- Some of the new therapies, while approved for third-line or later, will likely move to second-line as more data are gained.

BEFORE THE AVAILABILITY OF TARGETED therapy, breast cancer that overexpressed human epidermal growth factor receptor two (HER2) had a shorter median survival from time of diagnosis than breast cancer with normal HER2 expression (3 years versus 6 to 7 years).[1] The HER2 gene makes HER2 proteins (also sometimes referred to as HER2/neu proteins), which are receptors on breast cells. Normally, HER2 receptors help control how a healthy breast cell grows, divides, and repairs itself; however, in about 10 percent to 20 percent of breast cancers, the HER2 gene does not work correctly and makes too many copies of itself (HER2 gene amplification). All these extra HER2 genes tell breast cells to make too many HER2 receptors (HER2 protein overexpression). This makes breast cells grow and divide in an uncontrolled way.

Trastuzumab, an anti-HER2 antibody, was the first targeted therapy for this type of breast cancer, and it has changed the natural history of HER2 positive (HER2+) metastatic breast cancer (MBC). Patients with HER2+ MBC treated with trastuzumab now have comparable outcomes with HER2 negative MBC (Exhibit 1).[2] Median overall survival (OS) for HER2+ MBC increased from 39 months in 2008 to 58 months in 2013 and continues to increase.

Currently, there are numerous FDA-approved targeted agents for treating HER2+ MBC. In addition to trastuzumab, there is ado-trastuzumab emtansine (Kadcyla®, also known as T-DM1), fam-trastuzumab deruxtecan-nxki (Enhertu®), pertuzumab (Perjeta®), lapatinib (Tykerb®), neratinib (Nerlynx®), tucatinib (Tukysa®), and margetuximab (Margenza®). Trastuzumab and pertuzumab are often given together, so there is also a combination product (Phesgo®). Trastuzumab, pertuzumab, and margetuximab are all monoclonal antibodies that bind to the HER2 receptor. Lapatinib, neratinib, and tucatinib are oral tyrosine kinase inhibitors which target the intracellular part of the HER2 receptor. Ado-trastuzumab emtansine and fam-trastuzumab deruxtecan are antibody chemotherapy conjugates that lead the chemotherapy component into the tumor cell via HER2 receptor binding.

Exhibit 1: Impact of Trastuzumab[2]



First-line therapy for HER2+ MBC is the triple combination of pertuzumab, trastuzumab and docetaxel or paclitaxel (Exhibit 2).[3] This regimen would not be used in a patient who received either pertuzumab or trastuzumab in earlier stage disease treatment. The pertuzumab and trastuzumab are continued as maintenance therapy if there is response to four to six cycles of taxane chemotherapy. Because MBC is not curable, long-term durable responses to first-line therapy only occur in about 5 percent of patients.

There is a group of patients who are HER2+ and hormone receptor positive (HR+). HER2-targeted therapy adds modestly to endocrine therapy, but there is not great evidence that endocrine therapy adds anything to HER2-targeted therapy.[4-7] Because of this, the focus of therapy, in those who are positive for both HER2+ and HR+, is HER2-targeted therapy. Hormone receptor therapies such as an aromatase inhibitor are added during maintenance therapy.

Second-line therapy at disease progression is ado-trastuzumab emtansine.[3] This antibody/chemotherapy conjugate improves median OS by 5.8 months compared to lapatinib/capecitabine.[8] Several trials have shown that it is important to keep the brakes on HER2 through each line of therapy in order to keep control of the cancer.[9-11]

There are many different treatment options for third-line therapy and beyond, with no one regimen being preferred in most patients (Exhibit 2). Multiple lines of therapy are appropriate as long as the patient has a reasonable performance status and is willing to receive therapy. In one analysis looking at diverse types of MBC, patients with HER2+ disease received the most lines (median, 4; p = .032) of treatment and had the longest duration of chemotherapy for every line.[12] The median duration of chemotherapy response in HER2+ patients remained at more than four months, even out to sixth-line therapy.

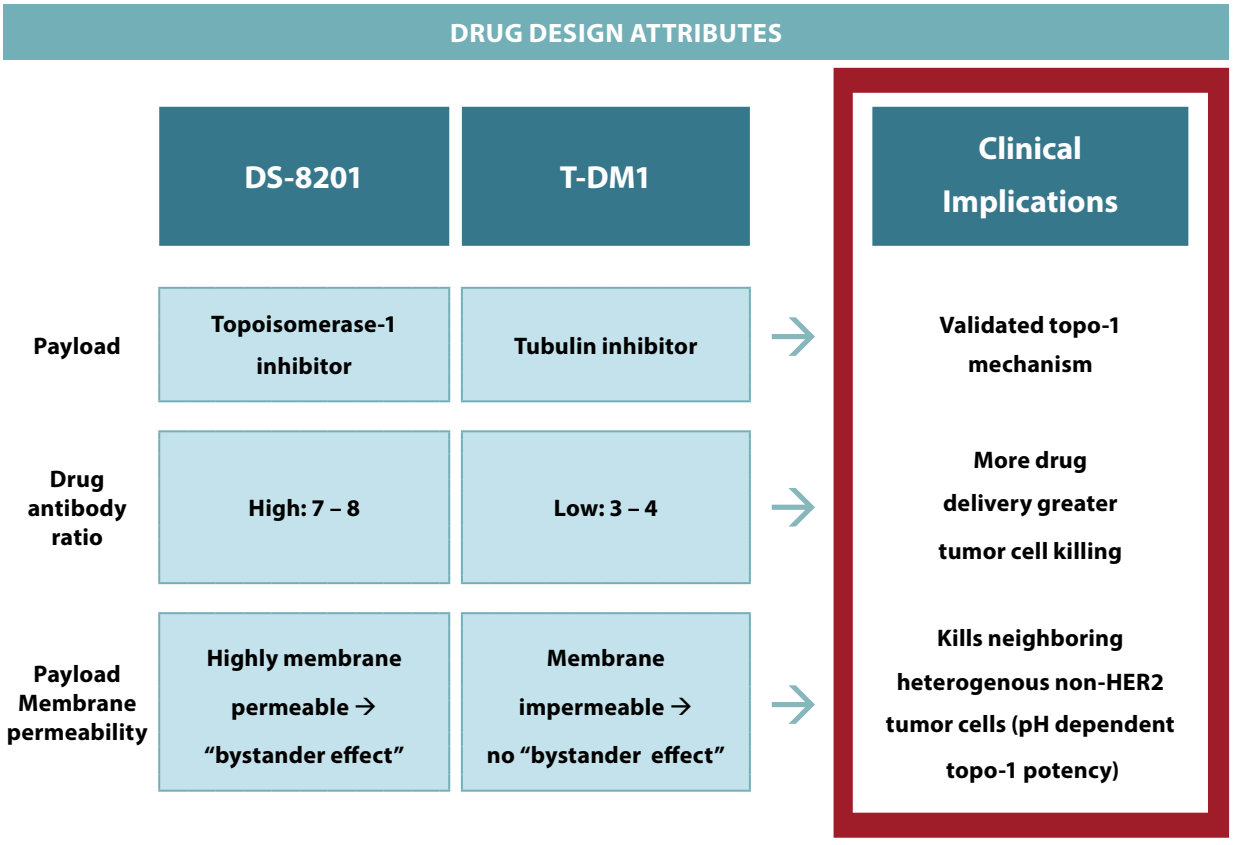
Fam-trastuzumab, deruxtecan, neratinib, tucatinib, and margetuximab have all been FDA-approved since 2019. Each is approved for the third-line or later setting; however, as more trial experience is gained with them, they may move into an earlier line or stage of treatment. Exhibit 3 compares some of the drug design attributes which may favor fam-trastuzumab deruxtecan over ado-trastuzumab emtansine.[13] Fam-trastuzumab deruxtecan's ability to kill neighboring non-HER2+ tumor cells has led to it also being evaluated in non-HER2+ breast cancer. In a heavily pretreated HER2+ 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 non-randomized study which led to FDA-accelerated approval.[14] Importantly, this agent can cause interstitial lung disease which has led to some deaths. This agent is being studied against ado-trastuzumab emtansine in the second-line setting.

Neratinib is a pan-HER inhibitor (HER2 and HER1). HER1 is also better known as epidermal growth factor receptor (EGFR). Because of EGFR effects, neratinib causes a significant rate of diarrhea and skin toxicity. When compared to lapatinib, neratinib treatment results in higher progression-free survival (PFS) (8.8 versus 6.6 months), similar OS, and more diarrhea (24% versus 13%).[15] Most

Exhibit 2: Systemic Regimens for HER2 Positive Metastatic Breast Cancer[3]

Setting	Regimen	Preference	Category of Evidence
First- line	Pertuzumab + trastuzumab + docetaxel	Preferred regimen	1
	Pertuzumab + trastuzumab + paclitaxel	Preferred regimen	2A
Second-line	Ado-trastuzumab emtansine (T-DM1)	Preferred regimen	1
Third-line and beyond	Various regimens which some include newest agents – tucatinib, fam-trastuzumab deruxtecan, neratinib, margetuximab	Other recommended regimen	2A, all but tucatinib+trastuzumab+ capecitabine, which is 1

Exhibit 3: Comparing fam-trastuzumab deruxtecan and ado-trastuzumab emtansine[13]



DS-8201= fam-trastuzumab; T-DM1= ado-trastuzumab emtansine

clinicians are reserving neratinib for fourth-line or later because of the incidence of severe diarrhea.

Tucatinib is a more selective HER2 agent than neratinib or lapatinib. It causes less EGFR-associated toxicity than the other agents, has better central nervous system penetration to treat brain metastases, is well tolerated, and is active in combinations (e.g., with ado-trastuzumab/emtansine, capecitabine, or trastuzumab). In heavily pretreated patients with HER2-+ MBC, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better PFS and OS outcomes

than adding placebo; the risks of diarrhea and elevated aminotransferase levels were higher with tucatinib.[16] In April 2020, the FDA approved tucatinib in combination with trastuzumab/capecitabine for treatment of advanced, unresectable or metastatic HER2+ breast cancer, including patients with brain metastases, who have received one or more previous HER2-targeted therapy in the metastatic setting. Up to 50 percent of those with HER2+ disease will develop brain metastases at some point during the course of their disease. The National Comprehensive Cancer Network (NCCN) guidelines note that tucatinib/trastuzumab/capecitabine is a choice as second-line treatment, especially for those with brain metastases, and is the preferred third-line regimen in patients with both systemic and CNS progression on ado-trastuzumab emtansine.[3]

Margetuximab in combination with chemotherapy was FDA-approved in December 2020 for the treatment of adult patients with HER2+ MBC who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. This monoclonal antibody was designed to improve immune system response over trastuzumab. The SOPHIA Phase III randomized, open-label trial compared margetuximab plus chemotherapy to trastuzumab plus chemotherapy. Eligible patients had disease progression on two or more prior anti-HER2 therapies and one to three lines of therapy for metastatic disease. Interim median OS was 21.6 months with margetuximab versus 19.8 months with trastuzumab (p = 0.33); final OS results are expected in 2021.[17] Margetuximab appears to be most efficacious in patients with a certain genetic mutation of the FC receptor (CD16A-185 F); the OS benefit is approximately four months compared to two months in those without the mutation. This particular mutation reduces binding of trastuzumab and thus reduces its efficacy. In patients without this mutation, the two agents appear equally effective. The CD16A-185 F mutation is found in about 80 percent of patients.

Although HER2-targeted treatment is a huge success, there is a major economic burden for HER2+ MBC. In a study of healthcare costs in the targeted therapy era, mean per patient total costs in the first year following MBC diagnosis were $218,171 and were $412,903 cumulatively over three years following diagnosis.[18] Primary cost contributors were outpatient visits ($195,162) and HER2-targeted therapy drug costs ($177,489). What this analysis did not take into account is the ability of the patient with MBC to continue to work and continue to be alive to contribute to the financial success of a family.

Conclusion

Although metastatic breast cancer is incurable, there are now many effective treatment options for those with HER2+ disease. First-line therapy continues to be the triple combination of pertuzumab, trastuzumab and docetaxel or paclitaxel, and current second-line therapy is ado-trastuzumab emtansine. Several new options for third-line and beyond therapy have recently been approved and will likely be used in earlier lines of therapy or stages of disease as new data are published.

Sara A. Hurvitz, MD, FACP is an Associate Professor of Medicine at the David Geffen School of Medicine at the University of California (UCLA) in Los Angeles, CA.

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Treating Chronic Inflammatory Demyelinating Polyradiculoneuropathy with Immunoglobulin: Managed Care Considerations in an Evolving Treatment Paradigm

Peter D. Donofrio, MD

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

Summary

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) can be difficult to diagnose and many patients get this diagnosis, yet they have another cause of neuropathy. Treatments to modulate the immune system can be effective in reducing symptoms and improving muscle strength. Many patients will need to have maintenance therapy to maintain function.

Key Points

- CIDP is an immune-mediated disease that leads to progressive weakness and impaired sensory function in the legs and arms.
- Treatments that are effective for CIDP include corticosteroids, plasma exchange, and immunoglobulins.
- Subcutaneous immunoglobulin is a newer option for maintenance therapy when the patient has responded to intravenous infusions.

CHRONIC INFLAMMATORY DEMYELINating polyradiculoneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder of the peripheral nervous system. In CIDP, the myelin sheath, the protective covering of the nerves, is damaged.[1] It is characterized by progressive weakness and impaired sensory function in the legs and arms. CIDP effects can worsen over time, leading to significant activity limitations and a decreased quality of life.

CIDP is the most common treatable chronic neuropathy worldwide; however, it is still a rare disease with an incidence of 1.6 cases per 100,000 persons per year.[2] Prevalence is estimated at 8.9 cases per 100,000 persons. The typical age at onset is 40 to 60 years, and it is more common in men than in women.

The diagnosis of CIDP is made using a combination of clinical history, physical examination, and electrodiagnostic and laboratory evaluation. The main tests used in diagnosis are nerve conduction studies, cerebrospinal fluid analysis, and MRI imaging of the spine. Nerve biopsy is an option for diagnosis, but it is rarely done. Although many sets of diagnostic criteria have been developed for CIDP, the criteria used most often in current clinical practice were developed by the European Federation of Neurological Societies and the Peripheral Nerve Society (Exhibit 1).[3] These criteria have 81 percent sensitivity and 96 percent specificity. The diagnosis of CIDP requires that it be distinguished from other neuropathies (Exhibit 2).

CIDP typically has a chronic onset, but acute onset occurs in 5 to 16 percent of patients. Initially, this disease is almost always diagnosed as Guillain-Barré syndrome. The diagnosis of acute onset CIDP is made retrospectively based on worsening of symptoms beyond two months after onset, or if

Exhibit 1: European Federation of Neurological Societies/ Peripheral Nerve Society Diagnostic Criterion for CIDP[3]

- At least 2 months duration
- Proximal and distal weakness
- Chronically progressive, stepwise, or recurrent
- Sensory loss, usually large fiber
- Cranial nerves 5 and 7 may be involved
- Absent or decreased tendon reflexes in 4 limbs

Exhibit 2: CIDP Mimicking Neuropathies

- Lyme Disease
- Hereditary Demyelinating Neuropathy
- Multifocal Motor Neuropathy
- IgM monoclonal gammopathy (with anti-MAG antibodies)
- POEMS syndrome (polyneuropathy, organomegaly, Endocrinopathy/edema, monoclonal protein).
- Osteosclerotic myeloma
- Peripheral Nervous System lymphoma
- Amyloidosis
- CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, M protein and cold agglutinins, and disialosyl antibodies).
- DADS (distal acquired demyelinating syndrome).

there are three or more treatment fluctuations.[4]

There are three treatments for CIDP:

- corticosteroids
- plasma exchange
- immunoglobulin (IG).

Considerations that drive the selection of initial therapy include disease severity, comorbid disorders, venous access, potential adverse events, and cost. The goals of therapy are to improve muscle strength and prevent permanent disability due to demyelination and secondary axonal loss. A sizable portion of patients subsequently become dependent on these treatments to maintain function.

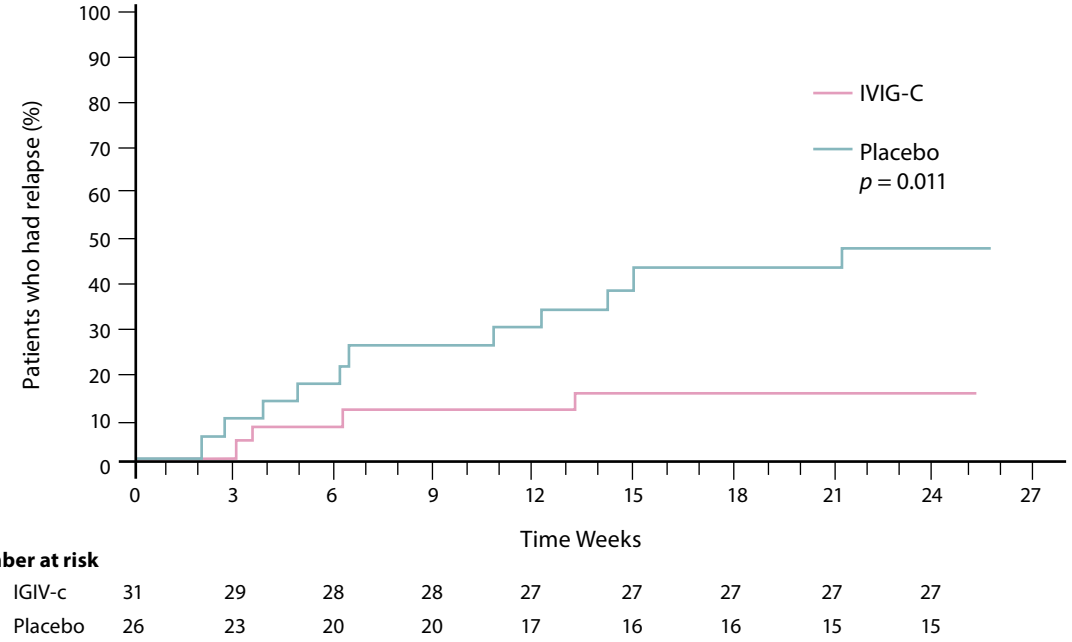
A Cochrane review of the evidence for corticosteroids found that although they are commonly used in practice this use is supported by very low-quality evidence from observational studies.[5] In practice, 60 percent to 65 percent of patients will respond to corticosteroids. Corticosteroids are inexpensive, but they have many long-term adverse events and drug interactions. Prolonged use carries a significant risk of adverse events (osteoporosis and fractures, adrenal suppression and Cushing's syndrome, hyper-glycemia, hypertension, psychiatric disturbances, cataracts, and weight gain).

Plasma exchange is an effective but expensive treatment for CIDP. This is a procedure that passes the patient's blood through an extracorporeal medical device to remove plasma and replace it with another fluid. The primary mechanism of action in treatment of CIDP and other autoimmune disorders is removal of autoantibodies. Twice-weekly exchange is effective for short-term improvement of disability in CIDP, based on a Cochrane review of two studies (n = 59) that compared it with a placebo exchange.[6] In these studies, response rates were 33 percent and 66 percent. Patients with CIDP initially receive 1 to 1.5 total plasma volume exchanges three times per week until they experience improvement.[7] After a response, it may be required at weekly to monthly intervals to maintain the response. Rare adverse events can include infections, anemia, hypocalcemia, hypomagnesemia, and coagulopathies. Plasma exchange is a technically challenging process that requires expertise and coordination among an apheresis team, a blood bank, a pharmacy, and a clinical laboratory. Access to specialized treatment centers offering it can be limited.

Immunoglobulins, given by intravenous infusion or subcutaneous injection, are effective and have a rapid onset of action, but they are very expensive. A total of three Phase III clinical trials supported the FDA approval of two intravenous immunoglobulin (IVIG) products and one subcutaneous infusion (SCIG) to treat CIDP in adults.[8-10] One of these trials compared 10 percent caprylate-chromatography purified immune globulin intravenous (IVIG-C) to placebo.[8] During the first period of this crossover trial, 32 of 59 (54%) patients treated with IVIG-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted inflammatory neuropathy cause and treatment (INCAT) disability score that was maintained through to week 24 (treatment difference 33.5%, 95% confidence interval (CI) 15.4 to 51.7; $p = 0.0002$). Improvements from baseline to endpoint were also recorded for grip strength in the dominant hand (treatment difference 10.9 kPa, 4.6 to 17.2; $p = 0.0008$) and the non-dominant hand (8.6 kPa, 2.6 to 14.6; $p = 0.005$). Results were similar during the crossover period. During the extension phase (24 weeks), participants who continued to receive IGIV-C had a longer time to relapse than did patients treated with placebo ($p = 0.011$, Exhibit 3).[8]

Another trial has compared IVIG and SCIG in treatment-naïve patients with CIDP. Twenty patients fulfilling the clinical and electrophysiological criteria for CIDP were included and treated with either SCIG (0.4 g/kg/week) for five weeks or

Exhibit 3: Time to Relapse for IVIG-C versus Placebo[8]



Number at risk

IGIV-c	31	29	28	28	27	27	27	27	27
Placebo	26	23	20	20	17	16	16	15	15

intravenous immunoglobulin (IVIG) (0.4 g/kg/day) for five days.[11] After 10 weeks, patients were switched to the opposite treatment arm and followed for an additional 10 weeks. Overall, combined isokinetic muscle strength (cIKS) increased by 7.4 ± 14.5 percent (p = 0.0003) during SCIG and by 6.9 ± 16.8 percent (p = 0.002) during IVIG, with the effect being similar (p = 0.80). Improvement of cIKS peaked two weeks after IVIG and five weeks after SCIG. Disability improved during SCIG treatment only. Muscle strength determined by manual muscle testing improved after five and 10 weeks during SCIG but only after five weeks during IVIG.

The most common adverse events of immunoglobulin are flushing, headache, malaise, fever, chills, fatigue, and lethargy, and they are transient and mild. However, some serious rare adverse events, including renal impairment, thrombosis, arrhythmia, aseptic meningitis, hemolytic anemia, and transfusion-related acute lung injury can occur.[12] Performing an early assessment of risk factors, infusing at a slow rate, premedicating, and switching from IVIG to SCIG can minimize these adverse events.

SCIG has been studied for maintenance therapy in patients who had been previously treated with IVIG and is now FDA-approved for maintenance therapy in CIDP.[10] After a run-in period designed to confirm that patients were IVIG-responders, patients (n = 172) were randomized to receive 24 weeks of weekly SCIG 0.2 g/kg or 0.4 g/kg or placebo. Fifty-eight percent of those receiving placebo had relapse, 35 percent with low-dose SCIG, and 22.4 percent with high-dose SCIG (p = .02 for low-dose versus placebo; p <.001 for high-dose versus placebo). The number needed to treat to prevent a relapse with low- and high-dose SCIG was 2.7 and 4.4, respectively. The low dose (0.2 g/kg) is the recommended dose in the approved package labeling.

Subcutaneous infusion offers an additional treatment option for patients with CIDP who respond to IVIG that may improve quality of life. After training, patients can self-administer SCIG at home with an infusion pump. Approximately 88 percent of patients in the published trial reported that self-administration of SCIG was easy.[10] Although 18 percent of SCIG-treated patients preferred their previous treatment with IVIG, 53 percent preferred SCIG and cited greater independence and fewer adverse events.

Patients may require trials with all three agents in order to find an effective treatment. In a retrospective review of 67 patients treated at one center over four years, the response rates among

plasma exchange, IVIG, and corticosteroids were similar, but functional improvement was greatest with plasma exchange.[13] Thirty-nine percent of patients responded to the initial therapy. Of the patients who failed to respond to an initial therapy, 35 percent benefited from the second treatment tried and of the 11 who required a third treatment (27%) improved. Overall, 66 percent responded to one of the three main therapies for CIDP.

Various other immunosuppressants have been tried in CIDP, including azathioprine, cyclosporine, mycophenolate, interferon beta, cyclophosphamide, and rituximab. A Cochrane review found that the limited data available does not show any of these agents are effective.[14] CIDP misdiagnosis is common. In one retrospective review of 59 patients, 47 percent of patients referred with a diagnosis of CIDP failed to meet minimal CIDP diagnostic requirements. Over-reliance on subjective patient-reported perception of treatment benefit, liberal electrophysiologic interpretation of demyelination, and placing an overstated importance on mild or moderate cytoalbuminologic dissociation are common diagnostic errors.[15] Utilization of clear and objective indicators of treatment efficacy might also improve the treatment decisions of clinicians.

Conclusion

CIDP is a chronic condition which can significantly impact patients. Misdiagnosis of CIDP when another issue is actually the cause of neuropathy is frequent. Treatments that are effective include corticosteroids, plasma exchange, and immunoglobulins. Subcutaneous immunoglobulin is a newer option for maintenance therapy when the patient has responded to intravenous infusions.

Peter D. Donofrio, MD is Chief, Division of Neuromuscular Diseases and Professor of Neurology at the Vanderbilt University Medical Center, in Nashville, TN.

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Evolving Treatment Strategies in the Management of Acute Myeloid Leukemia: Individualized Therapy for Improved Clinical and Economic Outcomes

Amir T. Fathi MD

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Summary

There have been significant advances in the treatment of acute myeloid leukemia (AML) in the past decade. Previously, the only treatment for the disease was potent chemotherapy regimens and hematopoietic stem cell transplant. Underlying poor health or comorbidities prevented many patients from undergoing these treatments. The emergence of effective, targeted therapies are providing improved survival outcomes for patients with selected genetically mutated disease.

Key Points

- The treatment for many older or frail AML patients is now oral, targeted therapy when an appropriate mutation is present or hypomethylation therapy. Maintenance therapy after the first remission is also now an option for many patients, and it is hoped this will reduce the relapse rate.
- AML is a cancer of the blood and bone marrow with excess immature white blood cells and is the most common leukemia affecting adults. In 2021, there will be an estimated 20,240 cases in the United States (U.S.) and 11,400 deaths.[1] The median age at diagnosis is 67 years, and the five-year overall survival rate is 29.5 percent.

JOHN HUGHES BENNET AND RUDOLF Virchow first described AML in 1845 by independently describing cases of spleen enlargement, cytopenias, and suppuration from autopsy specimens. Virchow termed it "Weisses Blut," white blood, or leukemia. In 1868, Ernst Neumann first suggested the bone marrow as the origin of blood cells. The classification of leukemia by cell surface immunohistochemistry and chromosomal analysis first occurred in the 1960s and 1970s. The 2000s have brought the identification of genetic mutations which drive the disease. Leukemia develops when there are genetic mutations in the myeloid cells, precursor cells of platelets, red blood cells and white blood cells derived from the hematopoietic stem cells. The genetic mutations prevent the myeloid cells from maturing normally and allow uncontrolled proliferation.

The traditional prognosis model of AML is based on patient age and medical comorbidities, whether the AML evolved from preceding marrow disease [e.g., myelodysplastic syndromes (MDS)], or the presence of certain molecular characteristics based on cytogenetic and mutational analysis (e.g., FLT3, NPM1, CEBPα). It is not always easy to determine if MDS preceded AML. An example favorable risk factor is mutated NMP1 without FLT3-ITD and an adverse-risk factor is complex karyotype. Based on all of these factors, patients could have favorable, intermediate 1 or 2, or adverse-risk disease. Favorable disease has the longest disease-free survival after treatment and best overall survival (OS) and adverse-risk disease has the shortest of these.[2]

Exhibit 1: FDA Approvals for AML since 2017

2017
• **Midostaurin (Rydapt7)**
◦ For adult patients with newly diagnosed AML who have a *FLT3* mutation.
◦ Companion diagnostic: LeukoStrat7 CDx *FLT3* mutation assay.
• **Enasidenib (Idhifa7)**
◦ For adult patients with relapsed/refractory AML who have an IDH2 mutation
◦ Companion diagnostic: RealTime IDH mutation assay
• **Gemtuzumab ozogamicin (Mylotarg™)**
◦ For the treatment of adults with two types of acute myeloid leukemia (AML): newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).
2018
• **Ivosidenib (Tibsovo7)**
◦ For adult patients with relapsed/refractory AML who have an IDH1 mutation.
• **Glasdegib (Daurismo™) and low dose cytarabine**
◦ For adult patients with newly diagnosed AML who are ≥ age 75 or are ineligible for induction due to comorbidity.
• **Venetoclax (Venclexta7) and hypomethylating therapy (or low dose cytarabine)**
◦ For adult patients with newly diagnosed AML who are ≥ age 75 or are ineligible for induction due to comorbidity
• **Gilteritinib (Xospata7)**
◦ For adult patients with relapsed/refractory AML who have a FLT3 mutation.
2020
• **CC-486 / oral azacitidine (Onureg7)**
◦ For adult patients achieving first remission following induction chemotherapy and not able to complete intensive curative therapy.

Prognostication has become more complicated as increased mutations have been identified in AML.[3] Depending on the underlying mutations, each case of AML has a different course, prognosis, and best treatment.

Before the development of targeted therapies, the treatment of AML had essentially been the same since the 1960s, using various chemotherapy regimens to treat every case the same by rebooting the bone marrow. This process destroyed all the current bone marrow cells with the hope that normal stem cells would begin replicating. Induction chemotherapy regimens (cytarabine and daunorubicin or idarubicin), which may be repeated twice, induce complete response (CR) in 75 percent of cases. Twenty-five percent of patients do not respond to induction regimens and have refractory leukemia. After induction chemotherapy that induces remission, consolidation therapy to attempt a cure is done with either high-dose cytarabine (most common) or allogeneic hematopoietic stem cell transplant. Patients with a more favorable disease typically get chemotherapy for consolidation because their leukemic cells are more sensitive to chemotherapy. Those with intermediate or adverse-risk who can tolerate a transplant have one for consolidation.

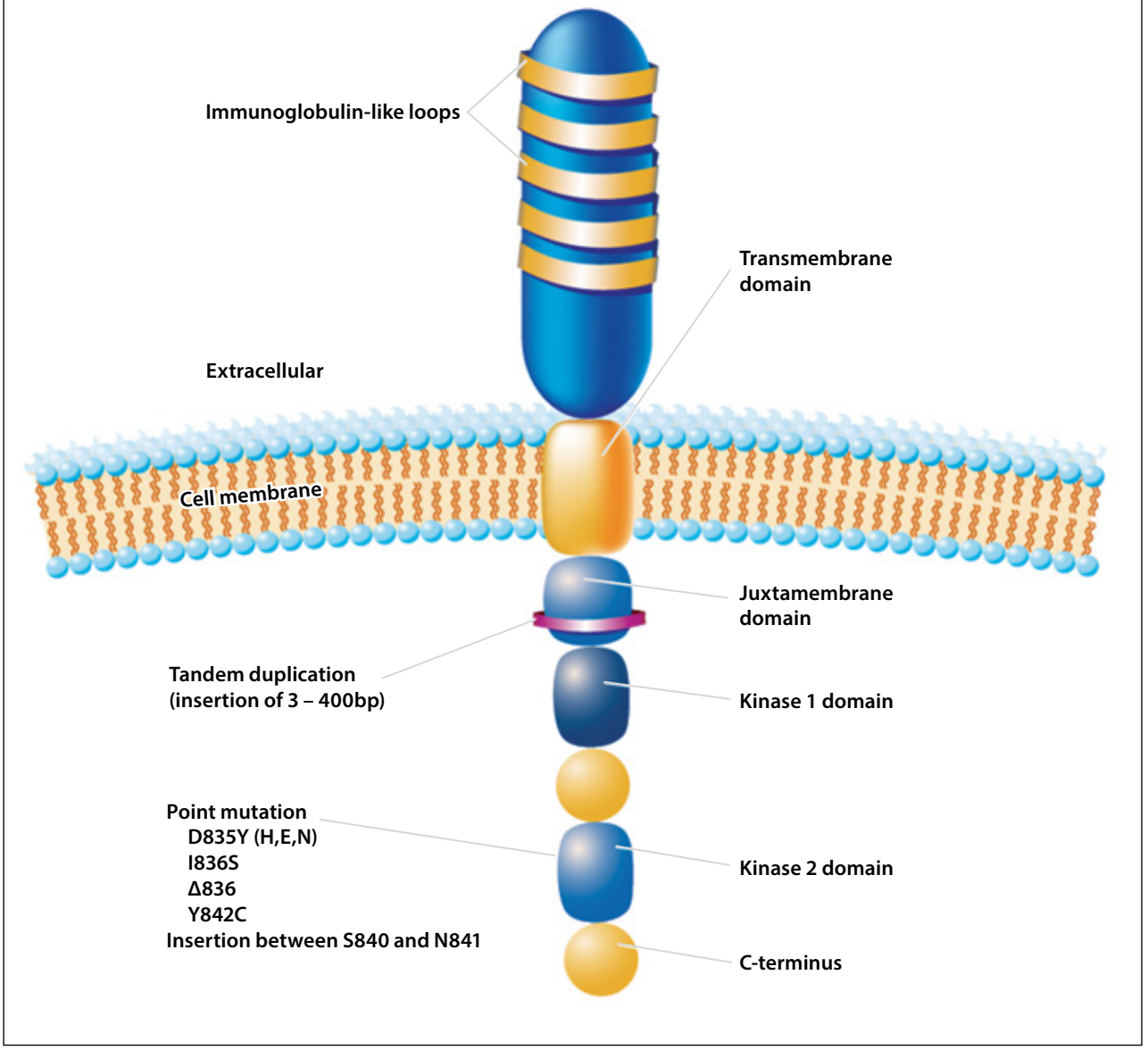
When relapse after initial treatment occurs, various chemotherapy regimens have been tried with varying success. The five-year survival rate with relapsed AML for those less than 55 years of age is 11 percent and 6 percent for those over 55 years.[4]

Several oral therapies targeting the underlying mutations which lead to the disease have changed the treatment landscape for AML. Ivosidenib, enasidenib, gilteritinib, and venetoclax are targeted therapies that have been approved by the FDA for treating AML (Exhibit 1).

Isocitrate dehydrogenase (IDH) is one target of new therapies to discuss. IDH proteins, essential to the Krebs cycle, catalyze decarboxylation of isocitrate to α-ketoglutarate (α-KG) in the cytoplasm (IDH1) and mitochondria (IDH2). Mutant IDH enzymes catalyze α-KG to 2-hydroxyglutarate (2-HG), which is an onco-metabolite that accumulates in IDH-mutant tumors. 2-HG suppresses key enzymes for bone marrow cell differentiation. Approximately 8 percent of patients with AML have an IDH1 mutation and 15 percent have IDH2 gene mutations.[5,6]

IDH inhibitors that target IDH mutations are now FDA-approved for treating IDH-mutated AML. These agents allow differentiation of the bone marrow cells that were previously stuck being immature. Enasidenib (Idhifa®) is an oral, selective inhibitor of mutant-IDH2 enzymes. Treatment of IDH2-mutated AML produced impressive results in relapsed/refractory AML (RR AML), untreated AML not eligible for chemotherapy, and MDS. Median OS was 9.3 months, and for the 34 patients (19.3%) who attained CR, overall survival was 19.7 months.[7] There is minimal toxicity with this daily oral, non-chemotherapy agent. Enasidenib is currently FDA-approved for treating RR AML with an IDH2

Exhibit 2: Activating *FLT3* Mutations in AML



mutation and is a Category 1 recommendation in the National Comprehensive Cancer Network (NCCN) guidelines for this indication.[8] It is also recommended as an option for first-line therapy in those aged 60 years and older who are not candidates for intensive remission induction therapies.[8]

Ivosidenib (Tibsovo®) targets IDH-1 and produces results similar to enasidenib in those with IDH-1-mutated AML. In patients with advanced IDH1-mutated RR AML, ivosidenib at a dose of 500 mg daily was associated with a low frequency of Grade 3 or higher treatment-related adverse events and with transfusion independence, durable remissions, and molecular remissions in some patients with CR.[9] Ivosidenib is FDA-approved for treating adult patients with newly-diagnosed AML who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy and adult patients with RR AML. The NCCN guidelines recommend it for those over 60 years of age who are newly diagnosed and cannot tolerate intensive induction.[8] Overall, even patients who do not achieve CR with the IDH inhibitors have some benefits, including reduced need for red blood cell transfusions, fewer clinic visits, fewer infections, and lower patient and caregiver treatment burden.

Differentiation syndrome, an overly robust differentiation of cells which leads to cytokine-mediated weight gain, plural effusions, pulmonary infiltrates, hypoxia, and fever, can occur with IDH inhibitor treatment. This is a potentially lethal clinical entity and occurs in 12 to 18 percent of enasidenib-treated patients with mutant-IDH2 RR AML.[10] It can also occur with ivosidenib and is treated with corticosteroids.

FMS-like tyrosine kinase 3 (FLT3) inhibitors are another class of targeted agents. FLT3 is a tyrosine kinase enzyme that resides on the surface of cells and acts as a receptor (Exhibit 2). Ligand (FL) in the blood binds to the FLT3 receptor to turn it off. When a FLT3 mutation is present, the FLT3 receptor is less sensitive to the ligand and thus the receptor is turned on all the time, allowing cells to constantly multiply. FLT3 mutations include internal tandem duplication (ITD) and tyrosine kinase domain (TKD). FLT3 ITD mutations occur in 25 to 30 percent of AML cases and results in poor prognosis and high rates of relapse.[11] FLT3 TDK mutations occur in 5 to 10 percent of cases.

The first agents developed to target FLT3 were aimed at numerous tyrosine kinases, including sorafenib (Nexavar®) and midostaurin (Rydapt®), but these have significant toxicity because of their nonspecific effects. The addition of midostaurin to standard chemotherapy significantly prolonged OS and event-free survival among patients with AML and a FLT3 mutation. Median OS was 74.7 months for the combination therapy group and 25.6 months for the group that received only chemotherapy.[12] There was a 23 percent reduced risk of death in the midostaurin arm. At four years, 51.4 percent were alive in the midostaurin arm as opposed to 44.2 percent in the placebo arm. Midostaurin is FDA-approved for treating adults with newly diagnosed FLT3 mutation-positive AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

Gilteritinib (Xospata®) is a next-generation, more specific FLT3 inhibitor. In the FLT3- mutated RR AML setting, the median OS in the gilteritinib group was significantly longer than the salvage chemotherapy group (9.3 months versus 5.6 months).[13] It is FDA-approved for adult patients with FLT3-mutated RR AML. Quizartinib is an investigational agent but has also improved OS in patients with FLT3 -mutated RR AML compared with salvage chemotherapy.[14] Exhibit 3 summarizes the current use of targeted therapies.

A newer use of targeted therapy, which is not yet FDA-approved, is as maintenance therapy at remission to prevent relapse, especially post-bone marrow transplant and in those with FLT3 mutation. In an open label trial, sorafenib, initiated between days 45 and 120 after transplant and continued for 12 28-day cycles in those with a first or second complete remission, improved OS compared to historical controls.[15] A randomized trial is ongoing examining this approach. The same approach is also being studied with IDH1 and IDH2 inhibitors.

Most patients with AML are older (> 75 years) and the older the patient, the poorer their prognosis.[16,17] There are many reasons for this, including poor performance status, preexisting heart and kidney disease, higher incidence of preceding bone marrow disease, higher rates of poor prognosis mutations, and higher rates of therapy-related morbidity and mortality. Older patients have a higher incidence of treatment-resistant disease, lower rates and duration of complete remission, shorter median OS, and are less likely to be eligible for allogeneic hematopoietic cell transplantation. Hypomethylating agents are a less intensive treatment increasingly used for less robust or older patients, in whom it is better-tolerated with lower rate of toxicity than traditional aggressive chemotherapy regimens. This therapy is typically administered in the clinic and can lead to therapeutic responses, including transfusion independence, decrease in leukemic burden, and less commonly, remissions (~20%). However, responses are often transient, with leukemic progression and

Exhibit 3: Integrating Targeted Therapies into Clinical Practice

• Midostaurin
◦ For adult patients with newly diagnosed AML, a FLT3 activating mutation, and eligible for induction.
◦ Midostaurin 50 mg twice daily administered on days 8 - 21 of induction and consolidation chemotherapy.
• Enasidenib
◦ For adult patients with relapsed/refractory AML and an IDH2 mutation (R140 or R172 alteration).
◦ Enasidenib 100 mg daily, administered continuously, with close monitoring for leukocytosis, differentiation syndrome, and bilirubinemia.
◦ Responses can occur weeks to months after initiation of therapy.
• Ivosidenib
◦ For adult patients with relapsed/refractory AML and an IDH1 mutation (R132 alteration).
◦ Ivosidenib 500 mg daily, administered continuously, with monitoring for leukocytosis, differentiation syndrome, and QTc prolongation.
◦ Responses can occur weeks to months after initiation of therapy.
• Gilteritinib
◦ For adult patients with relapsed/refractory AML and FLT3-ITD (and some TKD) mutations.
◦ Gilteritinib 120 mg daily, administered continuously.
◦ Responses can occur weeks after initiation of therapy.
• Venetoclax
◦ For older adult patients with newly diagnosed AML or other patients who are not candidates for intensive induction chemotherapy
◦ Venetoclax 400 mg daily with azacitidine or decitabine, administered continuously, with monitoring for cytopenias.
◦ Interaction with azoles and other agents are important to monitor, and dose adjustment of venetoclax is often necessary.

brief post-therapy survival.

Methyl groups which bind to DNA turn genes off and acetyl groups turn them on. In many patients with AML and MDS, genes are inappropriately turned off by methyl groups. The hypomethylating agents remove methyl groups and turn the genes for blood cell maturation back on. Decitabine (Dacogen®) and azacitidine (Vidaza®), the two intravenous agents currently used, are very well tolerated, but these agents can take several months to work.

The next evolution of therapy was to try to identify other things that could be given with hypomethylating agents to improve remission rates. Venetoclax (Venclexta®) 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. Although potent as a single agent for chronic lymphocytic leukemia, as monotherapy it is not as impressive against AML. In the pivotal clinical trials evaluating venetoclax in combination with hypomethylating agents, the rates of complete CR plus CR with incomplete hematological recovery were 54 percent and 67 percent, respectively and the median OS was 10.4 months and 17.5 months, respectively.[18] In a Phase III study of venetoclax plus low-dose cytarabine (LDAC), there was a 25 percent reduction in risk of death with venetoclax plus LDAC versus LDAC alone (p = .11), although not statistically significant; median OS was 7.2 versus 4.1 months, respectively.[19] Complete remission plus CR with incomplete blood count recovery rates were 48 percent and 13 percent for venetoclax plus LDAC and LDAC alone, respectively. Venetoclax in combination with azacitidine or decitabine or LDAC is FDA-approved for the treatment of newly-diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

The newest FDA approval in AML treatment is oral azacitidine (Onureg, also known as CC-486) for the continued treatment of adult patients with AML who achieved first complete remission or complete remission with incomplete blood count recovery following intensive induction chemotherapy and who are not able to complete intensive curative therapy. This approval, in September 2020, was

based on the results from the Quazar AML-001 study.[20] Median OS was significant longer with azacitidine maintenance than with placebo (24.7 months and 14.8 months, respectively; $p<0001$). Median relapse-free survival was also significantly longer with placebo (10.2 months and 4.8 months, respectively; $p<0.001$).

Conclusion

The treatment for many older or frail AML patients is now oral targeted therapy when an appropriate mutation is present or hypomethylation therapy. Maintenance therapy after the first remission is also now an option for many patients; this will hopefully reduce the relapse rate. There is also hope that the next decade will bring more approved AML therapies that continue to enhance outcomes.

Amir T. Fathi, MD is the Program Director for the Center of Leukemia at the Massachusetts General Hospital Cancer Center and an Assistant Professor of Medicine at Harvard Medical School, in Boston MA.

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Novel Treatment Advances and Approaches in the Management of Chronic Lymphocytic Leukemia: Expert Perspectives on BTK Inhibitors and MRD

Ian W. Flinn, MD, PhD

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

Summary

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in older adults. Oral targeted agents have replaced chemoimmunotherapy approaches as first-line choices for treatment of newly diagnosed disease.

Key Points

- Therapy has been revolutionized with the development of novel oral therapies.
- For newly diagnosed CLL, the Bruton's tyrosine kinase (BTK) inhibitors have become a common first-choice therapy for many patients.
- The future of treatment is additional BTK inhibitors to overcome disease resistance and a combination of BTK inhibitors and venetoclax to achieve remission.
- These agents have changed the natural history of CLL by dramatically improving survival in a variety of patient populations.

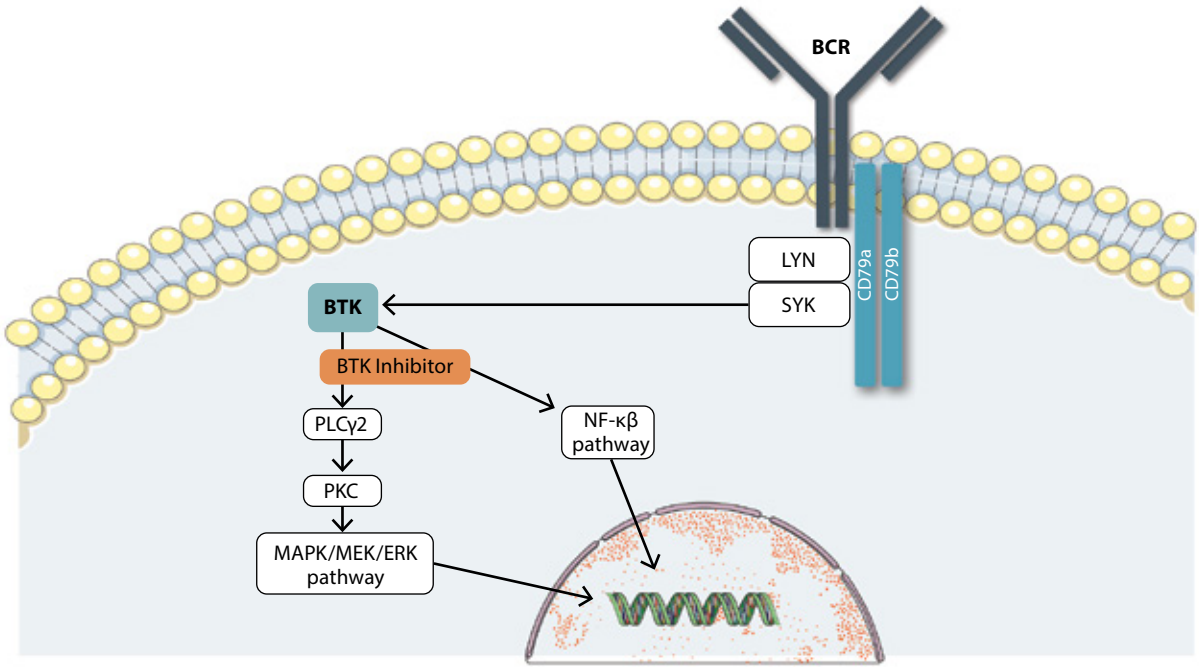
CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a lymphoproliferative disorder of monoclonal B cells and is the most common form of leukemia in older adults. In 2021, more than 21,000 new cases of CLL will be diagnosed in the United States (U.S.).[1] The median age at diagnosis is 70 years, and there is a male predominance. Historically, the five-year survival rate has been 66 percent (a range of a few months to normal lifespan); the most recent five-year survival rate is 87.2 percent.[2,3] This is likely to continue to improve with expanded uptake of the novel oral targeted therapies.

CLL and small lymphocytic lymphoma (SLL) are considered the same B-cell malignancy with different manifestations. CLL has greater than 5,000 clonal lymphocytes in peripheral blood and SLL is defined as presence of lymphadenopathy and/or splenomegaly and less than 5,000 clonal lymphocytes in peripheral blood. Both are referred to as CLL for this discussion.

The outcomes of CLL vary widely from patients with near normal lifespans to aggressive disease with much lower survival rates. Multiple genetic mutations account for the different outcomes and are now known to be prognostic for survival and response to therapy in CLL. Examples include 17p deletion, TP53 mutation or deletion, and immunoglobulin heavy chain variable region (IVHG) mutation. For many years, the standard treatment for initially diagnosed CLL was chemotherapy or chemoimmunotherapy (CIT). An example regimen would have been fludarabine, cyclophosphamide, and rituximab. Therapy has been revolutionized with the development of novel oral therapies.

For newly diagnosed CLL, the Bruton's tyrosine kinase (BTK) inhibitors have become a common first-choice therapy for many patients. BTK is a non-receptor kinase that is essential both for B-cell development and function of mature B cells. It also plays a crucial role in oncogenic signaling that is critical for proliferation and survival of leukemic cells

Exhibit 1: BTK Inhibitor Mechanism of Action[4]



in many B- cell malignancies. B-cell lymphomas, in general, are heavily dependent on B-cell receptor signaling. Blocking the BTK signal inhibits one of the key survival signals in these lymphomas and triggers cell death (Exhibit 1).[4] These agents are given continuously until disease progression, unlike prior chemotherapy and CIT regimens which were given for a limited period of time and also unlike the venetoclax/obinutuzumab combination therapy, which is also used as first-line therapy.

Ibrutinib (Imbruvica®) was the first BTK inhibitor approved by the FDA (2013) and is an irreversible inhibitor. It was initially approved for use in the relapsed/refractory setting and has since moved into the first-line setting for newly diagnosed disease. Three trials have shown that ibrutinib is superior to prior regimens, even for those with genetic mutations for poor survival. The combination of ibrutinib and rituximab (IR) was compared to fludarabine, cyclophosphamide, and rituximab (FCR), a typical CIT regimen, as front-line treatment in a fit patient population. The IR combination improved three-year progression-free survival (PFS, 89% versus 71%) and three-year overall-survival (OS, 98.8% versus 91.5%).[5] Fewer cases of neutropenia and infection occurred with IR compared to FCR, but a higher rate of hypertension occurred with IR.

In a trial comparing ibrutinib, ibrutinib/rituximab (IR), and bendamustine/rituximab (BR) for first-line therapy in a less fit patient population, ibrutinib and IR were equivalent and superior to BR for PFS (87%; 88%, 74% respectively).[6] PFS benefit with ibrutinib-containing regimens compared to BR was seen in all cytogenetic mutation subgroups, with del(17p13.1) being most pronounced. There was no significant interaction between IGHV mutation status and PFS benefit by regimen, but there was an increased PFS among patients with mutated IGHV disease compared to those with unmutated disease (hazard ratio: 0.51; 95% confidence interval: 0.32 to 0.81).

At five-year follow-up of continued use of ibrutinib compared to chlorambucil in the front-line setting, the PFS was 70 percent in the ibrutinib group compared to 12 percent for chlorambucil and the five-year OS was 83 percent compared to 68 percent, respectively.[7] After five years of follow-up, 58 percent of patients (n = 79) remained on ibrutinib. Ibrutinib benefit was consistent in patients with high prognostic risk (TP53 mutation, 11q deletion, and/or unmutated IGHV). Overall, ibrutinib has changed the natural history of CLL by dramatically improving OS and PFS in a variety of patient populations.

In addition to binding to BTK, ibrutinib can

Exhibit 2: Ibrutinib Off Target Binding[8]

• EGFR – Rash – Cardiac toxicity – Diarrhea	• **ITK** **– Antibody-dependent cellular cytotoxicity (antibody therapy efficacy).**
• ERBB4 – Cardiac toxicity	• **TEC** **– Platelet effects**
• BMX – Cardiac toxicity	• **JAK3** **– Immune effects**

bind to nine other kinases. These include four TFK members (ITK, TEC, BMX and RLK/TXK), three EGFR family kinases (EGFR, ErbB2/HER2 and ErbB4/HER4) and two other kinases, BLK and JAK3.[8] This binding can lead to off-target adverse events (Exhibit 2).[8] Overall, the most common adverse events with ibrutinib are atrial fibrillation (AF), hypertension, infection, bleeding, diarrhea, pneumonitis, rash, and arthralgia. Hematologic adverse events including neutropenia, anemia, and thrombocytopenia also occur. Most of the adverse events, except hypertension, improve over time.

In an analysis in 582 patients treated with ibrutinib, the estimated cumulative incidence of AF by time on treatment was 5.9 percent at six months, 7.5 percent at 12 months, and 10.3 percent at 24 months.[9] The median time to onset of AF was 7.6 months, and the rate of AF increased approximately fourfold with ibrutinib compared to non-ibrutinib therapy (3.3 versus 0.84 per100 person years). Risk of AF with ibrutinib is higher in those with a prior history of AF, male gender, hypertension, age over 75 years, and valvular heart disease.[10]

Bleeding can be an issue in those on ibrutinib because of antiplatelet events. All BTK inhibitors should be held prior to and after invasive procedures for three (minor) to seven days (major). Concomitant use of anticoagulants and antiplatelet agents (aspirin, clopidogrel, prasugrel, ticagrelor) may increase bleeding risk and should be used with extreme caution.

In a real-world analysis of ibrutinib use, 42 percent of patients had stopped it by a median follow-up of 17 months.[11] Most patients who stopped ibrutinib did so because of toxicity (50.2% relapse setting and 63.1% first-line) rather than disease progression. Arthralgia is the most common reason for discontinuation in the front-line setting.

Like all new cancer therapies, ibrutinib and the other BTK inhibitors are very expensive in terms of acquisition costs ($9,000 to $10,000 per month). However, a higher cost oral therapy can offset some of the costs associated with infusion of chemotherapy and the costs of managing the significant adverse events of chemotherapy. In one analysis, ibrutinib's higher pharmacy costs [mean monthly cost difference (MMCD) = $6,849; $p <$ .0001] were offset by lower medical costs (MMCD = -$10,615; $p <$ .0001), yielding net savings (MMCD = -$3,766; $p <$ .0001) compared to CIT.[12]

Acalabrutinib (Calquence®) was the second BTK inhibitor to be approved for use in November 2019. It is a highly-selective, potent kinase inhibitor that was designed to minimize off-target activity. This agent was FDA-approved for first-line treatment of CLL based on the results of the ELEVATE-TN trial. In this trial, acalabrutinib 100 mg BID until progression with or without obinutuzumab for six cycles was compared to chlorambucil plus obinutuzumab (CO) for six cycles. At a median follow-up of 28.3 months, PFS was not reached with acalabrutinib (A) or acalabrutinib plus obinutuzumab (AO) compared to 22.6 months with CO ($p <$ 0·0001).[13] The estimated PFS at 24 months was 93 percent with AO, 87 percent with A, and 47 percent with CO. The median OS was not reached at the time of publication for any of the treatment groups. Acalabrutinib and AO were beneficial in high- and low-risk category patients (overall 69% of subjects were high-risk, 12% were very high-risk). Even though there is an increase in PFS with the combination of acalabrutinib and obinutuzumab, many clinicians and patients are not sure that this small benefit is worth adding an intravenous agent

like obinutuzumab which negates the benefits of an all-oral regimen, especially given that adverse event rates are higher with the combination.

Acalabrutinib does cause hypertension, diarrhea, arthralgia, and bruising. Uniquely, it also causes headaches which do not seem to occur with ibrutinib. This headache typically occurs in the first two weeks of therapy, is mild, and does not usually require treatment. Acalabrutinib has been studied in ibrutinib intolerance. In this trial, most ibrutinib-related adverse events (72%) did not recur with acalabrutinib treatment.[14] A large, randomized Phase III trial is comparing acalabrutinib to ibrutinib which should show if acalabrutinib is truly better tolerated.

Another oral targeted therapy for CLL is venetoclax, which is a B-cell ligand two (BCL2) inhibitor. The combination of venetoclax/obinutuzumab has been shown to improve PFS over chlorambucil/obinutuzumab.[15] Diarrhea, nausea, and neutropenia are the common adverse events of venetoclax. Tumor lysis syndrome (from death of large numbers of CLL cells) can occur, but a slow titration of dose can reduce the risk. Patients with a large amount of disease may need to be observed in the hospital for 24 to 48 hours around the first two doses. AF does not occur with the combination.

One advantage of venetoclax over the BTK inhibitors is that it is given with obinutuzumab for a fixed duration. The combination is given for one year in the first-line setting and for two years in the relapsed/refractory setting. Most patients do not want to stay on therapy indefinitely.

Venetoclax can be stopped because it can get patients into remission with minimal residual disease (MRD) negative state. Achieving MRD negative state is rare with BTK inhibitors. MRD negative means less than one CLL cell is detected in 10,000 leukocytes. Venetoclax combinations achieve the highest MRD negative rates of any available treatments for CLL. In the venetoclax/obinutuzumab versus chlorambucil study, the MRD negative rate was 76 percent compared to 35 percent.[15]

MRD negative has become the best measure of true disease remission. There are still questions about when to assess, preferred methodology, peripheral blood sample versus bone marrow biopsy, and what clinical decisions to make based on the results. Immunosequencing of receptor genes through next-generation sequencing enables precise and sensitive MRD measurement, and this is the evolving preferred method to assess MRD. Because the tumor cells of CLL are clones of each other, immunosequence is retained over time even as the clones evolve, is a stable trackable marker of disease, and directly measures cancer cell burden at any given time throughout clinical management. The only disadvantage of this method is that the cancer cells need to be collected before any treatment is started. At this time, it is not known whether treatments such as BTK inhibitors should be stopped based on MRD.

The future of CLL management is reversible BTK inhibitors which can be used in those who have developed resistance to the already approved irreversible agents and the combination of venetoclax and a BTK inhibitor. Early data from trials of this combination are showing three-fourths of patients are achieving MRD negative status in both peripheral blood and the bone marrow.

Conclusion

Oral targeted therapies, especially BTK inhibitors, have changed the natural history of CLL. These agents and venetoclax are the first-line therapy choices for the majority of newly diagnosed patients. The future of treatment is additional BTK inhibitors to overcome disease resistance and the combination of BTK inhibitors and venetoclax to achieve remission.

Ian W. Flinn, MD, PhD is the Director of the Lymphoma Research Program at the Sarah Cannon Research Institute in Nashville, TN.

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Navigating an Increasingly Complex Treatment Landscape in Moderate to Severe Rheumatoid Arthritis: Managed Care Perspectives on the Role of Biomarkers

Jeffrey Curtis, MD, MS, MPH

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

Summary

Clinicians would like to be able to predict who will develop clinical rheumatoid arthritis (RA) and what is the ideal medicine for a given individual. The treatment of RA is moving into the personalized arena with some biomarkers currently being used and others under development. These biomarkers can be used to predict disease development, disease progression, and therapy selection.

Key Points

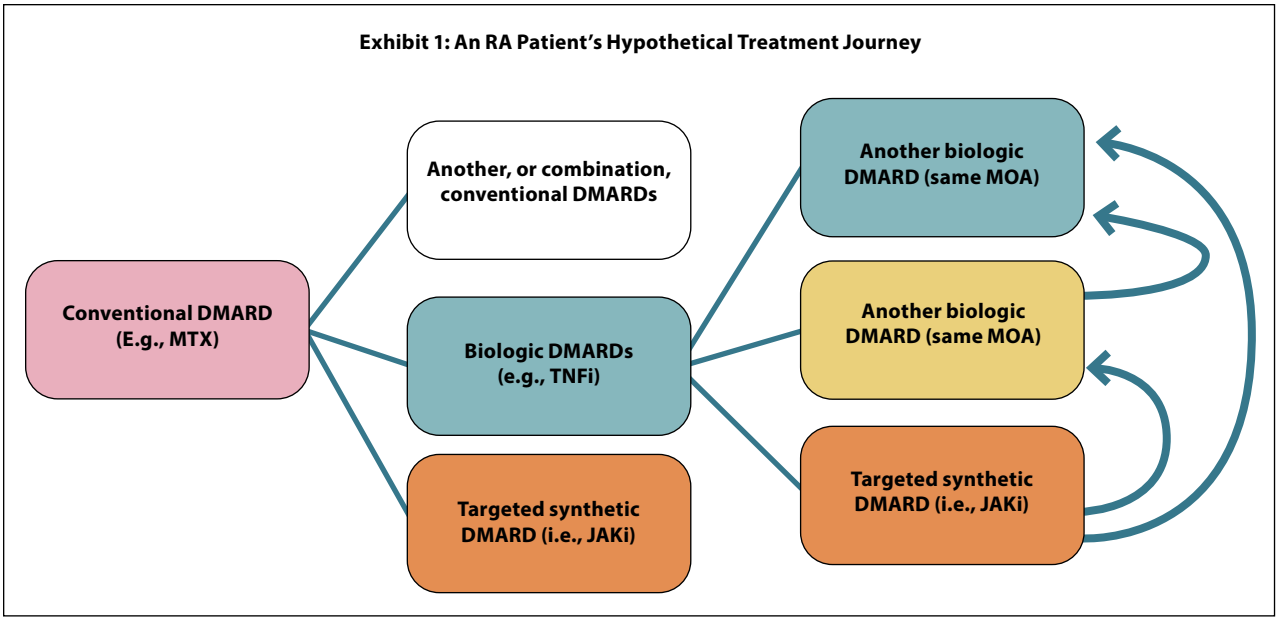
- Predicting treatment response at an individual patient level is important.
- Biomarkers may help optimize treatment choices.
- Patient-reported outcomes may make treatment changes more relevant to patients.
- Digital solutions offer the potential to optimize care in RA.

RHEUMATOID ARTHRITIS (RA) IS A systemic autoimmune inflammatory disease with a high incidence of comorbidities and extra-articular manifestations. It affects about 1.3 million Americans.[1] The common approach to new onset (or possible) RA is to perform clinical, imaging, and laboratory assessments. Clinical assessment includes tender or swollen joint count, patient and physician global assessment, and other patient-reported outcomes. Imaging may include various joints, especially the hands and feet, with or without musculoskeletal ultrasound to detect inflammation that is not clinically apparent. Laboratory evaluation will include several biomarkers used for diagnosis, including rheumatoid factor, an anti-cyclic citrullinated peptide antibody (ACPA) test, genetic profile (e.g., shared epitope), and a multi-biomarker disease activity (MBDA) test.

An ACPA is a more specific biomarker test for RA diagnosis than rheumatoid factor but it is currently measured less often by non-rheumatology professionals. Both are helpful in the diagnosis of RA. The shared epitope is a five amino acid sequence of major histocompatibility complex, Class II, DR beta (HLA-DRB) chains encoded by HLA-DRB1 alleles that are strongly associated with susceptibility to severe RA. MBDA is a panel of biomarkers which will be covered later.

In addition to diagnosis, biomarkers can be used in prediction of disease development. Those with positive ACPA testing without clinical synovitis and with the shared epitope are at higher risk for progression to clinical RA than those who do not have these biomarkers. In one trial, the factors that predicted development of clinical RA within a year were high titer ACPA, shared epitope, ultrasound erosions in the feet, and four or more inflamed joints on ultrasound.[2]

Once diagnosed, the standard of care in the United States (U.S.) and in many other countries



DMARD = disease-modifying anti-rheumatic drug; MTX = Methotrexate; TNFi = tumor necrosis factor inhibitor; JAKi = janus kinase inhibitor; MOA = mechanism of action

is to start therapy with methotrexate. The struggle for clinicians is selecting the next therapy to use if methotrexate fails or is insufficient for disease control (Exhibit 1). There are a large number of choices, including tumor necrosis factor (TNF) inhibitors, T cell inhibitors (abatacept), B cell depletion (rituximab), interleukin 6 (IL-6) inhibitors (sarilumab, tocilizumab) and janus kinase (JAK) inhibitors (tofacitinib, upadacitinib, baricitinib). Because they have been available longer and some have biosimilars available, the TNF inhibitors tend to be favored in managed care policies as the next step after methotrexate. When examining overall group data, the best response rate to all these agents is about 60 percent for ACR20 (20% improvement in a set of objective measures of disease), 40 percent for ACR50, and 20 percent for ACR70. Most clinicians are looking for patients to achieve at least an ACR50, and a minority of patients will achieve low disease activity or remission (ACR70 or better). Thus, a substantial portion of patients will be non-responders to the first therapy selected after methotrexate.

Because all the agents on average have about the same efficacy, there is no clear guidance for choosing second-line therapy in the American College of Rheumatology (ACR) treatment guidelines based on efficacy. The goal should be to optimize and personalize treatment selection for a given individual to maximize response rate and decrease costs of having to try multiple therapies which are not effective before finding the right medication.

There are a few head-to-head studies which show that certain therapies may be better than others in select situations. If a patient is not on methotrexate because of contraindications or adverse events, IL-6 inhibitor monotherapy with tocilizumab or sarilumab has been shown to be more effective than adalimumab, a TNF inhibitor, monotherapy.[3] Upadacitinib in combination with methotrexate has been shown to be more effective than adalimumab or abatacept. In the trial comparing upadacitinib to abatacept, the ACR50 and ACR70 rates were 59.4 percent versus 49.4 percent and 37.3 percent versus 26.5 percent, respectively.[4] Lastly, those who have failed on one or more TNF inhibitors should be switched to another mechanism of action agent.[5]

ACPA and shared epitope are up-and-coming biomarkers for selecting therapy. In a trial comparing abatacept and adalimumab, those with the highest quartile ACPA titers had the best response to abatacept (20% or more better).[6] TNF inhibitor efficacy was not predicted by ACPA levels. A prospective trial examined the use of abatacept compared to adalimumab in early moderate to severe RA in those with rheumatoid factor and high ACPA titers. In this trial, abatacept was approximately 30 percent better than adalimumab on ACR20, ACR50, and ACR70 in those who also had the shared epitope.[7] This trial has only been presented at a scientific meeting and has not yet been published. This is the largest difference seen

Exhibit 2: Cost per Responder in Biologic Naïve Patients with ACPA and Shared Epitope[8]

Response Metric	Abatacept	Adalimumab	Difference
ACR20	$30,303.74	$37,403.06	-$7,099.32
ACR50	$34,254.68	$48,077.83	-$13,823.15
ACR70	$46,337.46	$74,935.10	-$28,597.64
DAS28-CRP ≤ 2.6	$52,546.68	$96,155.65	-$43,608.97

between any two agents for moderate to severe RA. The accumulating data suggest that abatacept may be the preferred agent in biologic naïve patients with higher ACPA titers and the shared epitope.

Payers often limit the use of agents such as abatacept because of cost and require that patients be treated with and fail TNF inhibitors first before moving on to other agents. Allowing treatment selection based on biomarkers may actually be a cost saving. Exhibit 2 shows a reduced per responder acquisition cost for abatacept compared to adalimumab.[8] ACPA is also associated with greater treatment response to other RA therapies including sarilumab.[9] With TNF inhibitor treatment, shared epitope and ACPA minimally predict treatment response.[10] Since TNF inhibitors are typical first choices to add to methotrexate monotherapy, presence of ACPA and shared epitope could predict non-response to these agents.

A large number of studies have been conducted and are ongoing investigating numerous other biomarkers. There are still many questions to be answered about using biomarkers to optimize medication or mechanism of action selection in RA. One question that needs to be answered is the following: Are there differences in response within the same mechanism family (of action TNF inhibitor, IL-6 inhibitor, JAK inhibitor) based on biomarker use? The desired accuracy of a given biomarker needs to be defined (it likely needs to be 85% to 90%). Overall, there is the desire to predict future response to a medication with high certainty and for a substantial portion of RA patients. A modeling study showed that to be 85 to 90 percent accurate, the results will only apply to about 25 percent of patients, but if one settles for 80 percent accuracy, prediction can be done for almost everyone.[11] The best outcome measure to examine for determining efficacy also needs to be defined and many clinicians would say ACR50, but low disease activity measures and disease activity score (DAS) remission may also be options.

The use of MBDA is the newest method for predicting treatment response or disease activity and/or risk of progression. PrismRA®, a molecular signature test, identifies RA patients unlikely to respond to TNF inhibitor therapies. This test analyzes 23 biological features, including RNA expression data, demographic variables, and disease-associated clinical metrics, which are discriminatory between the molecular signatures of those who respond or do not respond adequately to TNF inhibitor therapies. Utilizing this test can improve patient response rate by up to 38 percent by accurately stratifying patients prior to starting or changing therapy.[12,13] The positive predictive value of this test is 89.7 percent and specificity is 86.8 percent.[14] Using this test can shorten the patient journey to effective treatment and may reduce overall costs (Exhibit 3).

Vectra® is another commercially available MBDA. A Vectra® test provides a personalized score of disease activity by measuring 12 biomarkers and incorporating information on age, gender, and adiposity to measure a patient's RA inflammation and predict their risk of radiographic progression. The included biomarkers are vascular cell adhesion molecule-1, epidermal growth factor, vascular endothelial growth factor a, Il-6, TNF receptor type 1, matrix metalloproteinase-1, matrix metalloproteinase-3, human cartilage glycoprotein 39, leptin, resistin, C-reactive protein, and serum amyloid. This test is complementary to the other biomarkers discussed. This test meets all the requirements from the ACR for regular routine use in RA care. A Vectra® score of less than 30 indicates low disease activity, 30 to 44 is moderate, and greater than 44 is severe. It has been validated as the best predictor of radiographic progression compared with other disease activity measures. This test is currently being studied in a large treat-to-target strategy trial. It may be useful to predict the ability to successfully taper patients in remission off biologics. Exhibit 4 summarizes the various biomarkers and their uses in RA diagnosis and treatment.

The classic treatment paradigm assumes that patients and clinicians are willing to consider

Exhibit 3: Patient Journey Using Molecular Signature Test

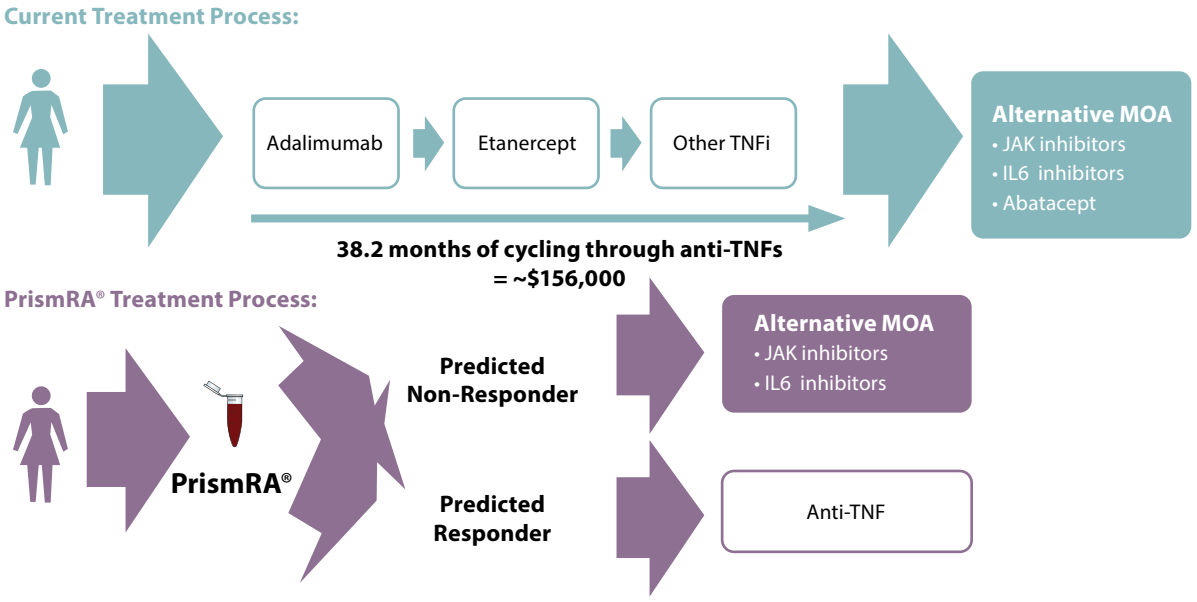


Exhibit 4: Biomarkers In Use in Rheumatoid Arthritis

Biomarker	Use
Rheumatoid factor	Diagnosis
Shared epitope	Diagnosis, prediction of disease, treatment selection
ACPA	Diagnosis, prediction of disease, treatment selection
PrismRA®	Predicting TNF inhibitor non-response
Vectra®	Disease activity measure, Predicting risk of radiographic progression

changing RA medications when the patient does not meet their goals. Patient refusal is the most common cause for lack of therapy escalation. Large treat-to-target trials find that despite still having disease activity about 50 percent of patients do not want to switch therapy.[15,16] In a cross-sectional survey drawn from patients enrolled in a rheumatology registry, 66 percent of RA patients waited on their clinicians to recommend a treatment switch.[17] In this survey, most participants trusted their rheumatologist's treatment decisions and prioritized their physician's treatment goals over their own. Primary patient motivations to switch are severe or worsened symptoms (51%) and not reaching a specified treatment goal (25%). Patients may not want to change therapy because they are worried about adverse events with the recommended agent or even poorer response to the new therapy. Helping patients understand their disease, what should be improved by medication, and the impact of the disease on their day-to-day life may make treatment changes more relevant and acceptable to patients.

Healthcare professionals typically collect many patient-reported outcomes as part of routine care, but they do not necessarily do it well. There are clinical practice tools to help assess the clinically relevant outcomes that most matter to RA patients, especially given that time at appointments is limited, and patients may only be seen every three to six months. One tool is the application READY® which is completed by the patient on a device in the waiting room before every visit. The data collected can be linked to the electronic medical record. Another example is ArthritisPower™ which can be done on a cell phone or the internet. Patients can be prompted to complete surveys between and before their appointments.

There are numerous benefits of collecting and using patient-reported outcomes. They allow clinicians to take better care of patients and collect more longitudinal data between visits (e.g., medication non-adherence with reasons, disease flares, daily functioning). They provide additional types of data, which informs patient care, that which clinicians are hard-pressed to obtain at visits (e.g.,

work productivity, vaccinations at outside location, depression screening, falls-risk assessment). The collected data can be used to justify expensive RA therapies as required by insurance and/or pharmacy benefits managers. Data collection systems can be used to conduct novel research studies, pragmatic trials, and assemble real-world evidence for a particular therapy. One study is ongoing that is combining a digital fitness tracker (activity, heart rate, sleep) and the ArthritisPower™ mobile app to collect daily and weekly electronic patient reported outcomes.[18]

Conclusion

It is ideal to be able to predict treatment response at an individual patient level. While some RA therapies may be preferred in certain settings, biomarkers may help optimize treatment choices for a wide range of patients. Patient-reported outcomes collected as part of real-world data generation may make treatment changes more relevant to patients. Digital solutions deployed as part of remote patient monitoring offer the potential to optimize care in RA.

Jeffrey Curtis, MD, MS, MPH is the Harbert-Ball Endowed Professor of Medicine in the Division of Clinical Immunology and Rheumatology, Department of Medicine, Department of Computer Science, and Department of Epidemiology at the University of Alabama at Birmingham, AL.

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Personalized Treatment Strategies in the Management of Castration-Resistant Prostate Cancer

Daniel P. Petrylak, MD

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

Summary

Treatment strategies for castration-resistant prostate cancer (CRPC) have evolved rapidly and continue to expand. Checkpoint inhibitor immunotherapy and poly (ADP-ribose) polymerase (PARP) inhibitors are two of the newer approved classes of therapy. Biomarkers to choose the best therapy are continuing to evolve for this disease.

Key Points

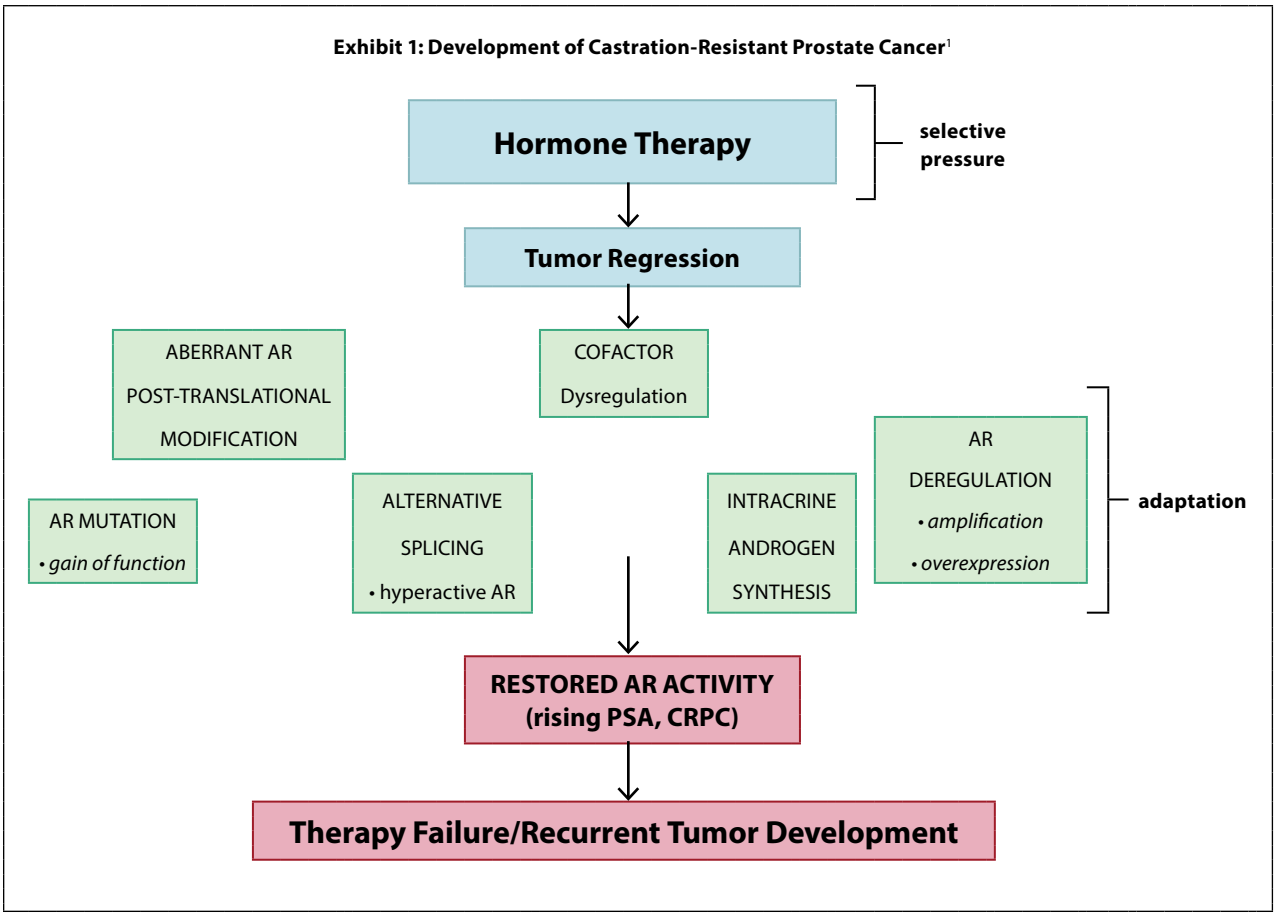
- Androgen receptor variant-7 (AR-V7) is a promising biomarker for sensitivity to enzalutamide and abiraterone.
- Olaparib and rucaparib are approved by the FDA for patients with DNA repair mutations.
- All CRPC patients should be tested for microsatellite instability-high (MSI-H) to identify those patients eligible for pembrolizumab.

ALTHOUGH SURGERY AND RADIATION are potentially curative in clinically localized prostate cancer, as many as one-third of patients will have disease progression after their initial treatment. At the time of disease progression, patients are offered androgen deprivation therapy (ADT) to achieve a castration level of testosterone. ADT results in dramatic tumor reduction, but after 18 to 24 months the prostate-specific antigen (PSA) begins to rise and disease increases on bone scans. This is now an androgen independent state (castration-resistant prostate cancer, CRPC). Treatment options once the disease is at this stage are limited and transiently effective.

CRPC is defined as increasing PSA levels or progressive disease on imaging despite a castrate level of serum testosterone (< 50 ng/dL). There are many different mechanisms how CRPC is thought to develop. Examples are androgen receptor mutations and splice variants and cancer cells learning how to make their own testosterone (Exhibit 1).[1] All of these alterations can lead to restored androgen receptor activity as evidenced by rising PSA. Common genetic mutations found in CRPC include ERG gene fusion (40% to 50%), androgen receptor gene point mutation or amplifications (50% to 60%), TP53 mutation or deletion (40% to 50%), PTEN deletion (40% to 50%), RB1 deletion (20%), and DNA repair genes (10% to 20%).[2]

The choice of therapy for metastatic CRPC (mCRPC) is based on clinical characteristics (symptomatic versus asymptomatic, visceral versus non-visceral disease, pre- versus post-docetaxel, other prior treatments) and biomarkers. Biomarkers that are in current use for treatment selection are MSI-H for pembrolizumab therapy, androgen receptor variant-7 (AR-V7) for ADT selection, and breast cancer gene (BRCA 1/2) and ataxia telangiectasia mutated (ATM) for poly (ADP-ribose) polymerase (PARP) inhibitor therapy. Adverse events of the various agents also are considered.

Like many other cancers, checkpoint inhibitor immunotherapy has been investigated in prostate cancer. Cancer cells develop many mutations that can make them appear foreign to the immune system. T cells can recognize, attack, and kill cancer cells, but these cells can evade immune attack by expressing programmed death ligand one (PD-L1),



AR = androgen receptor; PSA = prostate-specific antigen; CRPC = castration-resistant prostate cancer

which turns the immune system off. Clinically, blocking programmed death one (PD-1) or PD-L1 can reactivate the immune system. About 50 percent of hormone-sensitive prostate cancer specimens express elevated levels of PD-L1; the rate of PD-L1 positivity tends to be lower in mCRPC (~15%).[3,4] Expression may be hormonally-related; patients progressing on enzalutamide have significantly increased PD-L1 positive dendritic cells in blood compared to those not progressing on treatment.[5]

MSI-H, a state of genetic hypermutability that results from impaired DNA mismatch repair (MMR) may be a better indicator of checkpoint inhibitor immunotherapy efficacy in prostate cancer than PD-L1 expression. MMR corrects errors that spontaneously occur during DNA replication, such as single-base mismatches or short insertions and deletions. The proteins involved in MMR correct polymerase errors by forming a complex that binds to the mismatched section of DNA, excises the error, and inserts the correct sequence in its place. The aberrant process leads to DNA fragments with MSI structure that consists of repeated nucleotides, most often seen as GT/CA repeats. In prostate cancer, the prevalence of MSI-H or deficient MMR has been seen in approximately 2 to 3 percent of cases, based on different studies that used tumor tissue.[6-8]

Pembrolizumab (Keytruda®), a checkpoint inhibitor immunotherapy, is FDA-approved for treatment of MSI-H cancers, so it is an option for mCRPC with MSI-H. The KEYNOTE-199 trial showed a response in CRPC with pembrolizumab. About 11 percent of subjects experienced a 50 percent or greater PSA reduction from baseline and about 50 percent of subjects had some tumor reduction.[9] The patients who had BRCA 1/2 or ATM mutations appeared to have the best response. Whether this therapy changes overall survival (OS) in CRPC is not yet known. Because there is an approved therapy, all patients with CRPC should have a MSI-H analysis to see if they qualify.

Hormonal therapy with abiraterone (Zytiga®) or enzalutamide (Xtandi®) is another treatment option in mCRPC. Abiraterone is an androgen biosynthesis inhibitor that will inhibit cancer cell auto-synthesis of testosterone. In the pre-chemotherapy mCRPC

setting, abiraterone improved median OS by about three months. Enzalutamide binds to the androgen receptor so testosterone cannot bind. In the post-chemotherapy setting, it improves median OS by 4.7 months and reduces the risk of death by 37 percent.[10] Both abiraterone and enzalutamide are FDA-approved for the pre- and post-chemotherapy mCRPC setting.

AR-V7 is used to select hormonal therapy in mCRPC. AR-V7 is a truncated form of the receptor that lacks the ligand binding region, the target of abiraterone and enzalutamide, but remains constitutively active. In AR-V7–positive men, taxane chemotherapy (docetaxel or cabazitaxel) appears more efficacious than abiraterone and enzalutamide.[11] A recent trial found that detection of AR-V7 in circulating tumor cells by two blood-based assays is independently associated with shorter progression-free survival (PFS) and OS with abiraterone or enzalutamide. The authors concluded that AR-V7-positive men with mCRPC should be offered alternative treatments.[12]

In AR-V7–negative men, taxanes or hormonal therapy can be used, but there are unanswered questions on sequencing these two classes. There is clinical evidence of cross-resistance between abiraterone and enzalutamide. PFS and OS are shorter with either of these agents if the patient has previously been treated with the other one. There is also evidence of cross-resistance between abiraterone/enzalutamide and taxanes. In a recent trial, cabazitaxel significantly improved a number of clinical outcomes, as compared with the abiraterone or enzalutamide, in patients with mCRPC who had been previously treated with docetaxel and the alternative androgen-signaling-targeted agent (abiraterone or enzalutamide).[13]

The newest treatment choice for mCRPC is the PARP inhibitors. PARP repairs double-strand breaks in DNA; cells with BRCA or other DNA repair mutations only have PARP as an option to repair double-strand breaks and thus PARP inhibition leads to cell death. Between 10 and 20 percent of men with prostate cancer have BRCA 1/2 and other DNA repair mutations which would make their cancers susceptible to PARP inhibition.[14] Olaparib (Lynparza®) and rucaparib (Rubraca®), which were already FDA-approved for BRCA-mutated breast and ovarian cancers, were FDA-approved for BRCA-mutated mCRPC which had already been treated with androgen receptor-directed therapy in May 2020. All men with mCRPC should be tested for BRCA mutations to see if they would benefit from a PARP inhibitor.

The PROFOUND trial with olaparib was an open-label, Phase III, randomized trial that included 387 patients with mCRPC that had progressed on prior abiraterone or enzalutamide and had alterations in one or more of 15 qualifying DNA repair genes. Subjects were randomized in a two to one ratio to either olaparib or physician's choice of abiraterone or enzalutamide. Cohort A included patients with BRCA1/2 or ATM mutations, while Cohort B included all other DNA repair mutations. The primary endpoint was radiographic PFS in cohort A. Radiographic PFS was 7.4 months in the olaparib group compared to 3.6 months in the control group ($p < 0.001$).[15] There was significantly improved median OS with olaparib versus enzalutamide/abiraterone in Cohort A (19.1 months versus 14.7 months; $p = 0.0175$), despite crossover of 67 percent patients from the control arm to olaparib.[16] Sensitivity analyses adjusting for the impact of crossover suggested that the treatment effect of olaparib is likely to be greater than what was observed. In the overall population (patients harboring alterations in any of the 15 prespecified genes with a direct or indirect role in DNA repair), there was a trend towards improvement in OS.[16]

The TRITON2 Phase II trial with rucaparib enrolled 115 patients with mCRPC that previously progressed on an androgen receptor-directed therapy or one taxane-based chemotherapy and harbored a BRCA gene alteration.[17] The primary endpoint of objective response rate (ORR) was met in 33 percent of patients and a secondary endpoint of PSA50 (50% reduction) was achieved by 55 percent of patients. In addition, 25 percent of patients had stable disease. The FDA approval of rucaparib was an accelerated approval based on ORR and duration of response in this trial. Continued approval for this indication is contingent upon data from the ongoing TRITON3 trial, a Phase III trial that also includes those with ATM mutation.

Agents that specifically deplete disease targets rather than inhibit them are a future therapy for mCRPC. ARV-110 is among a new broad platform of therapies which engage a cell's own machinery for degrading proteins via a process known as the ubiquitin-proteasome system (UPS).[18] UPS is a cell's way of maintaining homeostasis by removing proteins to maintain the correct level, or to degrade mutated or misfolded proteins. The body has approximately 600 E3 ligases, each of which is responsible for tagging some subset of the proteome. E3 ligases tag target proteins with a small protein called ubiquitin. A chain of four ubiquitins is the normal signal for the protein to attach to the proteasome, which degrades the protein and recycles its amino acids.

ARV-110 is a PROTAC protein degrader targeted at the androgen receptor. PROTAC is short for proteolysis targeting chimera; chimera because it is a combination of three structural features combined in one small molecule. With ARV-110, there is formation of a trimer between an E3 ligase, the androgen receptor, and the PROTAC itself which is presented for degradation to the proteasomes. One important feature of a protein degrader is that it is iterative (or catalytic). Once the androgen receptor is marked for degradation, the PROTAC falls away and can then induce the degradation of additional copies of the androgen receptor. Each PROTAC can induce the degradation of hundreds of copies of the androgen receptor. ARV-110 is currently in Phase II trials for mCRPC that has failed prior treatments.

Conclusion

There are now several treatment options for mCRPC. AR-V7 is a promising biomarker for sensitivity to enzalutamide and abiraterone. PARP inhibitors (olaparib and rucaparib) are approved by the FDA for patients with DNA repair mutations. All CRPC patients should be tested for MSI-H to identify those patients eligible for pembrolizumab.

Daniel P. Petrylak, MD is a Professor of Medicine and Urology, Director of the GU Translational Working Group, and Co Director of the Signal Transduction Program at the Smilow Cancer Center at Yale University in New Haven, CT.

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Best Practices in the Management of Advanced Renal Cell Carcinoma: Expert Perspectives on Novel Therapies

Robert A. Figlin, MD, FACP

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

Summary

Advanced renal cell carcinoma remains incurable; however, there are numerous treatment options available for multiple lines of therapy. Significant gains in survival have been made since the early 2000s with the introduction of targeted therapies and especially now with the addition of immunotherapy to the standard regimen.

Key Points

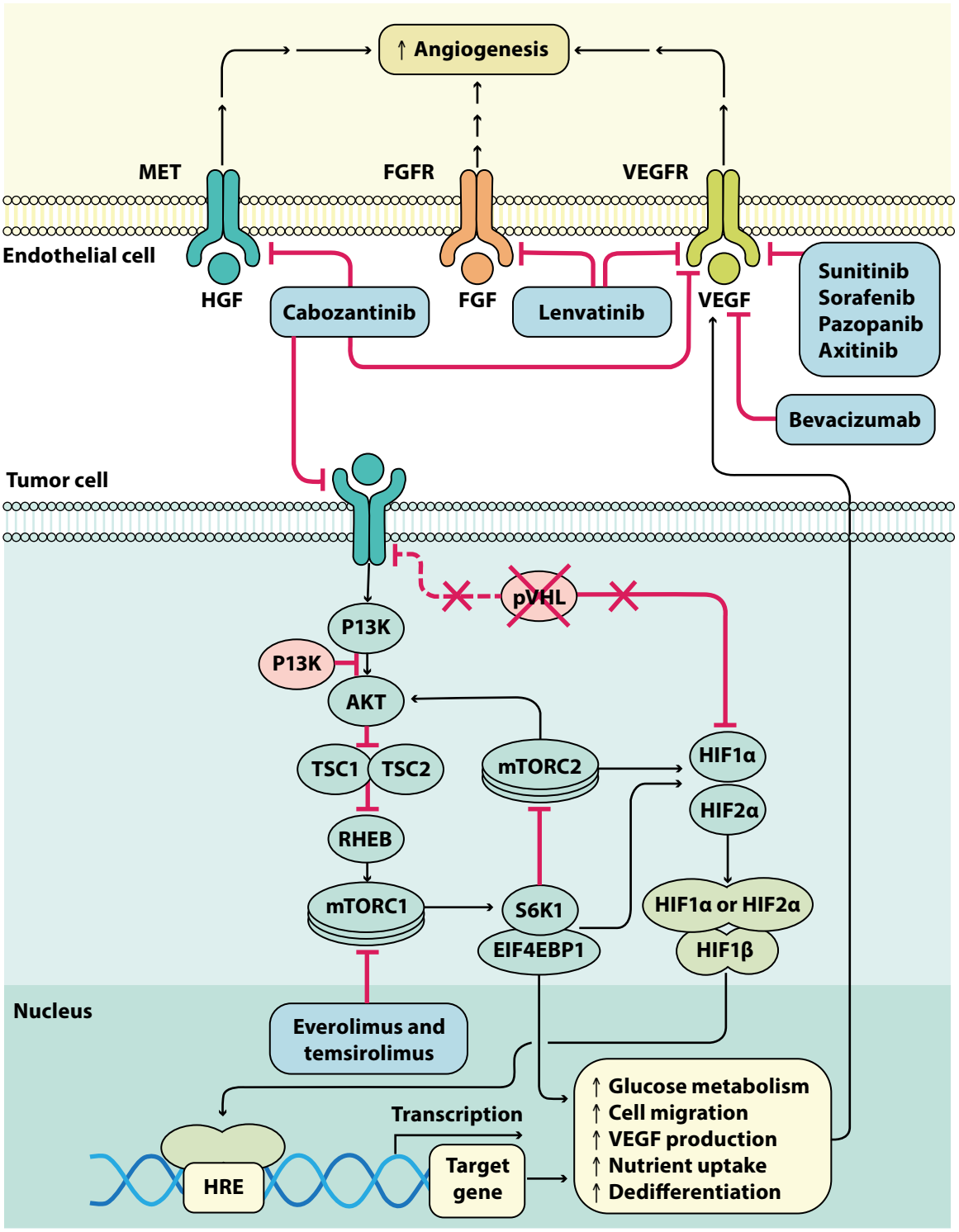
- Better adjuvant therapies are needed to prevent spread of disease after surgery.
- Metastatic disease is not curable, but survival gains have been made.
- Standard first-line treatment for advanced and metastatic RCC is a combination of targeted therapy and checkpoint immunotherapy.

THE AMERICAN CANCER SOCIETY ESTIMATES there will be 76,080 new cases of renal cell carcinoma (RCC) and about 13,780 people will die from this disease in the United States (U.S.) in 2021.[1] Unlike many other cancers, the majority of RCC cases are diagnosed when the disease is still localized to the kidney (56%), but only 16 percent of cases are metastatic at diagnosis.[2] RCC can often be cured by surgical resection if it is diagnosed and treated when still localized to the kidney and the immediately surrounding tissue. With surgical treatment about 60 percent of patients are cured and 40 percent go on to eventually develop metastatic disease. An effective adjuvant therapy is needed to prevent the development of metastatic disease post-surgery. Most of the advances in therapy have been with advanced or metastatic RCC.

Clear cell is the most common type of RCC (80% to 85%). The von Hippel-Lindau (VHL) gene is inactivated by either mutation or methylation in over 80 percent of RCC cases.[3] Kidney cancer is a hypervascular cancer, in large part because of VHL inactivation, which leads to vascular endothelial growth factor (VEGF) over expression. Targeting VEGF has been a primary treatment for RCC since 2005. Other growth factor pathways besides VEGF are activated in RCC, including MET proto-oncogene-encoded receptor tyrosine kinase (MET), AXL receptor tyrosine kinase (AXL), and fibroblast growth factor receptor (FGFR). Newer tyrosine kinase inhibitors cabozantinib and lenvatinib also block MET, AXL and FGFR, respectively, in addition to VEGF. Exhibit 1 shows were the various FDA-approved targeting agents work.[4]

RCC is also an immunologic cancer with a high tumor cytolytic activity and T cell tumor infiltration. Despite having a low mutational burden, RCC responds to immunotherapy because the immune system is already working against the cancer. The combination of checkpoint immunotherapy and VEGF inhibition are synergistic in killing cancer cells and have become the standard of care for first-line therapy for advanced clear cell RCC in the National Comprehensive Cancer Network (NCCN) guidelines

Exhibit 1: Oncogenic Signaling and Targeted Therapy in RCC[4]



FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; TSC, tuberous sclerosis complex; PI3K, phosphatidylinositol 4,5-bisphosphate 3-kinase; AKT, RAC-α serine/threonine-protein kinase; Rheb, GTP-binding protein Rheb; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; S6K1, ribosomal protein S6 kinase; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; HRE, HIF response element; HGF, hepatocyte growth factor receptor; MET, MET proto-oncogene-encoded receptor tyrosine kinase ; HIF, hypoxia-inducible factor

Exhibit 2: NCCN First-Line Therapy for Advanced Clear Cell RCC[5]

Risk	Preferred Regimens*
Favorable	Axitinib + pembrolizumab (category 1)
	Cabozantinib + nivolumab (category 1)
	Lenvatinib + pembrolizumab (category 1)
Poor/Intermediate	Axitinib + pembrolizumab (category 1)
	Cabozantinib + nivolumab (category 1)
	Ipilimumab + nivolumab (category 1)
	Lenvatinib + pembrolizumab (category 1)
	Cabozantinib

* The guidelines also list other recommended regimens and agents useful in certain circumstances

(Exhibit 2).[5] Treatment selection also depends on whether the patient has favorable or unfavorable disease (intermediate-risk or poor-risk). Those with favorable-risk have a longer average survival (median 43 months) than those with intermediate-risk (23 months) and poor-risk (8 months) when treated with VEGF inhibitors.[6] The use of VEGF inhibitors has significantly improved survival from 30, 14, and 8 months, respectively.[7] Overall, targeted therapy is delaying disease recurrence, improving disease-free survival, and maintaining quality of life, but patients are not cured. Checkpoint inhibitor immunotherapy is furthering the survival benefits, and immunotherapy monotherapy has produced survival out to 47 months.[8] Combination therapy is producing better progression-free survival and overall survival; however, final outcomes from the trials have not yet been published.[9-11]

As with most metastatic cancers, patients will eventually have disease progression on first-line therapy. There are numerous treatment options available for multiple lines of therapy. Once a patient has disease progression on the standard combination, second-line and later regimens will depend on which agents were used in first-line. The preferred subsequent therapy regimens from the NCCN guidelines are cabozantinib, lenvatinib/everolimus, and nivolumab.[5]

As mentioned initially, there is a need for better adjuvant therapies to prevent the development of metastatic disease in those with high-risk localized disease. Sunitinib is the only FDA-approved agent for adjuvant use in Stage III disease, but it only improves disease-free survival and not overall survival. Several trials are ongoing examining immunotherapy alone and in various combinations for adjuvant use (Exhibit 3).

Checkpoint immunotherapy does frequently lead to significant adverse events which must be monitored and managed. The immune-related adverse events (irAEs) which are related to unleashing the immune system can result in hospitalization and death and can affect any body system. Everyone involved in the care of patients receiving immunotherapy needs to adopt a systematic approach to preventing, identifying, and treating irAE (Exhibit 4).[12]

Several novel agents are under investigation for treating RCC. Two examples are MK-6482, a hypoxia-inducible factor 2α (HIF-2α) inhibitor, and TRC105, an anti-endoglin.

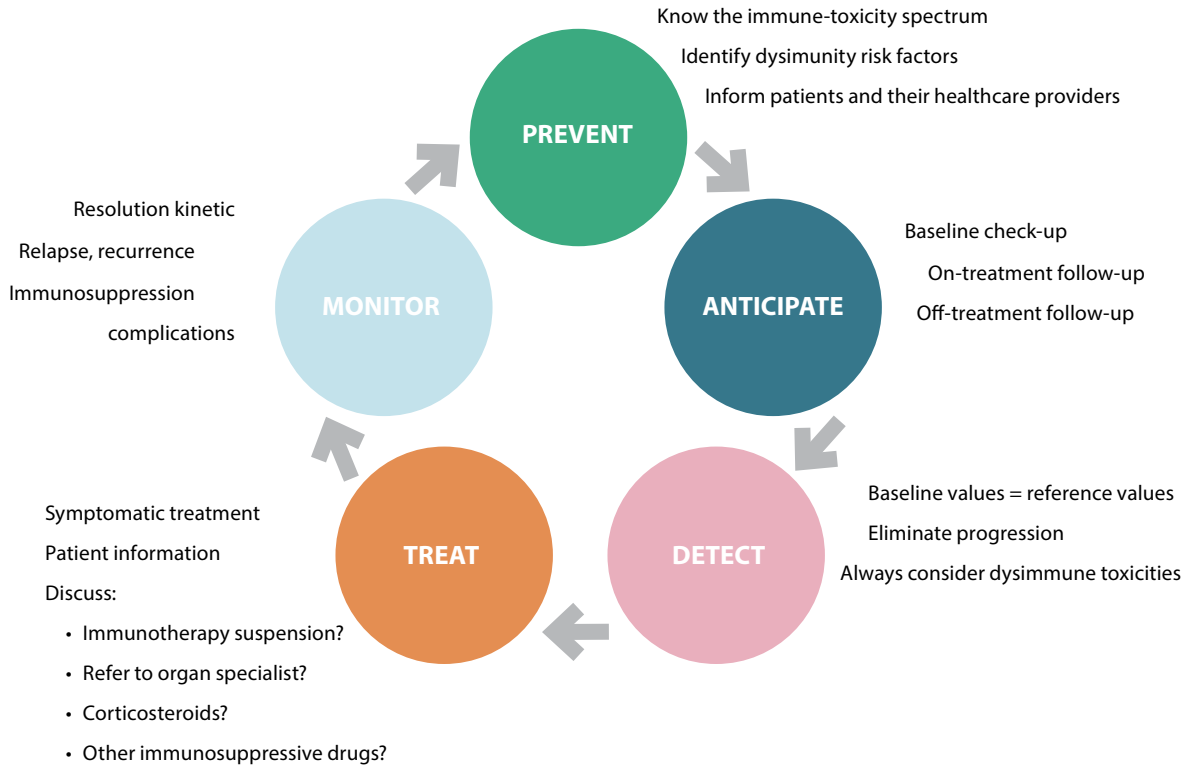
Conclusion

Better adjuvant therapies are needed to prevent spread of the disease after surgical treatment of RCC. Although metastatic disease is not curable, significant survival gains have been made with the newer therapies. Standard first-line treatment for advanced and metastatic RCC is a combination of

Exhibit 3: Trials Assessing Adjuvant Immunotherapy for High-Risk Localized RCC

Treatment Arms	Trial	ClinicalTrials.gov ID
Atezolizumab versus placebo	IMmotion010	NCT03024996
Pembrolizumab versus placebo	KEYNOTE-564	NCT03142334
Neoadjuvant nivolumab → surgery → adjuvant nivolumab versus observation	PROSPER RCC	NCT03055013
Nivolumab + ipilimumab versus placebo	Checkmate 914	NCT03138512
Durvalumab versus durvalumab + tremelimumab versus active surveillance	RAMPART	NCT03288532

Exhibit 4: Preventing and Managing Immune-Related Adverse Events[12]



targeted therapy and checkpoint immunotherapy. As additional agents reach the market, hopefully the survival gains will continue.

Robert A. Figlin, MD, FACP is the Steven Spielberg Family Chair in Hematology Oncology, Professor of Medicine and Biomedical Sciences, Deputy Director at Cedars-Sinai Cancer, and Deputy Director at Samuel Oschin Comprehensive Cancer Institute at the Cedars-Sinai Medical Center in Los Angeles, CA.

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New Developments in the Treatment and Management of Psoriasis: Key Considerations for Improving Outcomes

Paul S. Yamauchi, MD, PhD

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

Summary

Psoriasis is an immune-mediated inflammatory disease of the entire body. Treatment with biologics can produce significant skin clearing and reduce systemic inflammation. Managing these patients often requires a multidisciplinary team approach.

Key Points

- Multiple treatment options are available that target the underlying pathophysiology.
- 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.
- Patient preference should be considered when selecting therapy.

PSORIASIS IS A CHRONIC RELAPSING immune-mediated inflammatory disease characterized by psoriatic plaques, which are red, thick, and scaly. It affects 3.2 percent of the United States (U.S.) population.[1] It affects multiple parts of the body, is not just a skin disease, and there are multiple associated comorbidities related to systemic inflammation. Psoriasis is accompanied by significant clinical, social, emotional, and economic burden.

There is a bimodal age of onset with psoriasis. The first peak incidence is between 20 and 30 years of age, and the second peak is after 50 years of age. Onset at less than 15 years of age may indicate more severe, treatment-resistant disease. There is a

Exhibit 1: Plaque Psoriasis

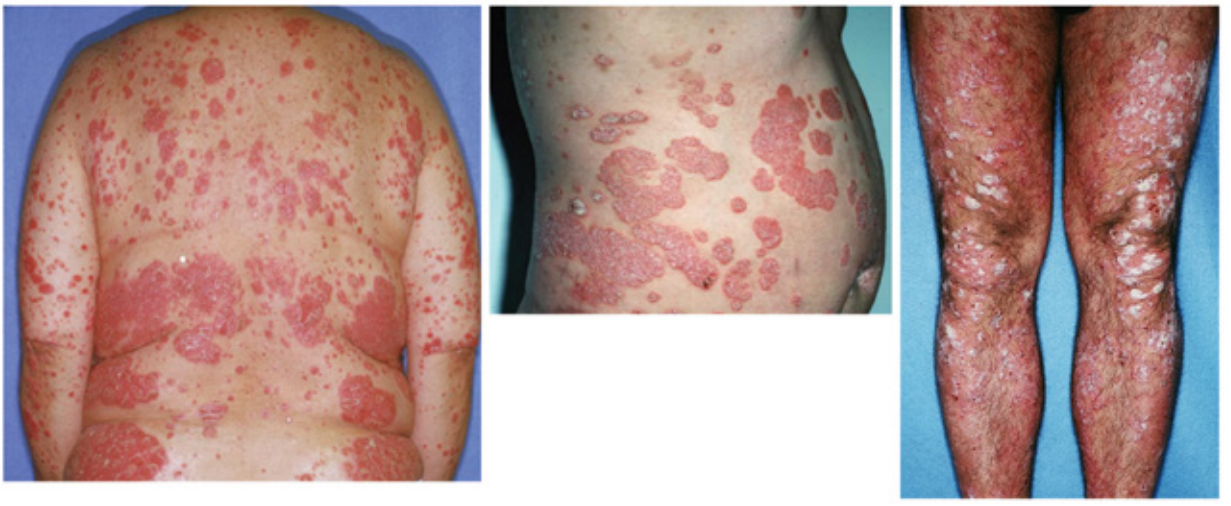
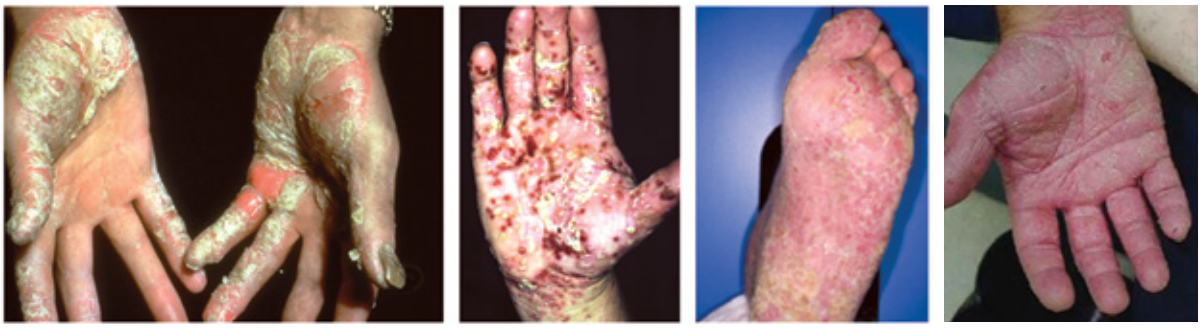


Exhibit 2: Palmar Plantar Psoriasis



genetic association, with up to 33 percent of patients reporting a family history.

There are several types of psoriasis – plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis represents about 80 percent of the cases and is the focus of this monograph (Exhibit 1). The differential diagnosis for plaque psoriasis includes atopic dermatitis, medication reaction, and tinea corporis. Palmar plantar psoriasis is a variant of psoriasis in which the palms of hands and soles of the feet are affected (Exhibit 2). This can be very debilitating and is the predominant manifestation of psoriasis in 5 to 10 percent of cases. Nail changes (pitting, dystrophy) occur in up to 50 percent of patients and are associated with psoriatic arthritis.

Because of the inflammatory state, psoriasis patients are more likely to have associated co-morbidities, including cardiovascular disease, psoriatic arthritis, obesity, diabetes, hypertension, and cancer.[2,3] Up to 30 percent of individuals with psoriasis will develop psoriatic arthritis, an inflammatory form of arthritis that can lead to irreversible joint damage if left untreated. Psoriatic arthritis usually develops 10 to 15 years after the onset of psoriasis. Those with psoriasis are also more likely to have depression, anxiety, psychological stress, and poor self-esteem because of the appearance of their skin.[4]

Psoriasis occurs on a continuum from mild to severe. Even patients who have minimal skin impact of the disease [i.e., less than 10% of body surface area (BSA)] can have major quality of life impact. Exhibit 3 shows how severity can be assessed using BSA, Psoriasis Area and Severity Index (PASI), Physicians Global Assessment (PGA), and Dermatology Life Quality Index (DLQI).[5-8] One caveat to this system of severity rating is that patients with palmar planter psoriasis may have less than 10 percent BSA affected, but they have severe impact from their disease and require systemic treatment.

Exhibit 3: Assessing Psoriasis Severity[5-8]

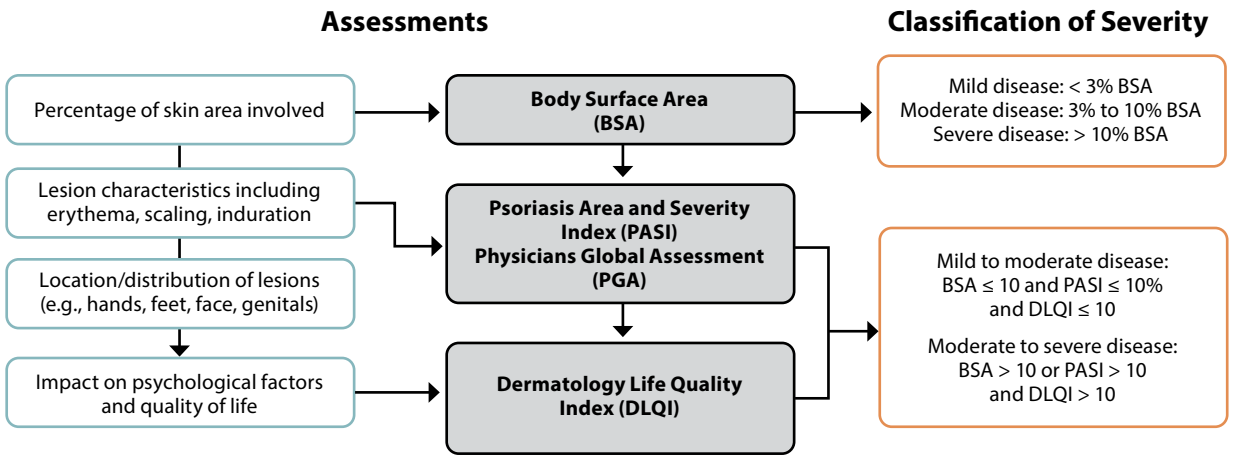
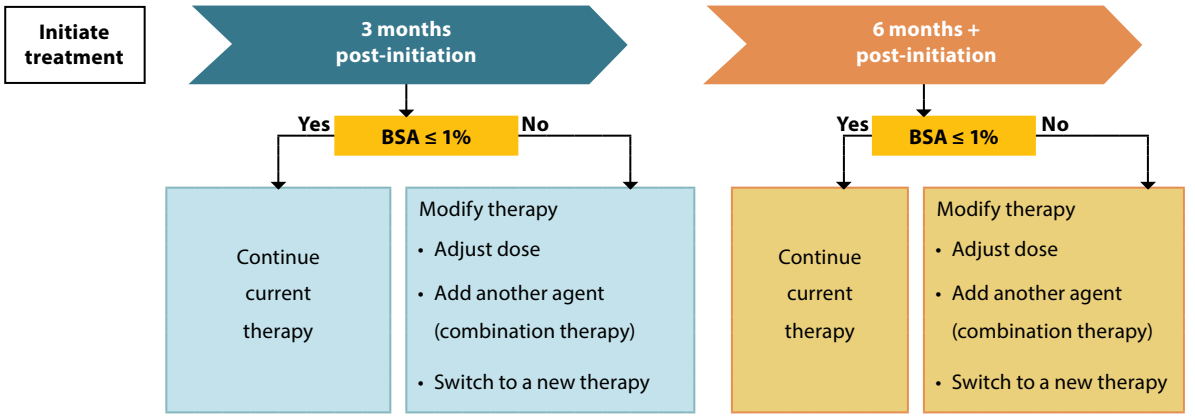


Exhibit 4: Treat-to-Target Approach[11]



Psoriasis pathophysiology involves keratinocyte hyperproliferation, which interferes with the keratinocyte terminal differentiation.[9] The psoriatic keratinocyte is driven by an immune-mediated chronic inflammatory response. Although the exact cause is unknown, the development of psoriasis involves a complex interplay between genetic predisposition and environmental factors (e.g., skin injury, infection, stress, certain medications, smoking, alcohol, and obesity). Both localized and systemic inflammation is caused by defects in T regulatory cells and upregulation of T helper one (Th1) and Th17 cells, antigen presenting cells, and cytokines [e.g., tumor necrosis factor (TNF), interleukins-12, 17, 22, and 23].

The American Academy of Dermatology and the National Psoriasis Foundation (NPF) have released two joint guidelines for the management and treatment of psoriasis. One set addresses common comorbidities seen with psoriasis (e.g., PsA, CVD, metabolic syndrome, mental health conditions, IBD) and how their presence impacts psoriasis management.[2] The other discusses the treatment of psoriasis using biologics.[10] The revised guidelines are designed to reinforce dermatologists' knowledge of psoriasis and how to treat it, provide other health care providers a reference to use when caring for people with psoriasis, provide health insurance companies up-to-date treatment information needed to design appropriate coverage policies for their members living with psoriasis, and provide patients with information that can help them improve their knowledge of psoriasis and how to work with their provider to achieve the best health outcome possible.

The goal of treatment is to use a treat-to-target approach to reduce affected BSA to 1 percent or less three months after initiating treatment (Exhibit 4).[11] Therapy should be assessed and adjusted until this goal is achieved. In addition to clearing skin, other goals are to minimize the adverse events of medications, enhance the quality of life the patient, and address any comorbidities. Clinicians need to involve the patient in treatment decision-making and to consider patient preferences when selecting therapy.[12,13] Mild to moderate disease is treated with topical therapies and phototherapy. Moderate to severe disease requires systemic treatment with or without phototherapy. Concomitant psoriatic arthritis also requires systemic treatment.

Several classes of biologic agents are available to target important steps in the pathophysiology of moderate to severe psoriasis, including TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors, and phosphodiesterase-4 (PDE-4) inhibitors (Exhibit 5). However, current data does not fully elucidate their ideal use, including matching patients with the most appropriate treatment and the ideal combinations and sequencing of agents.[10,14] Additionally, some of the agents are only FDA-approved for treating psoriasis and others are approved for treating both psoriasis and psoriatic arthritis.

In selecting a biologic or an oral targeting agent, it is important to note that not all psoriasis patients respond to any one type of agent or class of agents and a patient's perception of response to therapy can influence a physician's definition of an inadequate response. Choice of therapy can be influenced by medication onset of action, durability of response, and the need for and frequency of injections. It can also be influenced by the presence of psoriatic arthritis, enthesitis, dactylitis, and axial disease as well as comorbidities, contraindications, and relative contraindications (active hepatitis B, demyelinating

Exhibit 5: Targeted Therapies Approved for Psoriasis

Injectable biologics	
Type	**Generic Name**
TNF-alpha Inhibitor	Etanercept*
	Adalimumab*
	Infliximab*
	Golimumab
	Certolizumab pegol*
IL-12/23 Inhibitor	Ustekinumab*
IL-17A Inhibitor	Secukinumab*
	Ixekizumab*
IL-17 Receptor Inhibitor	Brodalumab
T cell Inhibitor	Abatacept
IL-23 Inhibitor	Guselkumab
	Tildrakizumab
	Risankizumab

Oral Agents	
Type	**Generic Name**
PDE4 inhibitor	Apremilast*
JAK inhibitor	Tofacitinib

* Also FDA-approved for treating psoriatic arthritis

disease, heart failure, and inflammatory bowel disease), and insurance coverage. Based on clearing of skin (PASI scores), the IL-17 and IL-23 inhibitors are the most effective biologics, but there are few head-to-head studies to identify the most effective agents.

In the case of an inadequate response to a biologic, monotherapy treatment strategies include increasing the dose or changing the interval of administration. For example, the secukinumab dose can be increased from 150 mg to 300 mg per month for psoriatic arthritis. The dosing interval for ustekinumab can be decreased to 8 weeks from every 12 weeks. Another option is to switch to another biologic agent. The switch should be to a different class if the patient is a primary non-responder, but it can be the same or different class if the patient is a secondary non-responder.

Combination therapy may also be necessary. Topical therapy can be added to biologics for relapse or recalcitrant plaques. Phototherapy or methotrexate (10 to 30 mg per week) can be added. Methotrexate has been demonstrated to enhance the efficacy of the biologics and decrease formation of neutralizing antibodies. Another option is to add a short course of another systemic agent for flare or initial control of unstable disease [i.e., cyclosporine (4 to 5 mg/kg)]. Apremilast can be added for relapse of psoriasis or if a biologic agent is not adequately controlling the skin or joints for a patient with psoriasis and psoriatic arthritis.

Early referral of a patient to a specialist is critical for psoriasis patients with joint symptoms and comorbidities (e.g., cardiovascular disease) for diagnosis and management of psoriatic arthritis and comorbidity management. Early detection and appropriate treatment of psoriatic arthritis can reduce long-term disability and minimize the use of healthcare resources. Unfortunately, psoriatic arthritis tends to be underdiagnosed. Patients with severe or complicated disease require care from a multidisciplinary team of providers to manage skin, joint, and cardiovascular involvement over the long term.

Conclusion

Multiple treatment options which target the underlying pathophysiology are now available for managing psoriasis. 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. Patient preference should be

considered when selecting therapy. Dermatologists should screen for joint involvement in their psoriasis patients and collaborate with rheumatologists to manage both skin and joint involvement over the long term.

Paul S. Yamauchi, MD, PhD is a cosmetic, medical, and surgical dermatologist in private practice at the Dermatology Institute and Skin Care Center in Santa Monica, CA. He is on staff at St. John's Health Center in Santa Monica, Ronald Reagan UCLA Medical Center in Westwood, and the UCLA Medical Center, Santa Monica. Dr. Yamauchi is a clinical assistant professor of medicine in the Division of Dermatology at the David Geffen School of Medicine at UCLA and Adjunct Associate Professor at the John Wayne Cancer Institute in Santa Monica, CA.

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Navigating an Increasingly Complex Treatment Paradigm in the Management of Multiple Sclerosis

Claire S. Riley, MD

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 has been a proliferation of new disease-modifying therapies for multiple sclerosis over the past 20 years which is exciting for those who treat multiple sclerosis. The new therapeutics make both the neurologist and managed care's jobs more challenging but also more rewarding because they are improving outcomes.

Key Points

- Early diagnosis and treatment are critical to minimizing long-term damage from the disease.
- The criteria for a diagnosis of MS have evolved over time to help achieve earlier diagnosis.
- A less aggressive escalation approach may be appropriate for some patients, whereas others would benefit from an aggressive induction approach.

MULTIPLE SCLEROSIS (MS) IS AN IMMUNE-mediated inflammatory disease of myelin, the insulating sheath around axons. Characterized by inflammatory plaques or scars predominantly 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.

The criteria for a diagnosis of MS have evolved over time to help achieve earlier diagnosis; the most recent version was updated in 2017 (Exhibit 1).[1] Diagnosis of MS requires attacks of symptoms with objective clinical evidence of brain lesions. An MS attack or relapse is a neurological disturbance of the kind seen in MS based on a subjective report or neurological examination and occurs for at least 24 hours duration in absence of fever or infection. Combined with MRI findings and clinical data, the presence of oligoclonal bands in cerebrospinal fluid helps facilitate a diagnosis of MS. Oligoclonal bands, immunoglobulins found in 90 percent to 95 percent of patients with definite MS, are indicative of chronic central nervous system (CNS) inflammation. The disadvantage of this test is it requires lumbar puncture, and it is not currently part of the diagnostic criteria.

It is important to note that as the diagnostic criteria have incorporated more sensitive testing, patients are being diagnosed earlier in the disease process. This earlier diagnosis combined with earlier treatment leads to a very different natural history among the more recently diagnosed cohort of patients compared to cohorts diagnosed under older criteria. The patients included in older medication studies were very different from those included in trials today.

There is one possible MS precursor and four clinical subtypes of MS. Radiologically isolated syndrome (RIS) is evidence of CNS damage suggestive of MS on an MRI, but no clinical symptoms have occurred. RIS is typically found incidentally when a person has an MRI for an unrelated medical indication. Only about one in 10 inflammatory episodes in the brain results in MS symptoms. The prognostic implications of RIS are controversial, but there are some data to suggest that patients with RIS are at increased risk of developing MS within five years. Trials are ongoing evaluating treating RIS. Clinically isolated syndrome (CIS) is the first acute or subacute episode of MS symptoms and most commonly presents as optic neuritis, partial myelitis,

Exhibit 1: 2017 Revised Diagnostic Criteria[1]

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks; objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack.	None
Two or more attacks; objective clinical evidence of 1 lesion.	Dissemination in space (DIS), demonstrated by: ≥ 1 T2 MRI lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord). **or** Await a further clinical attack implicating a different CNS site.
One attack; objective clinical evidence of ≥ 2 lesions.	Dissemination in time (DIT), demonstrated by: Simultaneous presence of asymptomatic gadolinium (Gd)-enhancing and non-enhancing lesions at any time. **or** A new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan. **or** Await a second clinical attack. **or** Positive CSF

or brainstem/cerebellar syndrome.[2] CIS is treated when identified to prevent disability progression. Relapsing-remitting MS (RRMS) are episodes of acute worsening of neurologic functioning (new symptoms or the worsening of existing symptoms) with total or partial recovery between episodes and no apparent progression of disease. RRMS can be further characterized as active or not active and worsening or stable. Primary-progressive MS (PPMS) is steadily worsening neurologic function from the onset of symptoms without initial relapses or remissions. Like RRMS, PPMS can be further characterized as active or not active and with or without progression. Secondary-progressive MS (SPMS) is defined as an initial relapsing-remitting course that becomes more steadily progressive, with or without relapses. These patients have an insidious onset of disability, and many cases of RRMS evolve over time into SPMS. Again, SPMS can be additionally characterized by activity and progression.

Early treatment of MS with disease-modifying therapy (DMT) is the standard in MS management for several reasons. It is easier to treat early because the immune system defects of the disease become more entrenched with time.[3] Irreversible nervous system damage occurs early in the disease process, and the early course influences long-term evolution of disability. Patients who start therapy early have a significant advantage in terms of disability accumulation over time compared with late starters (after 2 years of diagnosis). Recovery mechanisms from a given attack may become less effective over time. The available treatments are effective in RRMS but not as effective in progressive disease and do not restore damaged tissue. Another reason to treat early is that symptoms and relapses correlate poorly with the ongoing inflammation and resultant irreversible tissue destruction in early RRMS. Finally, efficacy of immunomodulatory drugs decreases with age; therefore, it is more effective to treat at a younger age (i.e., earlier in the disease process).[4] Delaying

Exhibit 2: FDA-Approved RMS or Active SPMS Therapies

Agent Grouped by Class	Administration
Glatiramer acetate	SC daily or TIW
IFNβ-1a /IFNβ-1a/IFNβ-1b /Peginterferon beta 1a	IM QWK/SC TIW/SC QOD/SC Q2wks
Natalizumab	IV Q4WK
Fingolimod, Siponimod, Ozanimod	PO daily
Teriflunomide	PO daily
Dimethyl fumarate, Diroximel fumarate	PO BID
Alemtuzumab	IV QD x 5D Y1, 3D Y2
Ocrelizumab	IV Q6 months
Cladribine	PO daily short course
Ofatumumab	SC monthly

any DMT, even for a few years, leads to a decrease in cumulative efficacy that cannot be easily regained by opting for more aggressive treatments at a later age. Currently, there is no cure for MS. However, several therapies have proven beneficial in reducing the annualized relapse rate (ARR) and slowing disability. There are now 16 agents which are FDA-approved (Exhibit 2).

Therapy should be tailored to an individual patient's prognosis and risk for disability worsening. MRI findings are an excellent prognostic predictor and are a very good early predictor of treatment response. It is now standard of care to begin patients with concerning prognostic features on high efficacy therapies (induction approach). An active escalation approach may be appropriate with lower risk prognostic features. No study has demonstrated worse outcomes by trying a therapy for six to 12 months and escalating for evidence of activity.[5] Exhibit 3 compares these two approaches. It should be noted that only alemtuzumab, cladribine, and maybe ocrelizumab/ofatumumab appear to have long lasting modification of the immune system (true induction). Although natalizumab is a higher-efficacy agent that provides good symptom and relapse control, it may not be modifying the underling immune pathology.

The TREAT MS study is comparing higher-efficacy (induction approach) versus traditional therapies (escalation approach) in 900 participants who meet 2017 criteria for RRMS over 54 months (Exhibit 4). The higher-efficacy agents are alemtuzumab, ocrelizumab, rituximab, natalizumab, cladribine, and ofatumumab. The standard therapy agents are the self-injectable and oral agents (glatiramer acetate, interferons, teriflunomide, dimethyl/diroximel fumarate, fingolimod, siponimod, and ozanimod). Planned to end in 2024, the results of this trial will hopefully settle the debate on the best way to start therapy in RRMS and on how to deal with breakthrough attacks.

Overall, the treatment goals of RRMS are to avoid relapse and delay or defer secondary progression. Relapses are disruptive for patients, potentially require intravenous corticosteroid treatment and hospitalization, and recovery may be incomplete, leading to stepwise accrual of disability. SPMS is the disease phase where the majority of disability accrues and delaying or preventing conversion from RRMS to SPMS is an important outcome.

Defining efficacy with DMT is important. It is no longer just acceptable that the patient is tolerating therapy. There needs to be clinical evidence of efficacy. In clinical practice, combining MRI activity and relapse frequency is a reasonable surrogate for disability in MS. Most studies measure change in the Expanded Disability Status Scale (EDSS), but this change can occur very slowly in some patients. Sormani and colleagues reviewed a dataset of interferon beta 1a (IFNβ-1a) treated RRMS patients applying criteria for surrogacy of MRI active lesions at one year and relapses for EDSS progression at two years.[6] All of the reduced disability progression with IFNβ-1a could be attributed to its effect on relapses and MRI lesions.

There are consensus guidelines on using MRI

Exhibit 3: Induction Therapy versus Escalation Therapy

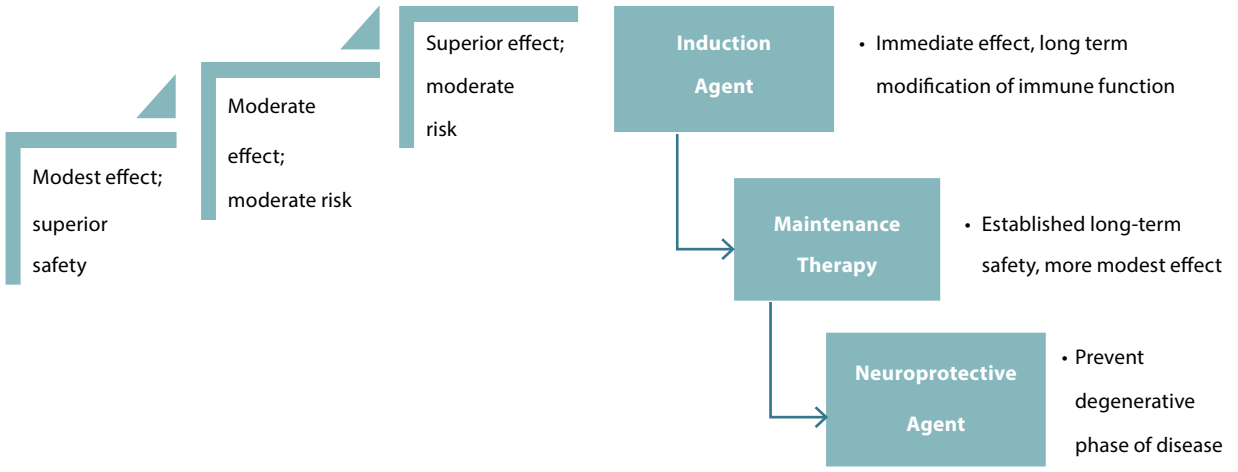
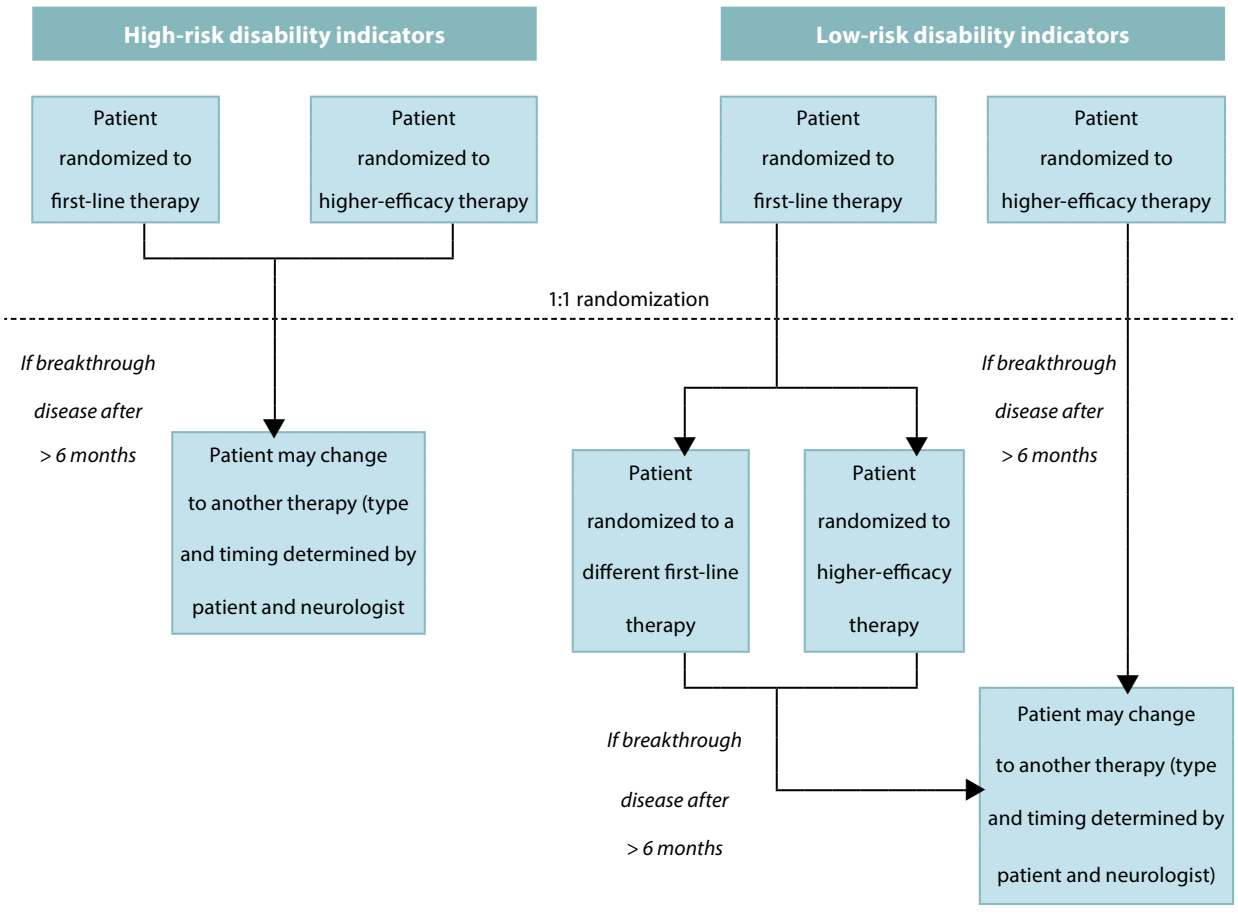


Exhibit 4: TREAT MS Trials



as a prognostic and monitoring tool in MS. These guidelines advise consideration of the mechanism of action of the DMT being used and timing of the baseline scan when interpreting new T2 lesions. The patient should have an MRI baseline reestablished approximately six months after treatment initiation and then follow-up MRIs every six to 12 months. When relying on MRI heavily to determine response to therapy, establishing a new baseline after a treatment has become fully effective is critical to avoid unnecessary escalation.[7] The time to new baseline is based on mechanism of action of the treatment. For example, with interferon beta, teriflunomide, dimethyl fumarate, fingolimod, and natalizumab, six months is recommended. For alemtuzumab, a new baseline scan should be done one year after the last dose.

No evidence of disease activity (NEDA) is becoming a goal in MS treatment. It is increasingly being reported in clinical trials and used in practice. NEDA is complete absence of detectable disease activity while on DMT.[8] The criteria include NEDA on MRI, no clinical relapses, and no disability worsening. The conversation around complete control of MS started when results of a pivotal trial with natalizumab were published.[9] In this trial, 37 percent of the patients had NEDA. The main criticism of the NEDA paradigm is concern that many patients will move to higher-efficacy, higher-risk agents, when some would have done well clinically on lower-efficacy, lower-risk agents.

In clinical studies, the range of NEDA is wide and of course varies based on baseline characteristics of the patient population and the efficacy of medication. Achievement of NEDA is less than 50 percent even with the most effective agents. Real-world cohorts like the CLIMB cohort can be instructive but should be interpreted with caution since patients are selecting specific treatments due to the degree of disease activity, and many of these patients were diagnosed under older criteria (later in disease process). In this cohort, 46 percent of patients achieved NEDA at one year, 27.5 percent at two years, and 7.9 percent at seven years.[10]

The NEDA definition is also being expanded. The current definition is referred to as NEDA 3 because of the three included criteria. NEDA 4 includes the additional criteria of no brain atrophy, and some trials are now using this. Brain atrophy correlates with the effect of DMT on two-year disability progression (explains 48% of variance) and combining brain atrophy with new or enlarging T2 lesions on MRI explains 75 percent of variance.[11]

Other proposed additions to the NEDA criteria include cognitive status, fatigue, depression, and quality of life. A multifactorial model [multiple sclerosis decision model (MSDM)] that includes the domains relapse, disability progression, MRI findings, and neuropsychology has been proposed. This model reflects the complexity of the disease even in the initial stages when scales such as the EDSS are not able to distinguish low levels of progression.[12]

B cells have become a major target of MS therapy. Oligoclonal bands, a product of B cells, have been a recognized feature of MS for decades. Subpial lymphoid follicles have been recognized as a home for B lymphocytes in the CNS.[13] These tertiary lymphoid tissues are a product of chronic inflammation. Rituximab, which targets B cells and is approved for other autoimmune diseases such as rheumatoid arthritis, has been used off-label in MS, and there are many patients who are still receiving rituximab.

Ocrelizumab (Ocrevus®) was the first B cell targeting therapy FDA-approved for MS (2017). It is a CD20-directed cytolytic antibody indicated for the treatment of CIS, RRMS, active SPMS, and PPMS, in adults. It is the only FDA-approved treatment for PPMS. It selectively depletes B cells and is given by infusion every six months. Ocrelizumab is similar to rituximab (> 90% epitope overlap), but it is humanized instead of chimeric, has a different though overlapping antigen site, and has slightly differing effects on the immune system. The higher percentage of human component should lead to fewer infusion reactions.

Compared with IFNβ-1a, ocrelizumab reduced ARR (46% to 47%), 12- and 24-week confirmed disability progression (40%), T1 enhancing lesions (94% to 95%), and new and/or enlarging T2 lesions (77% to 83%).[14] The NEDA was 47 percent with ocrelizumab and 29.2 percent with IFNβ-1a. The safety profile of ocrelizumab is similar to IFNβ-1a with first dose infusion-related reactions being the most common adverse event.[15]

Ofatumumab (Kesimpta®) became a FDA-approved agent for MS in August 2020 as a subcutaneous formulation. Previously this anti-CD20 monoclonal antibody was FDA-approved for chronic lymphocytic leukemia treatment. This agent has enhanced complement-dependent cytotoxicity (CDC) compared with antibody-dependent-cellular cytotoxicity (ADCC) activity and binds to a unique CD20 epitope. When compared to teriflunomide, ofatumumab reduced AAR 50 percent more than teriflunomide, reduced MRI lesions by 94 to 97 percent, and reduced disability worsening.[16]

Another new agent approved recently (2020) is ozanimod. Ozanimod (Zeposia®) is an oral sphingosine 1-phosphate receptor modulator, like siponimod (Mayzent®) and fingolimod (Gilenya®),

indicated for the treatment of relapsing forms of multiple sclerosis, to include CIS, RRMS, and active SPMS, in adults. It blocks the capacity of lymphocytes to exit lymph nodes, reducing the number of lymphocytes in peripheral blood. Ozanimod has been compared to IFNβ-1a in two trials. In a 24-month Phase III, double-blind, double- dummy study in participants with relapsing multiple sclerosis, ozanimod was well tolerated and associated with a significantly lower rate of clinical relapses than intramuscular IFNβ-1a (0.17 versus 0.28).[17] Similar efficacy results were shown in a 12-month trial with the same design (ARR 0.18 versus 0.35).[18]

In addition to ozanimod, siponimod and cladribine are also approved for active SPMS. SPMS is associated with insidious worsening of walking disability, which eventually results in increased dependence on a wheelchair. Siponimod has been shown to be efficacious in slowing down disability progression and cognitive decline in a typical SPMS population (EXPAND study).[19]

The active metabolite of cladribine disrupts cellular metabolism, inhibits DNA synthesis and repair, and causes apoptosis. Accumulation of the cladribine nucleotide produces rapid and sustained reductions in CD4+ and CD8+ cells lymphocytes. The CLARITY trial with cladribine was a relatively high-disability RRMS study. Thirty percent of patients had gadolinium-enhancing lesions at baseline. Cladribine decreased the rate of disability progression in this patient population, and the results of this trial have been interpreted as providing support for cladribine in active SPMS.[20]

Conclusion

DMT selection in MS needs to be individualized. A less aggressive escalation approach may be appropriate for some patients, whereas others would benefit from an aggressive induction approach. Defining these two patient populations is still an area of debate. Clinicians also have to work with individual patients to identify their goals and willingness to try more aggressive but more risky treatments.

Claire S. Riley, MD is an Assistant Professor of Neurology at the Columbia Irving Medical Center and Medical Director at the Columbia University Multiple Sclerosis Center in New York, NY.

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Innovative Approaches for Advanced Treatment and Management of Psoriatic Arthritis

Atul Deodhar, MD, MRCP

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

Summary

Psoriatic arthritis is a complex autoimmune disease which is underdiagnosed and undertreated in the United States (U.S.). It can effectively be treated with biologics that target the underlying pathology. The biologic agents reduce symptoms and inhibit joint damage which commonly occurs with this disease.

Key Points

- Psoriatic arthritis occurs in approximately 30 percent of patients with psoriasis and is underdiagnosed.
- Numerous therapies benefit all clinical domains and inhibit progressive structural damage.
- Minimal disease activity is the goal of treatment.

THERE ARE HUNDREDS OF TYPES OF arthritis which manifest as joint aches and pains, but only some types are inflammatory arthritis, such as psoriatic arthritis (PsA). PsA is a heterogeneous disease with a wide spectrum of clinical manifestations (Exhibit 1).[1] PsA has significant impact on those affected with the disease, including their ability to work, their quality of life, their comorbidities, and their finances. Most importantly, in the U.S., PsA is underdiagnosed and undertreated. Fifty-three percent of patients with moderate to severe PsA report not receiving any form of treatment or topical therapy, 55 percent are dissatisfied with their current treatment, and 40 percent do not think their current treatment meets their primary goals of therapy.[2-4]

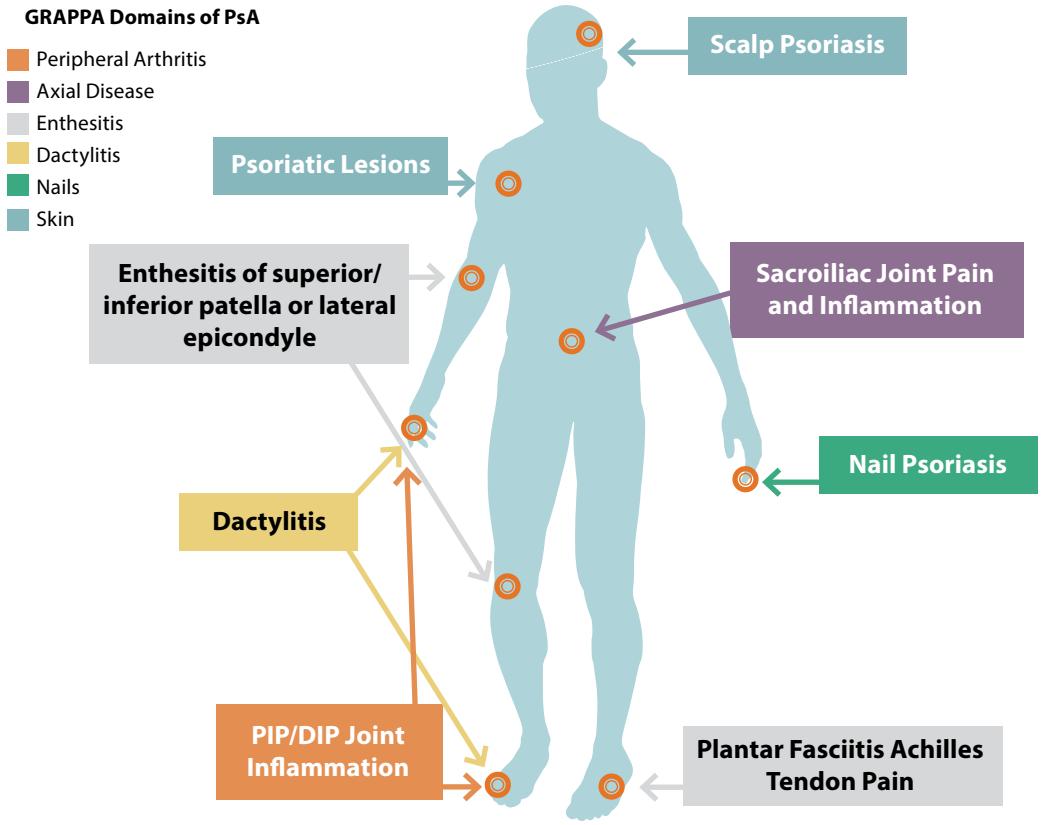
PsA is a peripheral spondyloarthritis. Spondyloarthritis is an umbrella term for inflammatory diseases that involve both the joints and the entheses (the sites where the ligaments and tendons attach to the bones).[5] PsA typically affects the ankles, knees, fingers, toes, and lower back. A patient with PsA can have many different manifestations of the disease at the same time in their hands – synovitis, dactylitis, ankylosis, and mutilans. PsA not only causes bone damage, but also causes new bone formation. The radiographic features of PsA are juxta-articular periostitis and ankylosis and joint osteolysis.

The U.S. prevalence of PsA is 3 percent, with approximately 2.3 million people affected.[6,7] It occurs in about 30 percent of people who have psoriasis. The onset is typically in those between 30 and 50 years of age. Psoriasis precedes PsA by 10 years in 85 percent of patients but PsA can also precede psoriasis in 10 percent of patients by 10 to 15 years, or both PsA and psoriasis can start together in 5 percent of patients. Unfortunately, many cases of PsA are overlooked by primary care providers and dermatologists.

The inciting event that starts the psoriatic disease process in those who are genetically predisposed is unknown, but it may be trauma or infection. There is dysregulation of the innate immune system in psoriatic disease.[8] Activated T cells infiltrate the dermal papillae of skin and the sub lining layer of the joint synovium, as well as the enthesial insertion. Dendritic cells, macrophages, and B cells are also involved and generate a number of proinflammatory cytokines. Key cytokines in psoriasis include Janus kinases and signal transducers and activators of transcription (JAK-STATs), tumor necrosis factor (TNF), interferon-γ, interleukin (IL)-1, IL-6, IL-23, IL-12, and IL-22 .

The pharmacologic treatment of PsA includes nonsteroidal anti-inflammatories, corticosteroids (occasionally), conventional synthetic disease-modifying antirheumatic drugs (DMARDs),

Exhibit 1: PsA is a Heterogeneous Disease with a Wide Spectrum of Clinical Manifestations[1]



GRAPPA = Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; PIP = proximal interphalangeal joint; DIP = distal interphalangeal joint

small molecule DMARDs, and biologic DMARDs. Exhibit 2 shows the currently approved targeted agents for PsA (small molecules and biologics) and some investigational agents. Many factors influence treatment selection in PsA, including disease factors (number of tender and swollen joints, joints involved, disability, structural damage, psoriasis severity), patient factors (age, gender, impact on life, treatment history, likelihood of adherence, patient expectations, fear of adverse events, and comorbidities), and treatment factors (efficacy, tolerability, safety, onset of action, ease of use, administration route, and cost/insurance coverage).[9] Exhibit 3 presents the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations (2015) based on the disease presentation.[10] Importantly, the janus kinase (JAK) inhibitor tofacitinib was FDA-approved since this update. The choice of therapy should address as many affected domains as possible. For patients with moderate to severe disease, an expedited therapeutic route is advocated by this group where the initial step of non-steroidal anti-inflammatory drugs (NSAIDs) is skipped, and therapy is started with DMARDs or biologics.

The 2018 American College of Rheumatology/ National Psoriasis Foundation (ACR/NPF) guidelines are shown in Exhibit 4.[11] These guidelines recommend using a treat-to-target strategy to make decisions based on individual patient factors being severity or activity of PsA, severity or activity of psoriasis, comorbidities, contraindications to medications, preferences of route or frequency of administration, concerns over therapies, and others. Clinicians should talk with the patient at each decision point since all recommendations are conditionally based on low or very low quality of evidence. Conditional recommendations are preference-sensitive and always warrant a shared decision-making approach.

For treatment-naïve patients with active PsA in the ACR/NPF, the use of a TNF inhibitor biologic or oral small molecule (OSM) is recommended over an interleukin-17 inhibitor (IL-17i) or IL-

Exhibit 2: Targeted Therapy in PsA

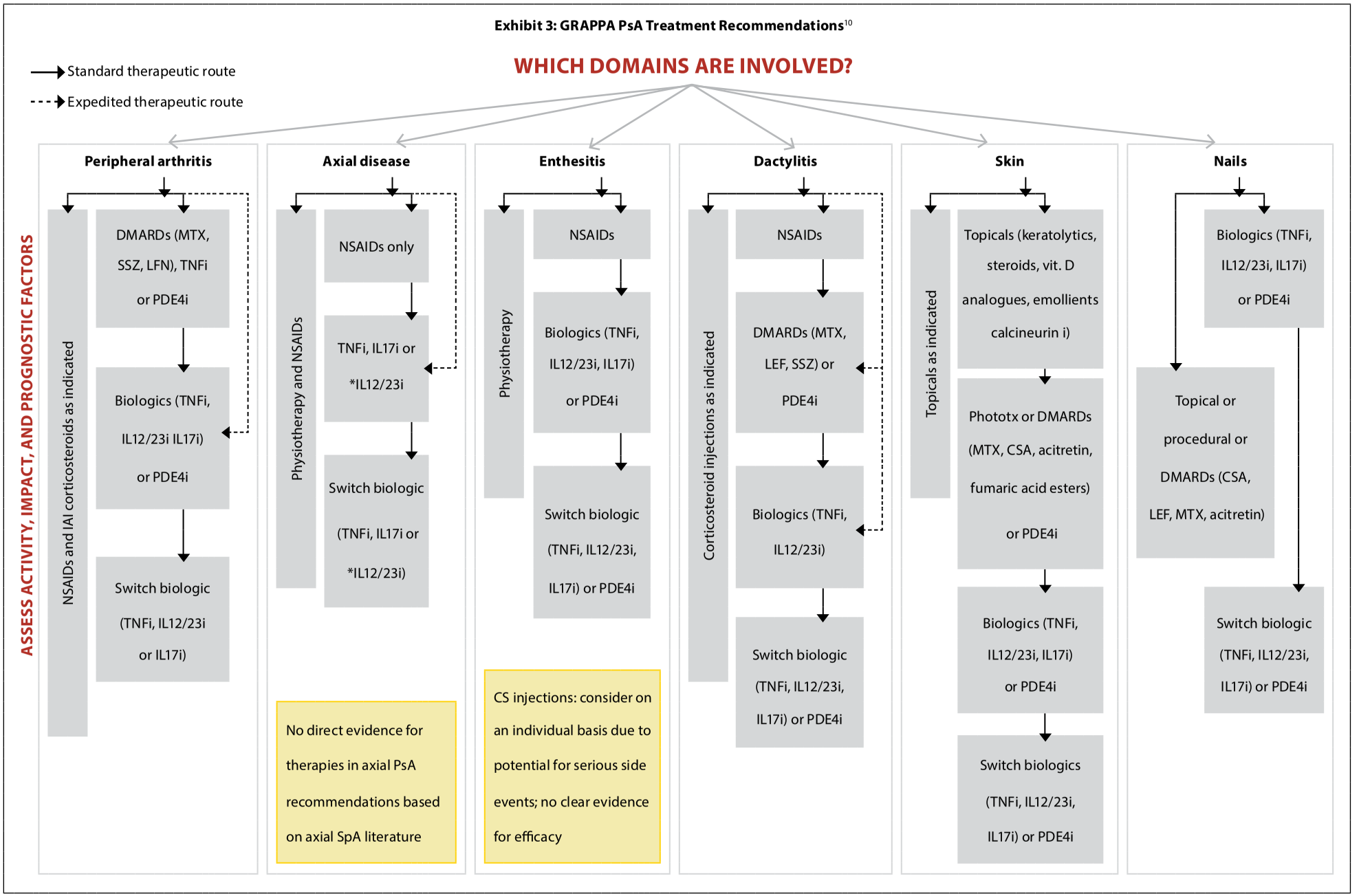
Mechanism of Action	Therapy	Administration	Also has PsO Indication	Indication for Axial Disease
Approved Therapies				
CD80/86	Abatacept	IV Q4W / SC QW	No	None
PDE4	Apremilast	Oral BID	Approved	None
JAK 1/3	Tofacitinib	Oral QD / BID	No	Phase III for AS
TNF-α	Etanercept	SC QW	Approved	AS
	Infliximab	IV Q8W	Approved	AS
	Adalimumab	SC Q2W	Approved	AS
	Golimumab	SC Q4W / IV Q8W	No	AS
	Certolizumab	SC Q2W / Q4W	Approved	AS and nr-AxSpA
IL-12/23	Ustekinumab	SC Q12W	Approved	None
IL-23	Guselkumab	SC Q4W / Q8W	Approved	None
IL-17A	Secukinumab	SC Q4W	Approved	AS and nr-AxSpA
	Ixekizumab	SC Q4W	Approved	AS and nr-AxSpA
Therapies in Phase III				
JAK 1/3	Upadacitinib	Oral QD	No	Phase III
		Oral QD	No	Phase III
IL-23	Risankizumab	SC Q12W	Approved	Phase II negative for AS
	Tildrakizumab	SC Q4W / Q12W	Approved	Phase II/III for PsA & AS or nr- AxSpA
IL-17A/F	Bimekizumab	SC Q4W	Investigational	Phase III

PsO = psoriasis; CD = cluster of differentiation; PDE4 =phosphodiesterase; JAK = janus kinase; TNF = tumor necrosis factor; IL = interleukin; AS = ankylosing spondylitis; nr-AxSPA = Non-Radiographic Axial Spondyloarthritis.

12/23i biologic or tofacitinib.[11] OSM is defined as methotrexate, sulfasalazine, leflunomide, cyclosporine, and Apremilast, and the preference for OSM is controversial given the higher efficacy of the biologic agents and tofacitinib. An IL-17i or IL-12/23i biologic may be used instead of TNFi biologics in patients with severe psoriasis or contraindications to TNFi biologics and may be used instead of OSMs in patients with severe psoriasis or severe PsA. Methotrexate (MTX) is recommended over NSAIDs in treatment-naïve patients with active PsA. NSAIDs may be used instead of MTX after consideration of possible contraindications and adverse event profile in patients without evidence of severe PsA or severe psoriasis and in those at risk for liver toxicity.

There is controversy over the use of MTX in PsA. Some data have shown that it does not work as a DMARD in PsA unlike in rheumatoid arthritis.[12] Although it can benefit synovitis in PsA, methotrexate is not effective for enthesitis or dactylitis. A recent trial found that MTX monotherapy can produce a 50 percent ACR20 response but was not as effective as etanercept monotherapy [ACR20, 60.9% versus 50.7% of patients (p = 0.029)] and did not add significant benefit when used in combination with etanercept.[13] Patients should not be required to step through treatment with methotrexate before moving on to a biologic. ACR20, ACR50, ACR90 are measures used in clinical trials for efficacy. ACR20 is a 20 percent improvement in various efficacy

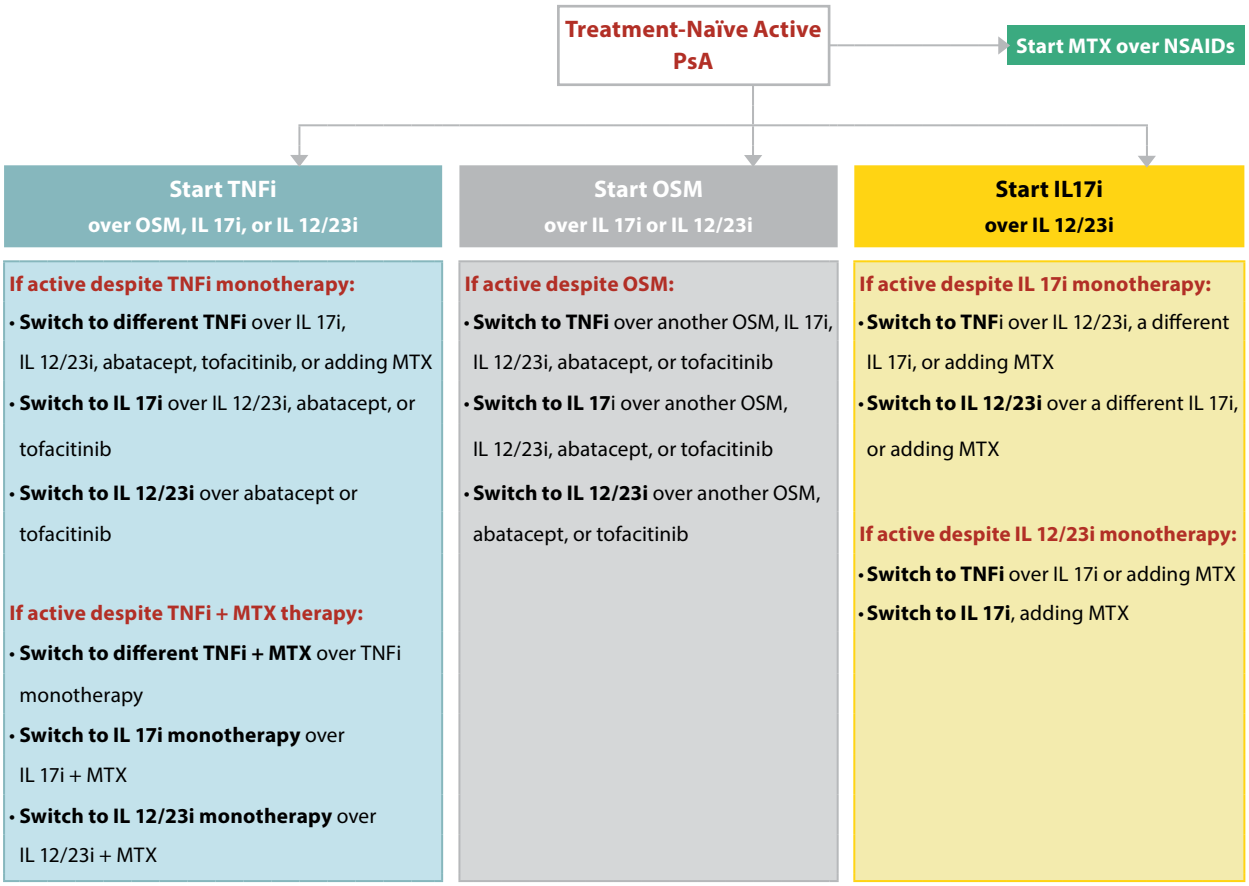
Exhibit 3: GRAPPA PsA Treatment Recommendations[10]



*Open-label data available

DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; PDE-4i = phosphodiesterase 4 inhibitor; IL-12/23i = interleukin-12/23 inhibitor; SpA = spondyloarthritis; CS = corticosteroid; vit = vitamin; phototx = phototherapy; CSA = cyclosporin A.

Exhibit 4: American College of Rheumatology and National Psoriasis Foundation Guidelines for the Management of Active PsA[11]



American College of Rheumatology and National Psoriasis Foundation Disclosure: The order of listing of various conditional recommendations or of different treatment choices within a conditional statement does not indicate any sequence in which treatment options would be chosen.
OSM = Oral Small Molecules (methotrexate, sulfasalazine, leflunomide, cyclosporine, and apremilast). Does not include tofacitinib or abatacept);
TNFi = tumor necrosis factor inhibitor; IL = interleukin

measures, such as the affected joint count.

Several of the TNF-alpha inhibitors are FDA-approved for PsA. Overall, 40 to 44 percent of patients have an ACR20. It is important to note that all efficacy benefits presented here are placebo corrected. This class of agents also improves enthesitis and dactylitis, functional ability, quality of life, and fatigue.[14,15] Psoriasis Area and Severity Index 75 percent clearing (PASI75) rates are 60 to 85 percent for infliximab, golimumab, and adalimumab and 45 to 50 percent for etanercept and certolizumab. PASI is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance.

T helper 17 (Th17) cells are implicated in PsA. The Th17 cell has an IL 23 receptor. A result of the interaction between the cell and IL-23 is the secretion of IL-17A. IL-17A, in turn, induces production of IL-6, TNF, IL-1, chemokines, and matrix metalloproteinases (MMPs) from a host of target cells perpetuating the inflammatory process. Treatment with secukinumab (Cosentyx®), an IL-17A inhibitor, achieves an ACR50 in 28 percent and PASI75 in 32 percent of patients.[16] Enthesitis resolution was 18 percent better than placebo. Ixekizumab, another IL-17A inhibitor, produces an ACR50 in 30 percent and PASI75 in 41 percent of patients.[17] Enthesitis resolution was 13 percent better than placebo.

Ustekinumab (Stelara®) and guselkumab (Tremfya®) are IL-23 inhibitors. In addition to IL-23, ustekinumab also inhibits IL-12. About 21 percent of patients treated with this agent will have an ACR20 response, 10.8 percent an ACR50 response, and 50 percent a PASI75.[18,19] Guselkumab, a fully human monoclonal antibody targeting the p19 subunit of lL-23, produces an ACR20 response in about 40 percent of patients, ACR50 in 24 percent, and PASI75 in 70 percent.[20] This agent is very effective

Exhibit 5: Head-to-Head Trials in PsA[13,25,26]

Trial	Drugs Examined	Patients	Results
EXCEED	SEC versus ADA	csDMARD-IR, biologic-naïve	• SEC did not meet statistical significance for superiority for ACR20 versus adalimumab at week 52. • SEC was associated with a higher treatment retention rate versus ADA.
SPIRIT- H2H	IXE versus ADA	csDMARD-IR, naïve to bDMARD and JAKi	• IXE was superior to ADA in achievement of simultaneous improvement of ACR50 and PASI100.
SEAM- PSA	ETN versus MTX	Naïve to treatment with ETN and other biologics, and had no prior use of MTX for PsA	• ETN monotherapy and ETN + MTX showed greater efficacy than MTX monotherapy according to ACR and MDA response rates and extent of radiographic progression. • Overall, combining MTX and ETN did not improve the efficacy of ETN.

SEC = secukinumab; ADA = adalimumab; IXE = ixekizumab; ETN = etanercept; MTX = methotrexate; bDMARD, biologic DMARD; IR = inadequate response; csDMARD = conventional synthetic disease-modifying antirheumatic drug; JAKi = janus kinase inhibitor; PASI = Psoriasis Area and Severity Index ACR = American College of Rheumatology.

in clearing psoriasis, with 40 percent of patients having 100 percent clearance. A recent trial found that guselkumab is as effective in those who were previously treated with TNF inhibitor as those who are treatment naïve.[21]

Tofacitinib (Xeljanz®) is an oral JAK inhibitor which is FDA-approved for PsA treatment. It is indicated for adults with active psoriatic arthritis in whom methotrexate or other similar DMARDs did not work well. The ACR50 response occurs in about 17 percent, PASI75 in 18 percent, and enthesis resolution in 15 percent of patients.[22] Baricitinib, upadacitinib, and filgotinib are other JAK inhibitors under study for PsA.

Apremilast (Otezla®) is an oral phosphodiesterase-4 (PDE4) inhibitor that modulates the production of pro-inflammatory and anti-inflammatory mediators. About 10.5 percent of patients with PsA will have a 50 percent improvement in symptoms (ACR50).[23] Although apremilast is a well-tolerated agent which improves joint symptoms, its ability to prevent joint damage is unproven.

Abatacept (Orencia®) is a selective T cell costimulation modulator indicated for the treatment of adult patients with active PsA. Because of the potent immune effects of this agent, its use with other immunosuppressives (e.g., biologics, JAK inhibitors) is not recommended. In PsA, ACR20 rates are 20 percent and PASI50 is 8 percent.[24] Few of the approved therapies for PsA have been compared directly. Exhibit 5 shows results from the three comparison trials.[13,25,26]

As with rheumatoid arthritis, treat-to-target is being used for PsA treatment. There is controversy over what target to aim for, but minimal disease activity (MDA) is the minimum target. A study found that tight control of psoriatic arthritis disease activity through a treat-to-target approach significantly improves joint outcomes for newly diagnosed patients, with no unexpected serious adverse events reported.[27]

Because those with PsA typically also have psoriasis and because of their psoriatic disease they are at risk for cardiovascular disease and other comorbidities related to chronic inflammation, physicians need to treat their patients holistically in managing this disease. Additionally, this disease can have significant psychologic impact including anxiety and depression. Multidisciplinary care, which includes at least rheumatology, dermatology, and psychology, is optimal for caring for these patients.

Conclusion

PsA is associated with multiple comorbidities and the whole patient, not just their PsA, needs to be treated and this requires multidisciplinary care. Based on disease pathogenesis, an entire range of new treatments have been and are being developed. Minimal disease activity is the goal of treatment.

Atul Deodhar, MD, MRCP is a Professor of Medicine in the Division of Arthritis and Rheumatic Diseases at the Oregon Health & Science University in Portland, OR.

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Recent Advances in the Management of Insomnia: New Considerations in Treatment Strategies

Larry Culpepper, MD, MPH

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

Summary

Insomnia is a prevalent condition that significantly impacts patient health and well-being. Management of insomnia is possible with cognitive behavior therapy and medications. Cognitive behavior therapy should be the first intervention in most patients.

Key Points

- Cognitive behavioral approaches are effective and preferred first-line therapy.
- Treatment with benzodiazepines is not preferred, but it is sometimes necessary.
- Orexin antagonists and low-dose doxepin are effective non-benzodiazepine options.
- Numerous barriers remain to provision of high-quality insomnia care.

INSOMNIA IS A COMMON SLEEP PROBLEM for adults. As shown in Exhibit 1, about 27 percent of good sleepers will have acute insomnia over the course of one year.[1] Of those who develop acute insomnia, 1.8 percent develop chronic insomnia. Insomnia disorder is defined as sleep difficulties three or more nights per week lasting for three or more months.[2] Components of insomnia disorder are dissatisfaction with sleep quantity or quality, daytime consequences of poor sleep, and sleep difficulty despite adequate opportunity for sleep (Exhibit 2).

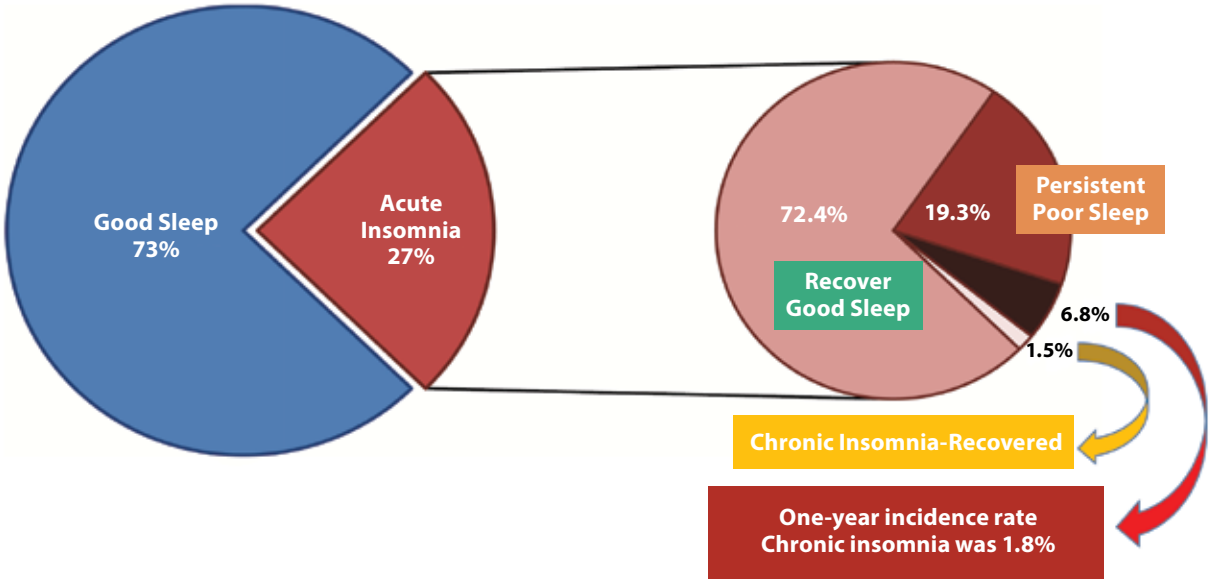
The negative outcomes of insomnia are substantial. There is increased risk of psychiatric disorders (depression, anxiety), cognitive decline including dementia, accidents (including motor vehicle, on the job, at home), and medical comorbidities including cardiovascular, diabetes, obesity.[3-5] There are also higher rates of healthcare utilization, absenteeism and presenteeism, and poor occupational performance and advancement in those with insomnia compared to those without. The recommendations for evaluation and testing from the American Academy of Sleep Medicine (AASM) guidelines are shown in Exhibit 3.[5] Most patients can be diagnosed clinically without expensive testing.

Hyperarousal is a key component in the current etiological models of insomnia disorder.[6] This leads to an imbalance in our daily cycles of sleep and wakefulness. Wakefulness depends on a network of cell groups that activate the thalamus and the cerebral cortex.[7] A key switch in the hypothalamus shuts off this arousal system during sleep. Other hypothalamic neurons stabilize the switch, and their absence results in inappropriate switching of behavioral states, such as occurs in narcolepsy.

The primary treatment goals of insomnia are to improve sleep quality and quantity and insomnia-related daytime impairments.[5] Improved sleep quality and quantity can be measured with the time-to-wake after sleep onset (WASO), sleep onset latency (SOL), number of nighttime awakenings, and total sleep time or sleep efficiency. Improvement of sleep-related psychological distress is also an important outcome of treatment.

Behavioral therapies are effective for treating insomnia in all ages, including older adults, and chronic sleep medication users. Behavioral therapies should be the first-line therapy when conditions allow.[5] At least one behavioral intervention should be instituted, and data suggest that combination approaches provide the most benefit. The best studied is cognitive behavioral therapy – insomnia (CBT-I), which is a combination of cognitive therapy, stimulus control, sleep restriction with or without relaxation therapy, and sleep hygiene. Examples of sleep hygiene measures are having a dark, quiet place for sleeping and avoiding caffeine. CBT-I is effective for chronic insomnia, can improve daytime symptoms, and can provide persistent improvements in sleep.[8-10]

Exhibit 1: Natural History of Insomnia in *Good* Sleepers[1]



There is insufficient evidence to show that sleep hygiene alone is effective for chronic insomnia and thus it should be used with other therapies. When initial behavioral therapies are ineffective, clinicians should consider changing to other psychological/behavioral therapies, combining therapies, or combining CBT-I and medication.

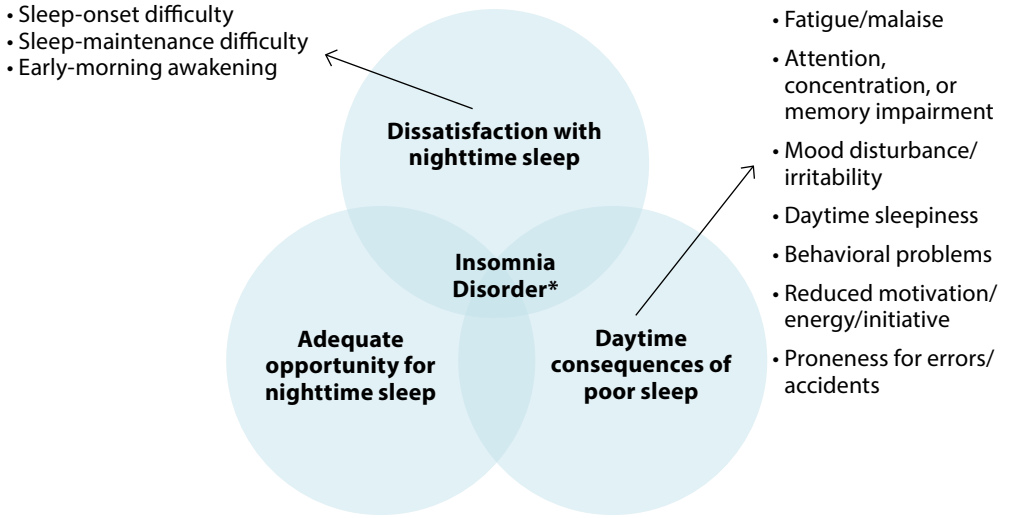
FDA-approved pharmacotherapy for insomnia includes benzodiazepine receptor agonists, a melatonin receptor agonist, a histamine receptor antagonist, and orexin receptor antagonists (Exhibit 4). Hypnotic medications are approved for reduction in sleep latency, enhancement of sleep maintenance, or both. The AASM recommends various hypnotics based on the type of insomnia – sleep onset, sleep maintenance, or both (Exhibit 5).[5] Although often used off-label for insomnia, sedating medications not approved for sleep, such as trazodone, should not be used.

Benzodiazepines approved for insomnia include triazolam, temazepam, estazolam, flurazepam, and quazepam. These should be avoided in the elderly, those with history of substance abuse, and in patients with untreated sleep apnea or chronic nocturnal hypoxia. All are labeled for short-term use only. The benzodiazepine receptor agonists include zaleplon (Sonata®), zolpidem (Ambien®, Ambien CR®, Zolpimist®, Edluar®, generics), and eszopiclone (Lunesta®). The benzodiazepine receptor agonists decrease sleep latency and increase total sleep time. All of the benzodiazepines and benzodiazepine receptor agonists are DEA Schedule IV controlled substances. In addition to avoiding benzodiazepines, the American Geriatrics Society Beers Criteria® of potentially inappropriate medication use in older adults recommends avoiding benzodiazepine receptor agonists because of the potential adverse events (delirium, falls, fractures, motor vehicle accidents, and increased use of emergency rooms/hospitalizations) and minimal therapeutic benefit.[11]

A low-dose formulation of doxepin (Silenor®, generic), an antidepressant which is a histamine 1 receptor antagonist, is now FDA-approved for treating insomnia (it decreases time awake during the night).[12] The insomnia dose is 3 to 6 mg 30 minutes before bedtime compared to the antidepressant dose of 150 to 300 mg daily. Importantly, doses greater than 3 mg may have anticholinergic effects, including orthostatic hypotension in older adults, and should be avoided in this population.

Orexins are neuropeptides that have been discovered to regulate arousal, wakefulness, and appetite. Elevated orexin levels have been shown in insomnia disorder.[13] Blocking the binding of wake-promoting orexin to its receptors is thought to suppress the wake drive. Suvorexant (Belsomra®) was the first dual orexin receptor antagonist (DORA) to be approved by the FDA for insomnia in 2014. It decreases sleep latency, time awake during the night, and total sleep time and is a Schedule IV agent.[14] It has also been shown beneficial in sleep in Alzheimer's disease patients.[15] Lemborexant (Dayvigo®) is the

Exhibit 2: Triad of Insomnia Symptoms[2]



*Occurs ≥ 3 nights per week and endures for ≥3 months

Exhibit 3: American Academy of Sleep Medicine (AASM) Guideline Recommendations[5]

Evaluation	Testing
• Requires associated daytime dysfunction in addition to appropriate insomnia symptomatology.	• Polysomnography and multiple sleep latency testing (MSLT) not indicated. ◦ Use if suspicion of other disorder (obstructive sleep apnea, parasomnias), treatment failures.
• Diagnose by clinical evaluation: sleep history, medical, substance, and psychiatric history.	
• Identify comorbid disorders	• Actigraphy if needed to characterize circadian rhythm patterns or sleep disturbances.
• Two-week sleep log (sleep-wake times and day-to-day variability); repeat to follow course during management.	• Other laboratory studies not routine
• Assess: sleep quality, psychological state, daytime function, quality of life, and dysfunctional beliefs and attitudes.	

newest DORA, approved in 2019. It has been shown to improve sleep latency and continuity in insomnia and is also a Schedule IV agent.[16,17] In older adults, lemborexant does not seem to impair cognition nor postural stability and in addition, patients taking it are easy to awaken.[18,19] The two DORAs have not been compared with each other and additional agents in this class are under development.

The most common adverse event of any of the hypnotics is daytime sleepiness. In 2019, the FDA added a boxed warning regarding complex sleep behavior (sleepwalking, sleep driving, and engaging in other activities while not fully awake) to package labeling for eszopiclone, zaleplon, and zolpidem.[20] It also added a warning to avoid use in patients who have previously experienced an episode of complex sleep behavior with any of these agents. Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating, such as tranquilizers, opioids, and anti-anxiety medicines. The underlying mechanisms by which insomnia medicines cause complex sleep behaviors are not completely understood.

If a patient has an inadequate or non-response to pharmacotherapy, the guidelines recommend

reassessing the diagnosis, other potential causes including undiagnosed comorbidities, sleep practices and hygiene, current medications including nonprescription and herbal products, and medication adherence.[5] A subset of chronic insomnia patients will have limited or transient

Exhibit 4: FDA-Approved Drug Classes

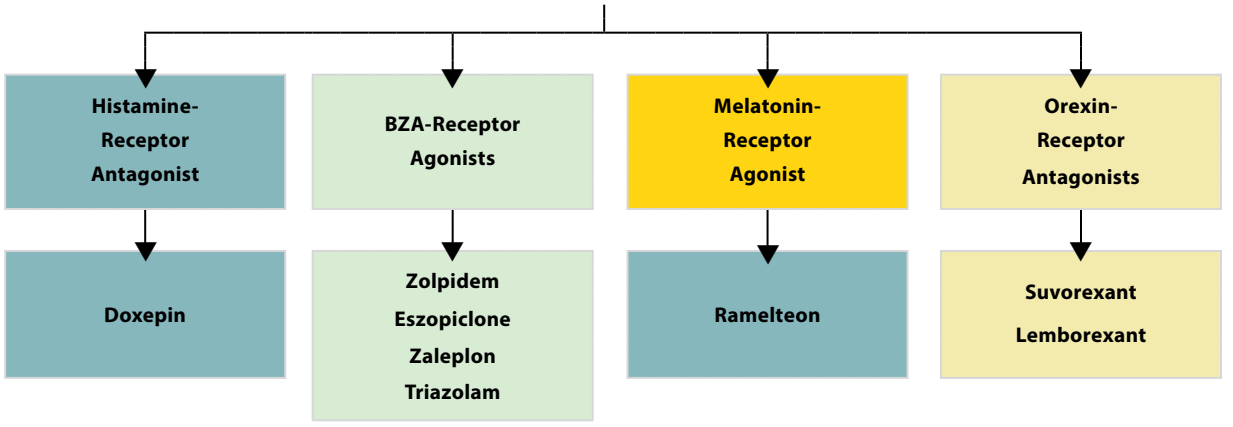


Exhibit 5: 2017 AASM Treatment Recommendations[5]

RECOMMENDED		NOT RECOMMENDED	
Type of Insomnia	**USE**	**Type of Insomnia**	**DO NOT USE**
Sleep onset	Ramelteon	Sleep onset OR sleep maintenance	Diphenhydramine
	Triazolam		Melatonin
	Zaleplon		Tiagabine
Sleep maintenance	Suvorexant		Trazodone
	Lemborexant		Tryptophan
Sleep onset and maintenance	Eszopiclone		Valerian
	Temazepam	**Versus no treatment, in adults**	
	Zolpidem	**Level of Evidence: WEAK**	

Note: Low dose doxepin was FDA-approved after these guidelines were published

Exhibit 6: Barriers to High Quality Insomnia Care[21]

Clinician	Patient
• Knowledge or an awareness that insomnia is a significant issue.	• Seeks help for other symptoms which reflect outcomes of insomnia (impaired daytime functioning, psychological distress/physical discomfort).
• Lack of training to identify insomnia as distinct from other sleep disorders.	• Feels he or she has to convince a medical professional as to the seriousness of insomnia-related symptoms.
• Lack of education being included in training curriculum.	• Lacks awareness of detrimental effects on mood, performance and other consequences.
• Lack of access to CME/professional development for primary care.	• Lacks awareness of treatment options.
• Gaps in knowledge for assessing insomnia.	• Reluctance to try available treatments.
• Competing priorities during visits.	

improvement with medication; alternative agents or combinations may be useful in these patients. If multiple medication trials are ineffective, cognitive behavioral approaches in lieu of or adjunct to medications should be started. Caution must be taken with polypharmacy, particularly in patients who have not or will not pursue psychological and behavioral treatments.

Chronic hypnotic medication may be indicated for long-term use for severe or refractory insomnia. All patients receiving long-term pharmacotherapy should have a trial of CBT-I to try and reduce or eliminate the need for medication. Long-term prescribing should only be done with consistent follow-up, ongoing effectiveness assessment, monitoring for adverse events, and evaluation for new onset or exacerbation of existing comorbidities. Long-term medications may be nightly, intermittent (e.g., 3 nights/week), or as needed.

Numerous barriers exist which prevent high-quality insomnia care. The most common barriers from the perspective of clinicians are related to knowledge, skills, and time (Exhibit 6).[21] From the patient perspective, barriers include their beliefs about the consequences of insomnia, social influences, and behavioral regulation of symptoms.

Conclusion

Insomnia is frequent and can become chronic. It leads to worse outcomes both day-to-day and long-term. Management guidelines, outcome measurement tools, and treatment options are available and effective. Cognitive behavioral approaches are the preferred first-line therapy. Treatment with benzodiazepines is not preferred, but it is sometimes necessary. Orexin antagonists and low-dose doxepin are effective non-benzodiazepine options. Numerous barriers remain in regard to the provision of high-quality insomnia care.

Larry Culpepper, MD, MPH is Professor of Family Medicine and was Founding Chairman of the Department of Family Medicine at the Boston University School of Medicine in Boston, MA.

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IDIOPATHIC HYPERSOMNIA

is a rare condition distinct from other sleep disorders[1-3]

In idiopathic hypersomnia (IH)...

GOOD SLEEP OUTWEIGHS MORE SLEEP

People with IH are getting plenty of sleep, but still feel excessively sleepy during the day[4,5]

IH is different from other sleep disorders like narcolepsy[1]

IH is a unique condition with specific AASM ICSD-3 criteria[4]

ICD-10-CM codes: G47.11, G47.12[4,6]

There are currently no FDA-approved treatments indicated for IH[7]

To learn more about IH, contact your Jazz Pharmaceuticals Account Manager or visit SleepCountsHCP.com

AASM=American Academy of Sleep Medicine; FDA=US Food and Drug Administration; ICD-10-CM=International Classification of Diseases, 10th Revision, Clinical Modification; ICSD-3=International Classification of Sleep Disorders, 3rd ed.

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