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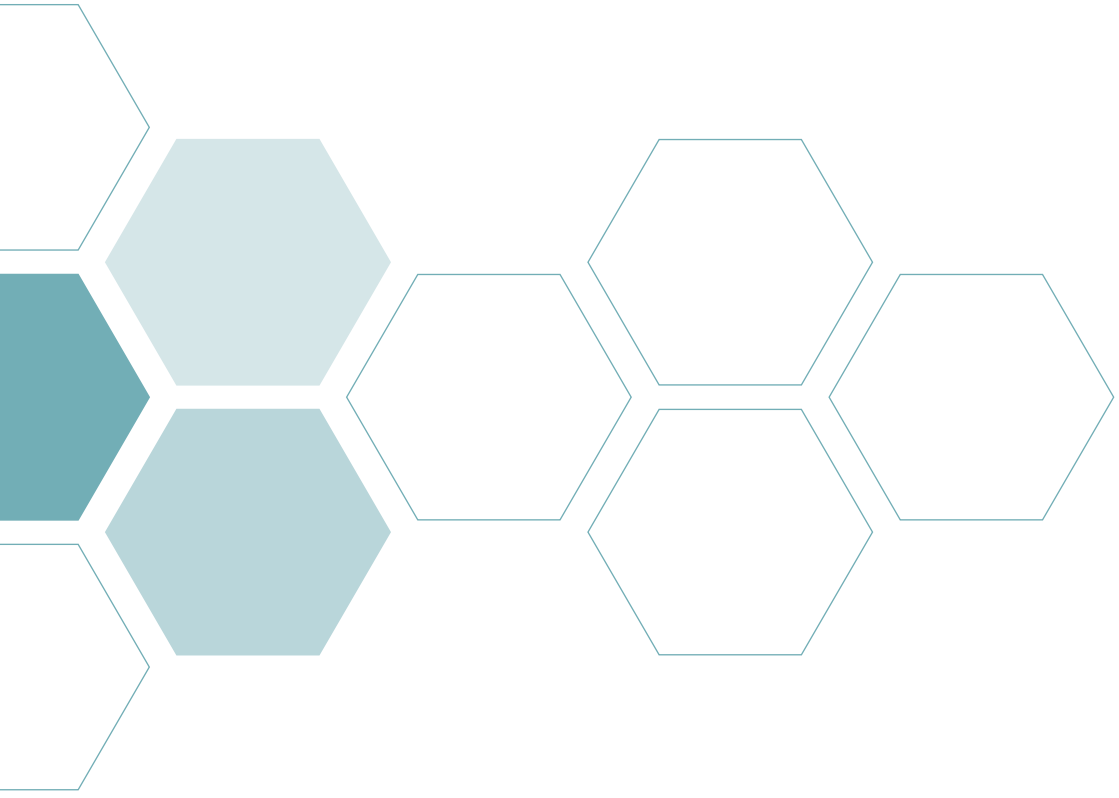
JOURNAL of MANAGED CARE MEDICINE

Educating Medical Directors of Employers, Health Plans and Provider Systems



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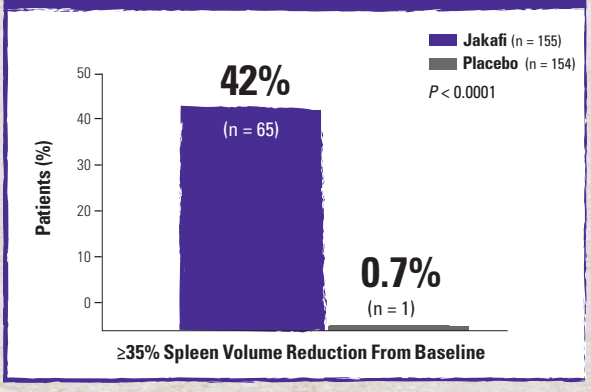
Provide your members with the option that's

FDA APPROVED FOR INTERMEDIATE OR HIGH-RISK MYELOFIBROSIS

In COMFORT-I* and COMFORT-II,† Jakafi® (ruxolitinib) significantly reduced spleen volume compared with patients receiving placebo or best available therapy, respectively[1-3‡]

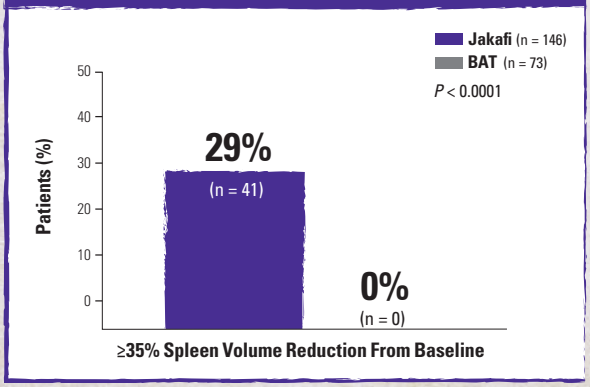
- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 24 as measured by CT or MRI[1,2]

COMFORT-I Primary End Point: Spleen Volume Reduction at Week 24[1,2]



- The primary end point was the proportion of patients achieving a ≥35% reduction in spleen volume from baseline at week 48 as measured by CT or MRI[1,3]

COMFORT-II Primary End Point: Spleen Volume Reduction at Week 48[1,3]



BAT, best available therapy.

* COMFORT-I (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-I) was a randomized, double-blind, placebo-controlled phase 3 study with 309 patients with intermediate-2–risk or high-risk myelofibrosis.[1,2]

† COMFORT-II (COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment-II) was a randomized, open-label phase 3 study with 219 patients with intermediate-2–risk or high-risk myelofibrosis.[1,3]

‡ Best available therapy in COMFORT-II included hydroxyurea (46.6%) and glucocorticoids (16.4%), as well as no medication, anagrelide, epoetin alfa, thalidomide, lenalidomide, mercaptopurine, thioguanine, danazol, peginterferon alfa-2a, interferon-α, melphalan, acetylsalicylic acid, cytarabine, and colchicine.[4]

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

Incyte

Jakafi® ruxolitinib (tablets)

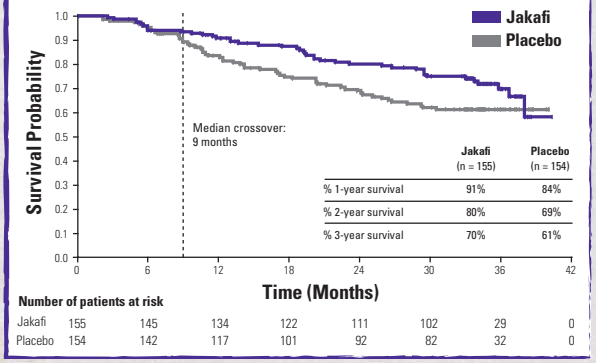
Indications and Usage

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

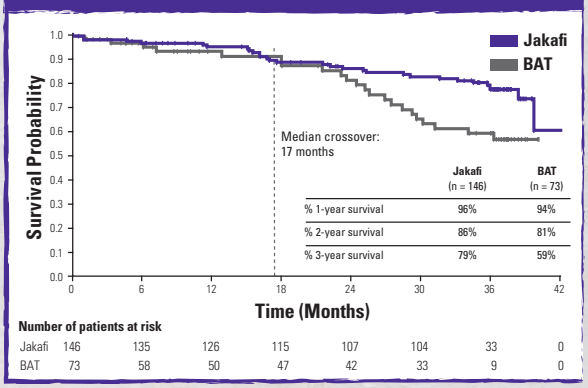
Overall survival was a prespecified secondary end point in COMFORT-I and COMFORT-II[1]

- COMFORT-I: At 3 years, survival probability was 70% for patients originally randomized to Jakafi and 61% for those originally randomized to placebo[1]
- COMFORT-II: At 3 years, survival probability was 79% for patients originally randomized to Jakafi and 59% for those originally randomized to best available therapy[1]

COMFORT-I Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



COMFORT-II Overall Survival: Kaplan-Meier Curves by Treatment Group[1]



BAT, best available therapy.

- Patients randomized to placebo (COMFORT-I) or best available therapy (COMFORT-II) were eligible to cross over to receive Jakafi because of progression-driven events or at the physician's discretion; however, these patients continued to be grouped within their original randomized assignment for analysis purposes[4]
- All patients in the control group either crossed over or discontinued[1]

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for two weeks after the final dose

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about Jakafi, visit **Jakafi.com/HCP**.

References: 1. Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **2.** Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9):799-807. **3.** Harrison C, Kiladjian J-J, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012;366(9):787-798. **4.** Data on file. Incyte Corporation. Wilmington, DE.

Jakafi®
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. **Clinical Trials Experience in Myelofibrosis** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions: Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS **Fluconazole** Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Strong CYP3A4 inhibitors** Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Strong CYP3A4 inducers** Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Clinical Pharmacology (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS **Pregnancy: Risk Summary** When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity (*see Data*). There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies. **Data:** *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Lactation: Risk Summary** No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed infant, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (*see Data*). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. **Data:** *Animal Data* Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m^2 twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose. The safety profile in children was similar to that seen in adults. **Geriatric Use** Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** Reduce the Jakafi dosage when administering Jakafi to patients with MF and moderate (CLcr 30 mL/min to 59 mL/min as estimated using Cockcroft-Gault) or severe renal impairment (CLcr 15mL/min to 29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for patients with PV and moderate (CLcr 30 to 59 mL/min) or severe renal impairment (CLcr 15 to 29 mL/min) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for all patients with ESRD on dialysis [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. **Hepatic Impairment** Reduce the Jakafi dosage when administering Jakafi to patients with MF and any degree of hepatic impairment (Child-Pugh Class A, B and C) and with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for patients with PV and hepatic impairment (Child-Pugh Class A, B and C) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.

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Editorial Review Board

Managing Castration-Resistant Prostate Cancer: Understanding the Therapeutic Landscape

Michael E Hurwitz, MD, PhD

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

There are several treatment options for castration-resistant prostate cancer (CRPC). The order in which to use these agents is not well defined, so selection is dependent on clinical symptoms and the adverse effect profiles of the agents. Molecular testing is becoming more common with CRPC and will likely be used in the future for therapy selection.

Key Points

- Many agents now exist for CRPC.
- Order of use is not well defined.
- Order agents on clinical symptoms and adverse effect profiles.
- Molecular testing can be used to identify best therapies.

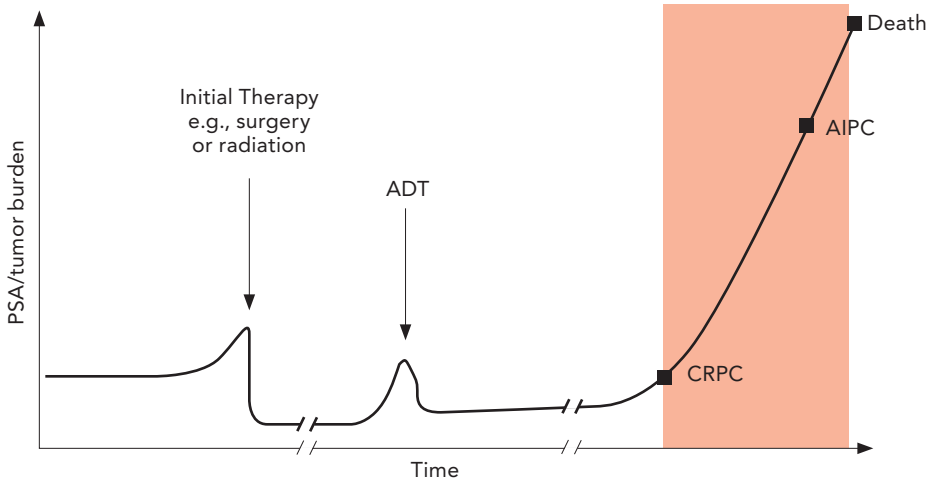
UNLIKE WITH OTHER CANCERS, MEN with prostate cancer can live for a long time with this disease without major symptoms. Exhibit 1 illustrates the natural history of prostate cancer. Typically, it is initially treated with surgery or radiation. If the cancer recurs, androgen deprivation therapy (ADT) to block the effects of testosterone can be effective in controlling the cancer for many years. Eventually the disease will no longer respond to ADT and is then considered castration-resistant prostate cancer (CRPC). The transition time from CRPC to androgen-independent prostate cancer (AIPC) and death are relatively short compared with the other stages.

CRPC is identified as a rising prostate-specific antigen (PSA) despite luteinizing hormone-releasing hormone (LHRH) agonist monotherapy [leuprolide (Lupron®, Eligard®), goserelin (Zoladex®), triptorelin (Trelstar®), histrelin (Vantas®)], LHRH antagonist [degarelix (Firmagon®)] therapy, or a combination of an LHRH agonist and an anti-androgen [bicalutamide (Casodex®)]. In CRPC, the tumor is still sensitive to testosterone. Because the tumor is still sensitive, an LHRH agonist or antagonist will be continued through all subsequent therapies.

It is important to determine if the patient really has CRPC. For some patients, the LHRH agonist agents do not lower testosterone to castrate levels, even when given in appropriate doses and used adherently. If a patient's testosterone is greater than 20 ng/ml, they can be switched to the LHRH antagonist (degarelix).

Treatment classes for CRPC include androgen signaling blockade agents (abiraterone acetate and enzalutamide), immunotherapy (Sipuleucel-T), bone targeting (Radium-223), and chemotherapy (docetaxel, cabazitaxel and mitoxantrone). As mentioned previously, these would be used with an LHRH agonist

Exhibit 1: Natural History of Prostate Cancer



ADT = androgen deprivation therapy
CRPC = castration-resistant prostate cancer
AIPC = androgen independent prostate cancer

or antagonist.

Exhibit 2 shows generally how androgens are produced and where ADT works. Testosterone is produced by the testes and the adrenal glands. As prostate cancer progresses, the tumor develops the ability to make its own testosterone from pre-cursers like DHEA, which is why disease progression occurs even while LHRH agents are still working to suppress testosterone production.

Two androgen signaling blockade agents are approved for CRPC. Abiraterone acetate (Zytiga®) is a potent inhibitor of extragonadal (and gonadal) production of testosterone (i.e., adrenals and intratumoral) via CYP17 inhibition. It is given with 5 mg prednisone bid. Coadministration of prednisone compensates for abiraterone-induced reductions in serum cortisol and blocks the compensatory increase in adrenocorticotropic hormone seen with abiraterone. This agent improves median overall survival (OS) by about four months.

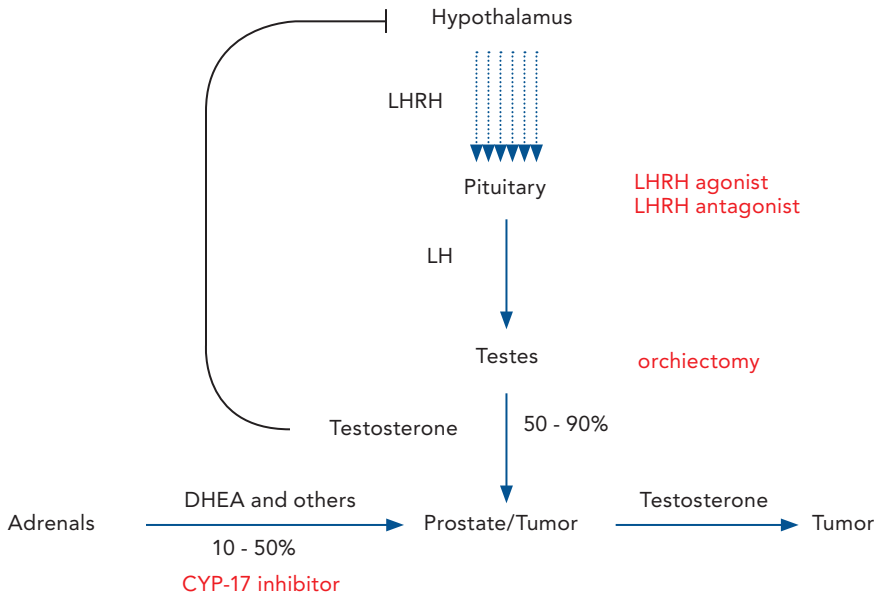
Enzalutamide (Xtandi®) is an anti-androgen which is much more potent than older anti-androgens. Given as 160 mg orally once a day, it is a true competitive inhibitor that blocks most nuclear translocation of the androgen receptor and DNA-binding. Within the nucleus, it inhibits AR binding to chromosomal DNA, which prevents further transcription of tumor genes. Adverse effects of concern with this agent are lowering the seizure threshold and fatigue. Treatment with enzalutamide improves median OS two to four months.

Immunotherapy is another option for CRPC. Sipuleucel-T (Provenge®) is a cellular therapy that is very different from the checkpoint immunotherapies being used in other cancers. With this treatment, a patient's antigen-presenting cells (APCs) are extracted in a leukapheresis procedure. The APCs are incubated with a fusion protein (PA2024) consisting of two parts, the antigen prostatic acid phosphatase (PAP), which is present in 95 percent of prostate cancer cells, and granulocyte-macrophage colony-stimulating factor that helps the APCs to mature. The activated blood product is infused into the patient to cause a T cell response against cancer cells carrying the PAP antigen. This therapy is for those with a rising PSA and asymptomatic or minimally symptomatic disease. It is given in two-week cycles for three cycles. There are few adverse effects and no effect on PSA or progression-free survival (PFS), but median OS is improved by 4.1 months.[1]

Radium-223 dichloride is an α-emitting isotope that targets bony lesions. It is indicated for patients with symptomatic bony metastases requiring analgesic medications and no visceral disease. Fifty-six percent of patients will have improvement in bone pain after two doses. Adverse effects are minimal, but this treatment can include nausea, vomiting, anorexia, and fatigue. Interestingly, it improves median OS by 3.6 months.[2,3] It also prolongs the time to first skeletal-related event (SRE, 15.6 vs 9.8 mo).

Chemotherapy for CRPC with docetaxel improves median OS by about two months.[4,5] Cabazi-

Exhibit 2: Androgen Production



LHRH = luteinizing hormone releasing hormone
LH = luteinizing hormone
DHEA = Dehydroepiandrosterone
CYP-17 = cytochrome P450 17

taxel compared to docetaxel is more effective, causes less neurotoxicity, but causes more of other toxicities. It results in a three-month increase in median OS.[6] Primarily because of the adverse effects, the standard of care is to give docetaxel first and then cabazitaxel; however, if someone already has neuropathy, they should receive cabazitaxel first.

The order in which all these agents for CRPC should be used is not well defined. Exhibit 3 gives some considerations in sequencing the agents. Exhibit 4 gives a strategy for selecting agents based on the considerations. The order of therapy appears to be irrelevant based on retrospective analyses.[7,8] It is important to note that benefit of any of these therapies decreases with each subsequent line of therapy.

Numerous agents are being investigated for CRPC. Olaparib, which is FDA approved for some types of breast and ovarian cancer, is a poly (ADP ribose) polymerase (PARP) inhibitor. Many late stage prostate cancers have double-stranded DNA repair defects and thus the cell is dependent on PARP to repair any DNA defects. PARP inhibitors prevent tumor cells from repairing those defects and lead to cell death. Olaparib monotherapy has been studied in heavily pretreated CRPC and produced a 33 percent overall response rate, but an 87.5 percent response rate occurred in those with DNA repair defects.[9] Veliparib, another PARP inhibitor, has also been studied in CRPC. The evidence from trials of PARP inhibitors has provided a rationale for conducting molecular testing in CRPC to identify DNA repair defects and other biomarkers of response.

Another area of investigation is determining which patients will respond best to androgen blocking therapy. Tumor cells circulating in peripheral blood can be tested for presence of an AR-V7 splice mutant which causes androgen receptor signaling to be always turned on even without the presence of an androgen. If any AR-V7 RNA is present on testing, there is almost no clinical response to enzalutamide or abiraterone.[10] These data are another reason to do molecular testing of CRPC tumors to decide who should not receive androgen blocking therapy.

There are also numerous androgen receptor mutations that are being shown to affect the outcome of therapy.[11-15] For example, one, F876L, actually makes enzalutamide into an agonist which will promote cancer cell growth.

CYP17 can also be upregulated. In this case, abiraterone will not work. Enzalutamide would work in this situation because it works later in the production of testosterone.

Although 95 percent of prostate cancer is driven

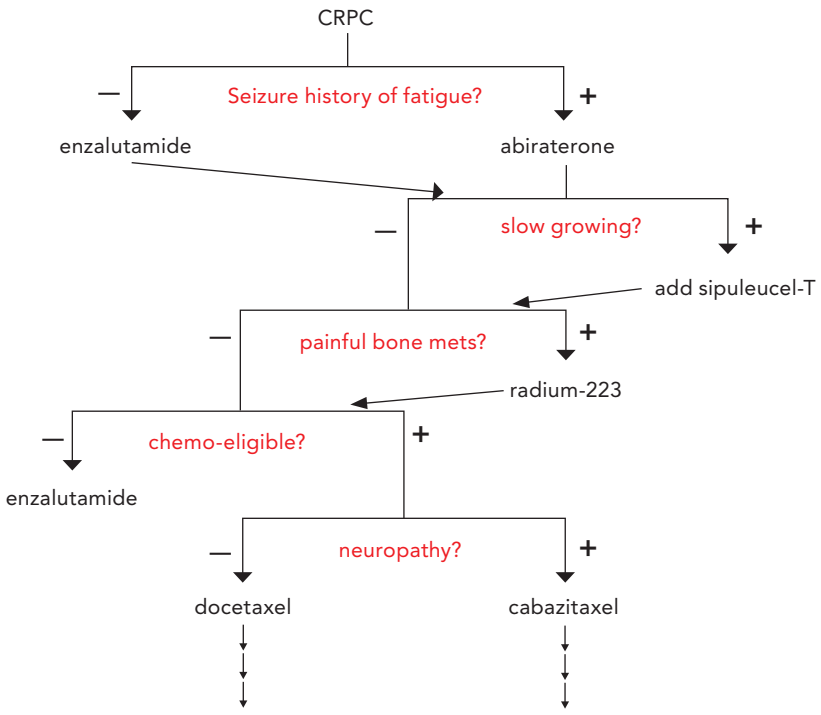
Exhibit 3: Considerations for Sequencing of Agents

Agent	Eligibility	Side Effects
abiraterone acetate	Requires 10mg prednisone daily	Exacerbates ADT and steroid side effects
enzalutamide	Seizure history?	Exacerbates ADT side effects Lowers seizure threshold Fatigue
sipuleucel-T*	Slowly growing disease Minimally symptomatic	Minimal Has little/no effect on PFS
Radium-223*	Pain requiring analgesics No visceral disease	Nausea, vomiting, anorexia, fatigue
docetaxel	Adequate hematologic function Adequate performance status	Hematologic Alopecia Neuropathy Fatigue Nausea
cabazitaxel	Adequate hematologic function Adequate performance status	More toxicity, less neuropathy than docetaxel

*Can be given with abiraterone or enzalutamide safely though unknown if efficacy is equivalent in combination

ADT = androgen deprivation therapy
PFS = progression-free survival

Exhibit 4: Example Strategy for Sequencing Treatment



by androgens, there is a variant which is not androgen dependent. This is a rare cancer with non-adenocarcinoma histology, exclusively visceral metastases, lytic bone lesions, bulky lymphadenopathy, low PSA, and evidence of neuroendocrine differentiation (i.e., acts like small cell cancers).[16] This variant is treated like small cell lung cancer with platinum-containing combinations (carboplatin/docetaxel or

cisplatin/etoposide). Unfortunately, the treatment is not very effective, so managing variant prostate cancer is a hot area of research.

Conclusion

Many agents now exist for CRPC. The order of using these agents is not well defined. At this time, the agents should be ordered based on clinical symptoms and side effect profiles. Molecular testing of the tumor cells can be used to identify best therapies and will be done much more often in the future.

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Optimizing Treatment Strategies in the Management of HIV/AIDS: Individualizing Therapy for Improved Patient Outcomes

Anne Monroe, MD, MSPH

For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title.
This activity is supported by an educational grant from ViiV Healthcare.

Summary

Identifying those with HIV infection and starting individualized antiretroviral therapy (ART) which optimizes viral suppression are important to improving patient outcomes. Keeping patients engaged in their care and under care are also important.

Key Points

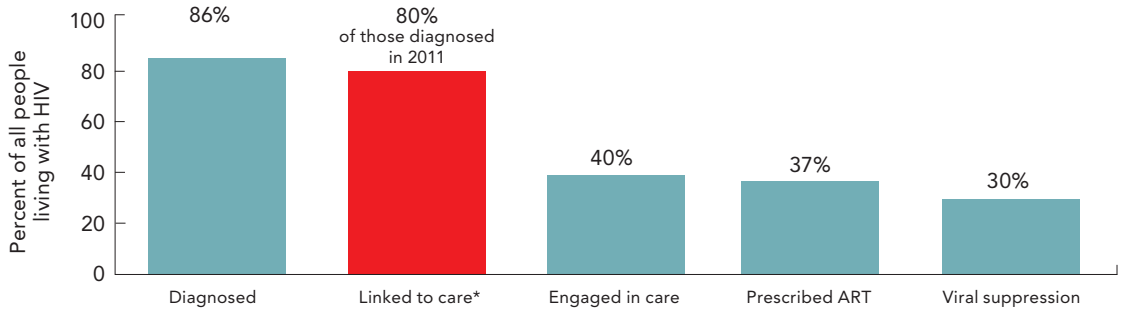
- Effective, well-tolerated ART should be individualized for the best chance of long-term success of the initial ART regimen.
- Multiple patient factors and drug-drug interactions must be considered when making therapeutic decisions.
- An HIV expert should be involved in designing regimens for treatment-experienced patients.
- Retention in HIV care is crucial for decreasing HIV-related morbidity and mortality and for decreasing HIV transmission.

MORE THAN 1,200,000 PEOPLE IN THE UNITED States (U.S.) are living with HIV infection.[1] In 2016, 39,782 people received an HIV diagnosis.[2] Significant progress is being made in preventing the spread of this disease. The number of new HIV diagnoses fell 19 percent from 2005 to 2014. Because HIV testing has remained stable or increased in recent years, this decrease in diagnoses suggests a true decline in new infections. The decrease may be due to targeted HIV prevention efforts. However, progress has been uneven, and diagnoses have increased among a few groups. Among white gay and bisexual men, diagnoses dropped steadily, declining 18 percent overall. Among Hispanic/Latino gay and bisexual men, diagnoses rose by 24 percent. Although diagnoses among African American gay and bisexual men increased 22 percent between 2004 and 2010, they have leveled off in the past five years, increasing less than 1 percent since 2010. Young African American gay and bisexual men (aged 13 to 24) experienced an 87 percent increase in diagnoses between 2004 and 2010. But since 2010, diagnoses have declined 2 percent.

Overall, HIV disproportionally affects African Americans and Hispanics/Latinos. African Americans represent 12 percent of the U.S. population, but account for 45 percent of HIV diagnoses. Hispanics/Latinos represent approximately 18 percent of the U.S. population, but account for 24 percent of HIV diagnoses.

The good news in HIV treatment is that there are numerous effective antiretroviral therapy (ART) regimens. With the use of these regimens, HIV-related morbidity and mortality have decreased.[3,4] Effective ART (i.e., viral load is suppressed) is also an effective form of prevention so those infected do not pass along the infection.[5] ART is now recommended as soon as an HIV diagnosis is made. Previously, ART was not initiated until the CD4 cell counts declined to below 350. Immediate initiation

Exhibit 1: Estimated Percentage of Persons Living in the U.S. in 2011 with HIV Infection by Outcome Along the HIV Care Continuum[7]



*Linkage to care measures the percentage of people *diagnosed with HIV in a given calendar year* who had one or more documented viral load or CD4+ test *within three months of diagnosis.* Because it is calculated differently from other steps in the continuum, it cannot be directly compared to other steps and is therefore shown in a different color.

Exhibit 2: Recommended Antiretroviral Regimen Options for Treatment-Naïve Patients (October 2017)[11]

- Abacavir/dolutegravir/lamivudine (only if HLA-B*5701 negative)
- Dolutegravir/emtricitabine/tenofovir DF or tenofovir AF
- Cobicistat/elvitegravir/emtricitabine/tenofovir DF or tenofovir AF
- Raltegravir/emtricitabine/tenofovir DF or tenofovir AF
- Darunavir/ritonavir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF

at the time of diagnosis significantly prolongs the time until first HIV-related morbidity, reduces serious AIDS-related events, and reduces death from HIV.[6] Two caveats are that some patients are still not diagnosed until late in the disease process so they will not have as much benefit from therapy, and early therapy initiation assumes that a patient is able and willing to be treated. A discussion of the commitment to life-long therapy has to occur with the patient before therapy is prescribed.

The HIV care continuum includes diagnosing the disease, getting those with HIV into care, treating them, and keeping them under care. This is a complex process and, overall, in the U.S., it is far from optimized. An estimated 86 percent of HIV cases are diagnosed in the U.S. Despite this high diagnosed percentage, a much smaller percentage of those living with HIV are engaged in their care, are on ART, and have suppressed viral loads (Exhibit 1).[7] Engaging people in their care, being on ART, and having suppressed viral loads through ART treatment adherence are all important in optimizing outcomes and in reducing the transmission of the infection.[8]

A few strategies for optimizing outcomes in HIV care can be implemented by various managed care organizations. The International Association of Providers of AIDS Care (IAPAC) has published guidelines for optimizing the HIV care continuum.[9] To optimize the HIV care environment, these guidelines recommend identifying and managing any mental health disorders (anxiety, depression, PTSD) or mental health issues related to an HIV diagnosis, disclosure of status, or HIV treatment. These guidelines also recommend enabling those living with HIV to take responsibility for their care (i.e., self-management, user-driven care). A linkage to care recommendation from the IAPAC guidelines is to routinely offer opt out HIV testing to all individuals who present at health facilities. This will help identify more patients. Care managers and care navigators are also recommended to increase linkage to

Exhibit 3: Minimizing Pill Burden and Dosing Frequency

Regimen	Number of Pills	QD or BID
Abacavir/dolutegravir/lamivudine	1	QD
Dolutegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF	2	QD
Cobicistat/elvitegravir/emtricitabine/tenofovir DF	1	QD
Cobicistat/elvitegravir/emtricitabine/tenofovir AF	1	QD
Raltegravir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF	3	BID
Darunavir/ritonavir plus either emtricitabine/tenofovir DF or emtricitabine/tenofovir AF	3	QD

care. Under increasing HIV treatment coverage, using first-line ART regimens with the highest level of efficacy, lowest rate of adverse effects, and delivered in a fixed-dose once-daily combination regimen is recommended to improve suppression and adherence rates. Additionally, managed care plans can monitor retention in care (defined as >2 primary care visits for HIV 90 days apart over one year) and adherence to therapy using pharmacy data to identify patients who need to be targeted for intervention. Lastly, to improve the HIV care continuum managed care can designate HIV specialists as primary care providers to make referrals unnecessary. This streamlines the care for the patients.[10]

The goals of ART are to reduce HIV-related morbidity and mortality, improve quality of life, restore and preserve immune function, and control HIV replication.[11] The recommended antiretroviral regimen options for treatment-naïve patients are constantly being updated and thus the clinician should consult the most up-to-date guidelines before prescribing. Both the Department of Health and Human Services and the International Antiviral Society (IAS) publish HIV treatment guidelines.[11,12] The recommended regimens in these guidelines have been selected because they are effective, have the lowest rates of adverse effects, and have lower dosing frequencies than other regimens (Exhibit 2).[11] A typical regimen will include several agents from different classes including integrase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs), and protease inhibitors (PI) to prevent emergence of resistance. Two differences between the guidelines are that the IAS guidelines recommend tenofovir AF over tenofovir DF and do not include a protease inhibitor-based regimen as a first-line option for treatment-naïve patients. Integrase inhibitor-based therapy is typically the first-line option chosen by most clinicians.

Several factors that will drive the clinician and patient therapy choice include achieving viral suppression, minimizing toxicity, minimizing pill burden, dosing frequency, drug–drug interactions, baseline resistance, and potential for development of resistance. Other factors include cost, copays, comorbidities, and food restrictions.

Virologic suppression is excellent with both integrase inhibitor and protease inhibitor-based regimens.[13-15] One trial has shown superior efficacy of an integrase inhibitor-based regimen. The integrase inhibitors are better tolerated than protease inhibitors.

Minimizing toxicity is also important in selecting therapy. For example, minimizing renal and bone toxicity can be done by selecting tenofovir AF over the DF formulation. Integrase inhibitor-based regimens are more lipid friendly than protease inhibitor regimens.

Today's regimens for HIV are much easier to take than those in the past. As shown in Exhibit 3, there are one pill once a day regimens which are much easier to take than the regimens of the past that involved taking multiple tablets several times a day.

Baseline resistance, both before any treatment and as the result of past treatment, is an issue that has to be considered in selecting therapy. Transmitted resistance mutations are present in 17.4 percent of gay and bisexual men with HIV and 15.5 percent in heterosexual men with HIV.[16] In one trial, transmitted resistance mutations were present in 11.2 percent of treatment-naïve patients being screened for clini-

cal trials.[17] The majority of transmitted resistance is NNRTI resistance, which is typically efavirenz, which is not used first line; transmitted resistance to integrase inhibitors is low.

Cost can be a major issue for some patients. The first-line regimens cost approximately $3,000 per month for the rest of someone's life. Although expensive, ART is cost-effective based on decreased morbidity and mortality.[18-20] High out-of-pocket costs correlate to worse adherence with medications for chronic diseases; clinicians and managed care should try to minimize out-of-pocket costs for HIV therapy.

Generic ART, although less expensive, may increase pill burden/frequency and decrease adherence. Several agents which are no longer used first line will be going off patent in the next few years and managed care will have to balance the lower cost of these generics compared with the potential impact of using a less efficacious or more complicated regimen.

Following laboratory monitoring guidelines can be cost saving. The recommendations for monitoring CD4 cell counts have changed significantly over the last few years, but some clinicians may still be doing the previously recommended more frequent CD4 counts. In patients with a stable viral load, a CD4 count can be checked annually rather than every six months.

Sometimes after patients have been on a stable regimen for a while, clinicians may consider switching therapies. Some of the reasons for switching may include improved tolerability, lower toxicity, preservation of treatment options for the future, avoidance of drug-drug interactions, simplification of the regimen to improve adherence, decreased cost, and fewer administration restrictions. In women, therapy may need to be switched to optimize ART use in pregnancy or for planned pregnancy.[11] If switches in therapy are made in someone with viral suppression, it is important to select a new regimen that will maintain viral suppression and not compromise future treatment options. Switches can be proactive to avoid adverse effects or to improve potential for optimal adherence, or they may be reactive, such as after an adverse event. Prior to making any switches, clinicians have to keep in mind any possible documented resistance mutations, initial acquisition of drug-resistant virus or selection of resistance mutations during failure of previous regimen, duration of suppression prior to switch, and the patient's adherence. Switch strategies with good supporting evidence include within-class switches (e.g., tenofovir DF to AF) and between-class switches (e.g., protease inhibitor to integrase inhibitor).

Another clinical switching situation is because of virologic failure, which is defined as the inability to achieve or maintain suppression of viral replication to an HIV RNA level less than 200 copies/mL. The most common reason for virologic failure is suboptimal medication adherence. It is important to identify and address the underlying cause(s) for nonadherence and, if possible, to simplify the regimen. Virologic failure can also occur because of drug resistance or drug interactions which lower the ART therapeutic levels. An example would be the interaction between over-the-counter antacids and integrase inhibitors.

Conclusion

Effective, well-tolerated ART should be individualized for the best chance of long-term success of the initial ART regimen. Multiple patient factors and drug-drug interactions must be considered when making therapeutic decisions and an HIV expert should be involved in designing regimens for treatment-experienced patients. Retention in HIV care is crucial to reap the long-term benefits of ART, both for decreasing HIV-related morbidity and mortality and for decreasing HIV transmission.

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What's New in CFTR Modulator Therapy in the Management of Cystic Fibrosis

Christian A. Merlo, MD MPH

For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title.
This activity is supported by an educational grant from Vertex Pharmaceuticals.

Summary

It is an exciting time for treating patients with cystic fibrosis (CF) because medicine is on the brink of a cure for the disease with the availability of medications that are reversing the genetically-induced dysfunction of the CF transmembrane conductance regulator (CFTR) in some patients. These agents are improving lung function, reducing pulmonary exacerbations that lead to lung damage, and improving symptoms. Many more medications targeting CFTR are anticipated in the future.

Key Points

- Survival with CF has greatly improved with various treatment improvements.
- Effective therapy improving the function of CFTR is now available for select patients with CF.
- More therapies targeting various genetic mutations of CFTR anticipated in the future.

IN 1936, DR. DOROTHY HANSINE ANDERSEN was the first physician to recognize cystic fibrosis (CF) as a disease. The gene for CF was discovered in 1989 and with this breakthrough, the quest to cure this disease began.

CF is caused by dysfunction in the protein of the cystic fibrosis transmembrane conductance regulator (CFTR), which is found on the surface of epithelial cells. The gene for this protein is located on chromosome 7, and over 2,100 mutations are known to cause CF. It is an autosomal recessive disorder, requiring two copies of a mutation for the disease to be manifested and is the most common genetic disorder of Caucasians, with 4 percent of Caucasians being a carrier. CF affects one in 3,200 births.

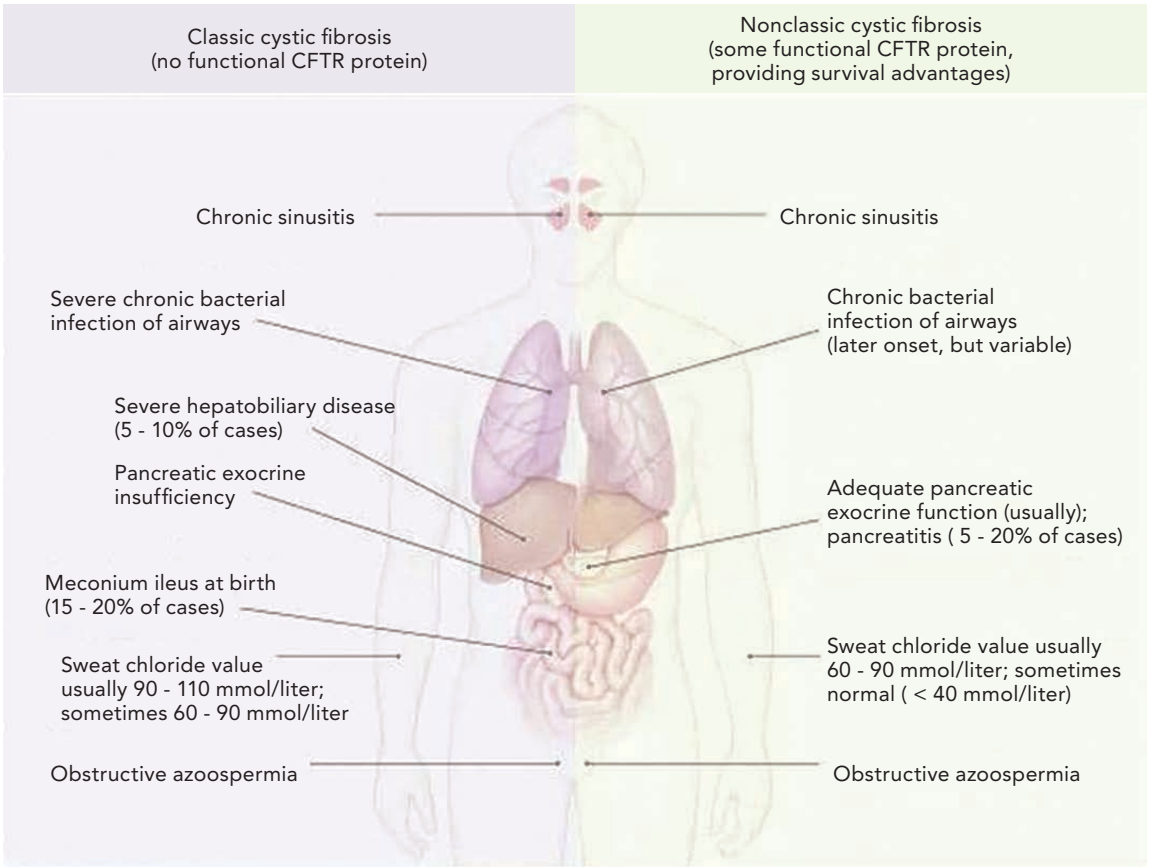
The CFTR protein is a chloride channel present in the epithelium of most lumens of the body, and contributes to sodium and water balance. Chloride is transported through the CFTR channel into the lumen of the airway. CFTR also regulates a nearby epithelial sodium channel (ENaC). Through regulating chloride and sodium transport, CFTR regulates water balance in most lumens of the body.

CF is a multi-system disorder that leads to significant bronchiectasis (chronic pulmonary infections), and also causes chronic sinus disease, pancreatic insufficiency, CF respiratory disease (CFRD), CF-related liver disease (CFRLD), and infertility. It can affect any part of the body with epithelial cells. The majority of CF patients die from respiratory complications. CF can be divided into classic, which has no functioning CFTR, and non-classic, which has some functioning CFTR that confers a survival advantage (Exhibit 1).[1]

The diagnosis of CF requires clinical and laboratory evidence of CFTR dysfunction. Classic clinical evidence includes bronchiectasis and chronic pulmonary infections. Laboratory evidence includes elevated sweat chloride, known CF mutations on both alleles, and characteristic bioelectric abnormalities in nasal epithelium in vivo.[2]

It is important to understand how CFTR works in order to understand how therapies aimed at improving outcomes in CF work. When the CFTR protein functions normally, hydration of the airway is maintained. Chloride is secreted into the airway through the CFTR protein. The chloride ions are more numerous on the extracellular lumen in the airway. Sodium and water are also regulated by this chloride channel, and a nice water balance

Exhibit 1: Classic and Nonclassic Cystic Fibrosis[1]



is maintained, creating a hydrated surface airway liquid. Cilia on the surface of the epithelial cell beat and move mucus and bacteria out of the lungs. Overall, CFTR regulates sodium/water balance to keep mucus thin.

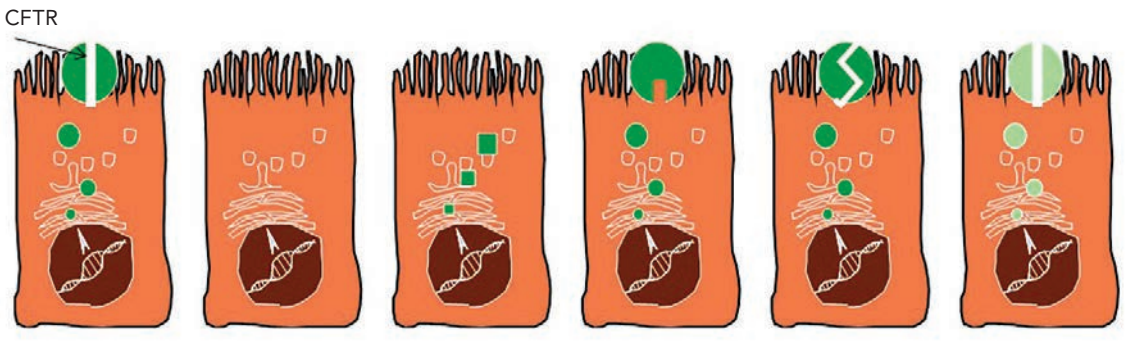
In the absence of CFTR function, chloride is not secreted extracellularly, and therefore sodium is hyper-absorbed from the airway into the epithelial cells to maintain isoelectric potential. Water follows sodium into the cells, subsequently disrupting the water balance. This leads to dehydration of the airway surface liquid, resulting in impaired mucociliary clearance. Cilia become damaged (shortened or nonexistent), bacteria become trapped, and mucous is thickened.

Chronic infection from decreased clearance of bacteria/mucus leads to permanent damage in the lungs. This is bronchiectasis with dilated and thickened airways which are incapable of clearing the bacteria/mucus. The two most common organisms in these chronic infections are *Staph aureus* and *pseudomonas*.[3] Bronchiectasis leads to decreased lung function and survival. Over 90 percent of individuals with CF die from respiratory complications of the disease.

Despite the dismal prognosis, tremendous improvements in survival have occurred over the past six decades. In the 1950s, median survival was around 5 years old. In the mid-1970s, median survival was 16. It is just in the past two to three decades that CF individuals began surviving into adulthood. The median predicted age of survival as of 2012 was 41 years old.[3] This survival increase is secondary to improvements in therapies – better airway clearance techniques, new inhaled therapies and antibiotics, and more aggressive treatment with intravenous antibiotics, which in turn improves or preserves lung function[(as measured by forced expiratory volume in one second (FEV1)] and nutritional advances. Patients with CF tend to have difficulty with nutritional status without pancreatic enzyme support. It is hoped that the survival curve will continue to rise with the availability of the new CFTR-targeting medications.

The main therapies for CF are airway clearance, inhaled antibiotics, oral antibiotics, nutritional sup-

Exhibit 2: CFTR Mutation Classes



Normal	I	II	III	IV	V
	Defective Synthesis	Defective Processing	Defective Regulation	Reduced Conductance	Reduced Synthesis
	Nonsense G542X W1282X R553X	F508del N1303K	G551D	R117H R347P	3849 + 10kbC – > T 5T A455E
	Splice Junction 1717-1G – > A				

port with pancreatic enzymes, and therapies to improve CFTR function. Airway clearance can be with a vibrating vest, acapella and flutter valves, and airway coughing or breathing techniques. Pulmozyme® and hypertonic saline are both therapies to help thin out the mucous so that mucous can be cleared more easily. Inhaled antibiotics help fight off the bacteria that CF patients are chronically infected with. Most of these show an average of a 5 percent increase in FEV1, in clinical trials. Azithromycin has been shown to increase FEV1 as well as decrease the rate of exacerbations and hospitalizations.

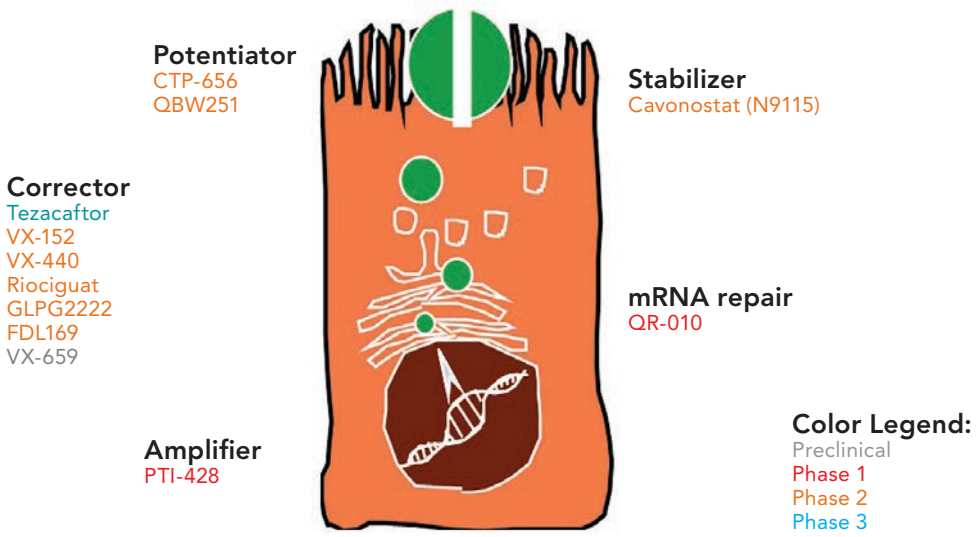
The newest treatments in CF are CFTR gene correctors or potentiators. CFTR mutations can be categorized into different classes, which all result in different degrees of CFTR function (Exhibit 2). Homozygous F508del, a Class II mutation that results in defective processing, occurs in about 50 percent of CF patients.

Ivacaftor (Kalydeco®) is a potentiator in those with a Class III defect, which is approximately 4 percent of CF patients. It is an oral agent that increases the time the chloride channel remains open. Studies have shown tremendous improvements in FEV1 (10.5% increase), reduction in pulmonary exacerbations by 55 percent, and improved symptoms.[4] Patients gain an average of 3.4 kg and their sweat chloride normalizes from 100 to <60. The improvement in lung function and the secondary endpoints was maintained through week 48 of the trial. Improvements in quality of life scores (CFQ-R respiratory domain) were also reported.

There have been many additional studies completed with ivacaftor showing its efficacy. These have included use in children ages 2 to 5 with gating mutation, children and adults with non-G551D gating mutation, R117H mutation, and G551D mutation and good lung function. A study is now enrolling babies with gating mutation. Ivacaftor is now FDA indicated for patients ages 2 years and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. This includes following mutations: G551D, R117H, G178R, S549, G551S, G1284E, S1251N, S1255P, and G1349D which account for about 10 percent of the CF population.

Lumacaftor is a gene corrector which is only used in combination with ivacaftor. Lumacaftor binds to the misfolded CFTR protein so the cell does not discard it and thus it can move to the cell surface. It is combined with ivacaftor, which enhances the CFTR function once it reaches the cell surface. Lumacaftor-ivacaftor (Orkambi®) is FDA approved for CF patients ages 6 years and older who are homozygous for the F508del mutation in the CFTR gene, which is the most common genetic mutation in CF.

Exhibit 3: Therapies in the Pipeline



Two Phase III, randomized, double-blind trials for 12 weeks in patients homozygous for F508del found a mean absolute improvement of 2.6 to 4.0 percent FEV1 predicted, a relative improvement of 4.3 to 6.7 percent FEV1 predicted, and a reduction in exacerbations by 30 to 39 percent.[5] Patients also gained weight in these trials and the therapy was well tolerated. Less effect on sweat chloride is seen with the combination compared with ivacaftor alone in those with Class III defects. A unique and significant adverse effect of the combination is chest tightness.

The development of these two agents has been great news for CF patients, but neither are a cure. The search is on for other agents that can better improve CFTR function. A carrier of CF, meaning someone who has one CF gene and does not have CF, has 50 percent functioning CFTR (one normal and one defective). Ivacaftor for G551D restores CFTR function to about 50 percent or that similar to a carrier state. This is why such dramatic improvements in FEV1 are seen with this therapy. Lumacaftor/ivacaftor in patients with homozygous F508del improved CFTR function about 20 to 30 percent, which is why lung function does not improve as much. However, recent results from two trials with tezacaftor (investigational) plus ivacaftor improved outcomes somewhat better than lumacaftor/ivacaftor. In vitro, tezacaftor, ivacaftor and either VX-152 or VX-440, both investigational, appear to restore chloride transport even better than that of ivacaftor for G551D mutation, highlighting the notion that we are entering the dawn of a new day of therapy for CF and rapidly approaching a cure. There are other therapies in the pipeline that are in various stages of development to target the different cellular stages of CFTR production and processing (Exhibit 3).

Conclusion

Survival with CF has greatly improved with various treatment advancements. Effective therapy improving the function of CFTR is now available for select patients with CF. More therapies targeting various genetic mutations of CFTR are on the horizon. It is hoped that these newer agents will continue to improve survival in this disease.

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New Horizons in the Diagnosis and Management of Idiopathic Pulmonary Fibrosis (IPF)

Leann Silhan, MD

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

Effective, but not curative, pharmacotherapies for IPF are now available. These agents slow the decline in lung function. Lung transplant and pulmonary rehabilitation are other important treatments. Because of the deadly nature of the disease, shared decision making is important.

Key Points

- Clinicians should follow the evidence-based guidelines for management and treatment of IPF.
- Shared decision making is important for optimal management of this disease.
- Pirfenidone and nintedanib appear to slow the decline in lung function.
- Pulmonary rehabilitation is also a significant part of effective treatment.

IDIOPATHIC PULMONARY FIBROSIS (IPF) IS an interstitial lung disease. The interstitium is a potential space between the air sacs and capillary bed in the alveoli. Interstitial lung disease occurs when there is inflammation or fibrosis in this space. The interstitium becomes thick and scarred and thus oxygen exchange is impaired. IPF is a specific type of interstitial lung disease characterized by progressive decline in lung function and usual interstitial pneumonia (UIP) histology of unknown cause in adults.[1] IPF is the most common of the idiopathic interstitial lung diseases and has the worst prognosis. It is a deadly, incurable disease with a median survival after diagnosis of three to five years.[2]

If an adult patient has progressive exertional shortness of breath and/or chronic cough, IPF can be suspected. It has to be differentiated from many other diseases which cause similar symptoms (Exhibit 1). Other symptoms and signs of IPF include inspiratory crackles and digital clubbing. On lung function tests, the patient will have evidence of restriction and impaired gas exchange. Forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) will both be reduced. IPF is diagnosed when there is no alternative cause of interstitial lung disease (e.g., environmental exposures, medication toxicity, and autoimmune disease) and UIP pattern on high resolution CT (HRCT) scan is found or a possible UIP pattern is seen on HRCT with UIP on surgical lung biopsy.[3]

Exhibit 2 provides a general overview of the treatment of IPF. Until 2014, the only treatment options were oxygen and supportive care. Because the disease affects many different aspects of life and can be rapidly progressive, a holistic approach which addresses end-of-life care is recommended.

Comorbidities are very common with IPF (Exhibit 3). Gastroesophageal reflux disease (GERD),

Exhibit 1: Differential Diagnosis

Collagen Vascular Disease/ Autoimmune
- Anti-synthetase syndrome
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Systemic sclerosis
- Mixed connective tissue disease
- Sjogren's
- Granulomatous polyangitis

Interstitial Pneumonia with Autoimmune Features (IPAF)

Idiopathic
- Idiopathic pulmonary fibrosis
- Nonspecific interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonitis (Hamman-Rich Syndrome)
- Respiratory bronchiolitis interstitial lung disease
- Lymphocytic interstitial pneumonia
- Pleuroparenchymal fibroelastosis

Environmental
- Hypersensitivity pneumonitis (avian, molds, isocyonates, other organic dusts)
- Pneumoconioses (silicosis, asbestosis, berryliosis, coal miner's lung disease)

Medications
- TNF-alpha inhibitors (Eternacept, Infliximab, Adalimumab)
- Chemotherapy (bleomycin, busulfan, etc.)
- Amiodarone
- Methotrexate
- Siroliums/Everolimus
- NSAIDS, antibiotics (eosinophilic)

Other
- Eosinophilic pneumonia (idiopathic, parasitic)
- Sarcoidosis
- Lymphangioleiomyomytosus
- Histiocytosis X (Langerhan's cell)
- Chronic aspiration
- Lymphangitic carcinomatosis
- Pulmonary alveolar proteinosis

Exhibit 2: Management of the Patient with IPF

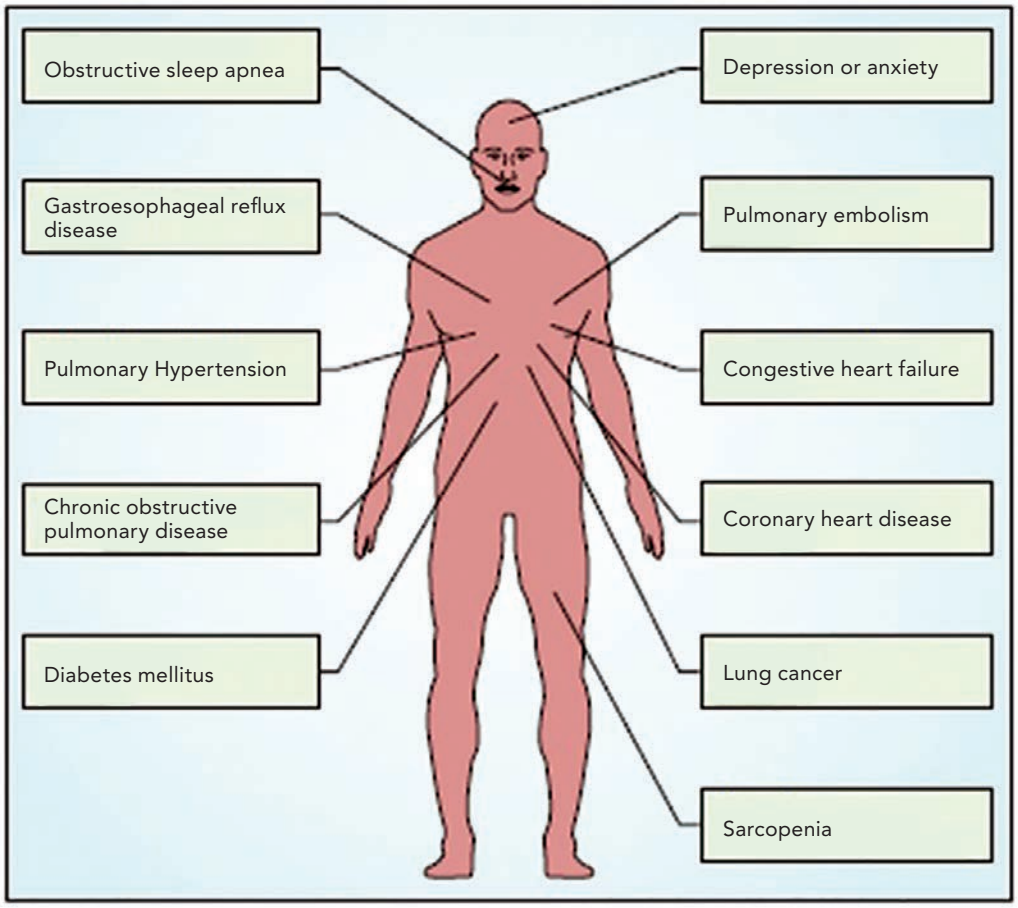
- √ Risk factor reduction
  - Smoking cessation
- √ Patient education
  - Advocacy group involvement
- √ Focus on comorbidities
  - GERD, OSA, CAD, PH, VTE, etc.
- √ Supplemental oxygen
- √ Age-appropriate vaccinations
- √ Discussion about nintedanib and pirfenidone
- √ Pulmonary rehabilitation
- √ Clinical trials
- √ Lung transplant evaluation
- √ Mental health needs
- √ Address end of life issues: Palliative and hospice care

obstructive sleep apnea (OSA, 80%), coronary artery disease (60%), and pulmonary hypertension (50%) are all very common. To maximize outcomes in this disease, the comorbidities need to be optimally managed. For example, fatigue is a very common symptom in IPF; addressing sleep-disordered breathing from OSA improves this.

The most recent information for pharmacologic treatment of IPF has recommendations for which medications to use and which to avoid.[3] Anticoagulation (warfarin); imatinib; combination prednisone, azathioprine, and N-acetylcysteine (NAC); and selective endothelin receptor antagonist (ambrisentan) are not recommended for use. For each of these, the risks of treatment or lack of benefit are too costly. Phosphodiesterase-5 inhibitor (sildenafil) and dual endothelin receptor antagonists (macitentan, bosentan) for treating pulmonary hypertension secondary to IPF have a conditional recommendation for not using in the most recent edition of the guidelines.[3] Some IPF centers will try these agents in selected patients.

GERD and clinically silent acid has been observed in up to 90 percent of patients with IPF.[3] Refluxed acid is a risk factor for aspiration and microaspiration, which could subsequently cause pneumonitis,

Exhibit 3: IPF Comorbidities



a mechanism that has been postulated to cause or worsen IPF. Some clinicians believe reflux is a cause of IPF and others believe that it is just a common comorbidity that worsens the disease. The guidelines have a conditional recommendation that antacid treatments, such as proton pump inhibitors (PPIs) or histamine2 blocker receptor antagonists, are recommended. Since the publication of these guidelines, subgroup analyses of a pirfenidone trial found that those on PPIs did no better than those not receiving these agents, and they had more infections, including pneumonia.[4] Patients likely should only be receiving these if they have symptomatic GERD, but acid suppression therapy is still an area of much controversy.

Treatment of IPF changed dramatically with the approval of two agents specially targeted to the disease. Pirfenidone (Esbriet®) is an oral antifibrotic drug with pleiotropic effects. In vitro, it has been shown to regulate important profibrotic and proinflammatory cytokine cascades and reduces fibroblast proliferation and collagen synthesis in animal models of lung fibrosis. Pirfenidone treatment compared to placebo reduced the combined endpoint of lung function decline (FVC) and death by 48 percent at the end of one year.[5] Over three one-year trials, there has been a significant preservation of FVC (148 ml/year) and progression-free survival (PFS), which is defined as time to investigator reported acute exacerbation.[6]

The management guidelines give pirfenidone a conditional recommendation. "This recommendation puts a high value on the potential benefit of pirfenidone on patient-important outcomes, such as disease progression as measured by rate of FVC decline and mortality, and a lower value on potentially significant adverse effects and the cost of treatment."[3] The guidelines note that some patients may not be willing to tolerate certain adverse effects of pirfenidone, even in the setting of treatment benefit.

Nintedanib (Ofev®) is a tyrosine kinase inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptors.

Treatment with it reduced the annual rate of change in FVC by 45 to 52 percent.[7] This agent also significantly preserved FVC (111 ml/year) and improved PFS.[7,8] Nintedanib treatment also reduces acute exacerbations by about 20 percent which is important. Acute exacerbations can lead to a dramatic acceleration of the disease process and death.

The use of nintedanib in patients with IPF is also a conditional recommendation in the guidelines which make an identical statement to the one for pirfenidone.[3] The guidelines note that nintedanib has not yet been shown to have a significant effect on overall mortality.

There are many tolerance issues with keeping patients at the recommended doses for both nintedanib and pirfenidone. The dose can be reduced temporarily to manage adverse effects but should be increased back up as soon as possible since the lower doses have not been shown to be efficacious. Unfortunately, many adverse effects improve on the lower dose and return with dose escalation.

The main adverse effects of pirfenidone include nausea, sun sensitive rash, dyspepsia, anorexia, GERD, weight loss, insomnia, dizziness, and vomiting. It is important that patients use sunblock at all times. Diarrhea and nausea are the major adverse effects with nintedanib. Diarrhea from nintedanib can be managed by taking it with meals, adding loperamide, or making a dosage reduction. Loperamide is automatically prescribed along with nintedanib. Nintedanib should be used cautiously in those with coronary artery disease. Both agents can cause elevated liver function tests, so these need to be monitored monthly for the first six months of therapy and then quarterly thereafter.

There are many factors involved in making the decision about which therapy to select. These include patient age, patient wishes/desires, comorbidities, lung function, disease severity, functional status, and frailty. The two available therapies have similar efficacy. One area of controversy is whether patients who have IPF but still have normal lung function should receive pharmacotherapy. The trials used patients with declines in lung function. Shared decision making between clinicians and patients should be used, and patients starting nintedanib or pirfenidone must be educated on all potential adverse effects. In addition, both are currently very costly interventions which do not cure the disease, and this must be factored into the decision-making process.

For patients with functional limitations, pulmonary rehabilitation is also very important to the treatment of IPF. Breathlessness from the disease leads to deconditioning and fatigue which leads to reduced physical and social activity. Patients can have anxiety and depression because of the disease symptoms and secondary effects. Pulmonary rehabilitation can help patients deal with the symptoms, improve their exercise capacity, provide conditioning, and improve quality of life.

Lung transplantation is an option for younger patients; those who may fit the criteria should be referred for evaluation early in the disease process. On the horizon are various other therapies for IPF. Immunomodulatory medications, antimicrobials, immunosuppression, and stem cell therapy are all being studied.

Conclusion

Clinicians need to suspect IPF when classic signs and symptoms are present. Once diagnosed, clinicians and managed care providers need to be aware of recommendations for management and treatment of IPF. Shared decision making with the patient is important to optimal management of this deadly disease. Two agents, pirfenidone and nintedanib, approved for managing this disease, appear to slow the decline in lung function. Pulmonary rehabilitation is also a significant part of effective treatment.

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Exploring the Role of PCSK9 Inhibitors in the Reduction of LDL-C in Patients with Dyslipidemia

Michael Miller, MD, FACC, FAHA, FNLA

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

Exciting new evidence has shown that lowering LDL-C to unprecedented low levels with newer agents in combination with statins is both safe and effective in reducing cardiovascular events. For patients who do not achieve sufficient lowering of LDL-C with maximally tolerated statins, the addition of ezetimibe or the PCSK9 inhibitors are both options.

Key Points

- Shared decision making is important in selecting which agent to add to statin therapy.
- PCSK9 inhibitors have been evaluated in patients with familial hyperlipidemia, with high atherosclerotic cardiovascular disease (ASCVD) risk and not at desirable LDL-C with maximally tolerated statins, and intolerant to statin therapy.
- In patients with known CV disease, PCSK9 inhibition with evolocumab significantly and safely decreased major CV events when added to statin therapy.
- Benefit can safely be achieved with lowering LDL-C well below current targets.

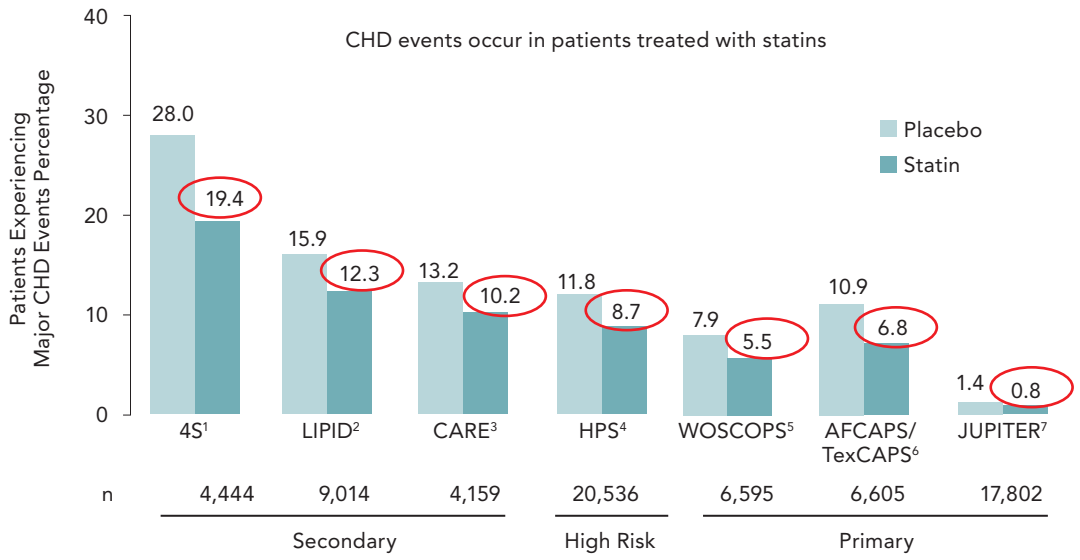
AS SHOWN IN EXHIBIT 1, THE USE OF statin therapy provides significant CV risk reduction in the 25 to 35 percent range, but there is still residual risk.[1-7] CV events still occur in those with optimal statin therapy. The rate of events varies from 10.2 to 19.4 percent in those who already have CV disease (CVD).

Clinicians and patients should not neglect the importance of lifestyle modifications, including dietary changes, physical activity, and stress reduction, which are also an important part of CVD risk reduction. Exhibit 2 shows some recommendations from a recent evidence-based review of various heart healthy-dietary interventions.[8]

The 2013 American College of Cardiology/American Heart Association lipid management guidelines recommend that "clinicians treating high-risk patients who have a less than anticipated response to statins, who are unable to tolerate a less than recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a non-statin cholesterol-lowering therapy. High-risk individuals include those with ASCVD, those with low-density lipoprotein cholesterol (LDL-C) greater than or equal to 190 mg/dL, and those with diabetes 40 to 75 years of age. In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in randomized controlled trials (RCTs) to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences."[9]

The 2016 ACC Expert Consensus Decision Pathway made several recommendations for optimizing risk reduction in patients with stable clinical ASCVD without comorbidities.[10] This is just one of several settings for potential use of non-statin therapies for additional LDL-C lowering. The recommendations are to treat with maximally tolerated statins to achieve at least a 50 percent or more LDL-

Exhibit 1: Despite Benefit, Substantial Residual CV Risk Remains with Statin Treatment[1-7]



C reduction. If this reduction is not achieved with the statin alone, initiate patient clinician discussion and consider non-statins to target a LDL-C treatment threshold of 100 mg/dL or less.

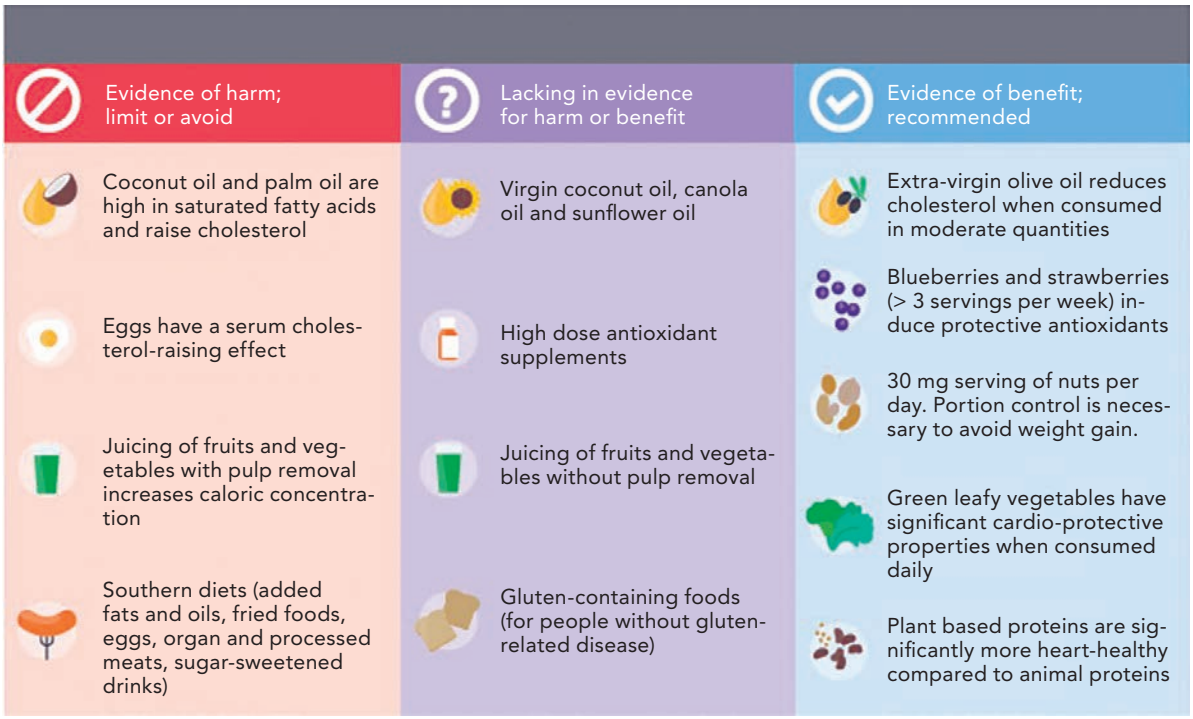
Exhibit 3 shows all the non-statin classes of lipid-lowering agents which have some efficacy in lowering LDL-C levels. Ezetimibe is recommended as the first non-statin to add; a bile acid sequestrant can be considered if the patient's triglycerides are less than 300 mg/dL.[10] Ezetimibe added to statin therapy provides about a 16 mg/dl reduction in LDL-C, a 6 percent reduction in CVD risk and a 2 percent absolute reduction in CVD events with a number needed to treat of 50.[11] The 6 percent reduction in risk is on top of what is achieved with a statin alone. Lomitapide and mipomersen are typically reserved for patients with homozygous familial hyperlipidemia (HoFH). Niacin and fibrates are not used as extensively as in the past. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are also an option to add to maximized statins.

PCSK9 is a secreted serine protease that chaperones the LDL receptor from the cell membrane for destruction. When the LDL receptor is not present on the cell membrane, circulating LDL-C is not taken up into the cell. Gain of function mutations in PCSK9 lead to high LDL-C levels while loss of function mutations result in low LDL-C. PCSK9 inhibitors reduce circulating LDL-C by allowing the LDL receptor to function longer. Exhibit 4 shows the FDA approved indications and dosing regimens for the two approved PCSK9 inhibitors which are both fully human monoclonal antibodies given by subcutaneous injection.

In a trial of 2,341 patients with heterozygous familial hyperlipidemia (HeFH), ASCVD, or a coronary heart disease (CHD) risk equivalent with an LDL-C greater than 70 mg/dL, alirocumab (Praluent®) reduced LDL-C by 60 percent to a mean of 57.9 mg/dl compared to placebo over 78 weeks.[12] Although not designed as an outcomes trials, a post-hoc analysis showed that alirocumab reduced major adverse cardiovascular events (MACE), CHD death, and nonfatal myocardial infarction Myalgia was the only statistically significant adverse event over placebo. There was a slight increase in subjective neurocognitive events with alirocumab (1.2 vs 0.5%); the FDA has mandated that cognitive outcomes be objectively measured in the long-term outcomes studies with PCSK9 inhibitors. The final results from an outcomes trial in those with recent acute coronary syndrome treated with alirocumab should be published in 2018.

Evolocumab (Repatha®) has been shown in a trial of 27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD) with LDL-C over 70 mg/dl on high or moderate intensity statin therapy (± ezetimibe) to reduce LDL-C by a mean of 59 percent and reduced the primary endpoint of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization by 2 percent (15% reduction).[13] The

Exhibit 2: An Evidence-Based Review of Heart-Harmful and Heart-Healthy Diets[8]



median achieved LDL-C was 30 mg/dl. When each of the components of the primary endpoint were examined, there was no difference in CV death, but the study was not specifically powered for this conclusion. It would have been difficult to show a difference in CV death since this was a very stable study population with a low incidence (0.8/year) of CV-related death.

When prior intensive lipid-lowering trials were combined in a meta-analysis, there was no clear benefit on CV mortality (HR 0.96). In a subgroup analysis of the evolocumab trial, there was a 16 percent relative risk reduction (RRR) of CV death, MI, or stroke at 12 months of therapy and a 25 percent RRR at 36 months. These findings illustrate the cumulative effect of continued intensive LDL-C reduction.

Evolocumab was well tolerated in the trials. There were similar rates of adverse events including new onset diabetes and neurocognitive events in both the treatment and placebo groups. The rates of evolocumab discontinuation were low and no greater than those with placebo. No neutralizing antibodies developed, which has been an issue with an investigational PCSK9 inhibitor that is discussed later.

The lack of neurocognitive events with major LDL-C reduction with evolocumab was documented in a cognitive sub-study of the trial previously discussed.[14] The brain synthesizes its own cholesterol locally and should not be impacted by the PCSK9 inhibitors because they are too large to cross the blood-brain barrier. However, a meta-analysis of reported adverse events from six PCSK9 inhibitor trials suggested an increased risk of cognitive events.[15] In the evolocumab cognitive trial, over 20 months, there were no differences between the evolocumab and placebo groups on a battery of cognitive tests, patient reported everyday cognition, nor adverse cognition events reported by physicians. There was no evidence of cognitive events even when LDL-C was reduced below 25 mg/dl.

Bococizumab was another PCSK9 inhibitor under investigation, but the sponsor discontinued development in late 2016. Bococizumab was a 95 percent humanized monoclonal antibody to which antidrug antibodies developed. There was wide individual variation in percent change in LDL-C at 52 weeks with bococizumab, even among those who were antidrug antibody negative, but this agent lead to a 20 percent reduction in CV events.[16,17] The combination of antidrug antibody development and less potent LDL-C reduction than the two already marked agents may have been the reason the manufacturer stopped development of bococizumab.

Inclisiran is an investigational PCSK9 inhibi-

Exhibit 3: Non-Statin Agents with Efficacy in Reducing LDL-C Levels

Drug Class	Agents
Bile Acid sequestrants	Colestipol, Colesevelam, Cholestyramine
Cholesterol absorption inhibitors	Ezetimibe
Fibric acids	Fenofibrate*
Microsomal triglyceride transfer protein inhibitor	Lomitapide+
Nicotinic Acid	Niacin*
Oligonucleotide inhibitor of apo B-100 synthesis	Mipomersen+
Proprotein convertase subtilisin/kexin type 9 (PCSK9) Inhibitors	Alirocumab, Evolocumab

*In April 2016, the FDA withdrew approval of fenofibric acid delayed-release capsules and Niacin extended-release tables in combination with statins due to lack of evidence that coadministration further reduced CV risk.
+FDA-approved as an adjunct to lipid-lowering treatments and diet for people with HoFH.

Exhibit 4: FDA-Approved PCSK9 Inhibitors

Alirocumam

- Indicated as adjunct to diet and is maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL-C.
- Dose: Initiate 75 mg SQ every 2 weeks (the majority of patients achieve sufficient LDL-C reduction with this dosage). If LDL-C response is inadequate, may be increased to 150 mg every 2 weeks.

Evolocumab

- Indicated as as an adjunct to diet and:
  a) Maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercho lesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
  b) Other LDL-C-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
- Dose: ASCVD or HeFH; 140 mg every 2 weeks or 420 mg once monthly. For HoFH: 420 hg once monthly Note: The 420 mg dose can be administered: a) over 9 minutes by using the single-use on-body infusor with prefilled cartridge, or b) by SQ.

tor that inhibits PCSK9 synthesis by RNA interference rather than binding to the receptor. In the early trials presented thus far, it lowers LDL-C by greater than 50 percent compared to placebo and appears safe. This is a very long- acting agent which may be dosed once or twice a year.

It is important to note that lowering LDL-C below 70 mg/dl provides additional benefit in terms of CV risk reduction and is safe. In the past, people were concerned that achieving very low levels would lead to cognitive effects or worse since the body does need a certain amount of cholesterol to produce cell membranes. Individuals with very low LDL-C values (25 mg/dl range) because of specific genetic mutations have been identified, are very healthy, and are protected against CV disease.

Conclusion

Making the decision to add non-statin therapies to maximized statin therapy requires a clinician-patient discussion about the risks and benefits. Ezetimibe added to statins has been shown to improve

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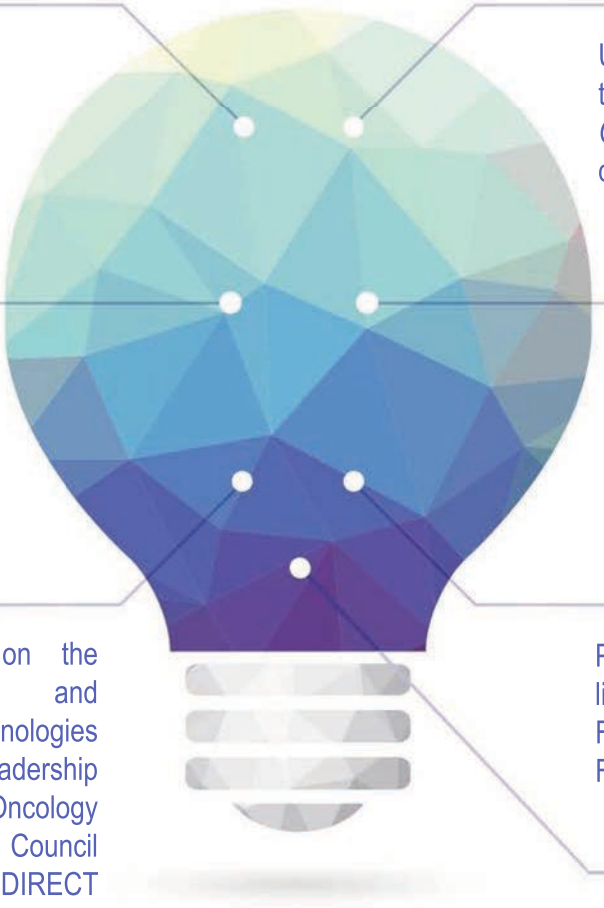

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YES CAR T IS HERE

YESCARTA®, THE FIRST CAR T THERAPY FOR CERTAIN TYPES OF RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA

The following data reflect results from the ZUMA-1 pivotal trial*[1]

// PROVEN EFFICACY

51%

Patients achieved a best response of complete remission (CR) (52/101)

NR

Response duration was not reached at a median follow-up of 7.9 months in patients who achieved CR

// CYTOKINE RELEASE SYNDROME

13%

Grade ≥3 incidence

94%

Overall incidence

// NEUROLOGIC TOXICITIES

31%

Grade ≥3 incidence

87%

Overall incidence

// RAPID & RELIABLE MANUFACTURING

17 DAYS

Median turnaround time†

99%

Manufacturing success of CAR T cells engineered and expanded ex vivo

VISIT **YESCARTAHCP.COM/CENTERS** TO FIND A LIST OF AUTHORIZED TREATMENT CENTERS

*ZUMA-1 was an open-label, single-arm study in 101 adult patients who received YESCARTA® therapy. Patients received lymphodepleting chemotherapy prior to a single infusion of YESCARTA® at a target dose of 2 x 10^6 viable CAR T cells/kg body weight (maximum of 2 x 10^8 viable CAR T cells). Patients had refractory disease to their most recent therapy, or had relapsed within 1 year after autologous hematopoietic stem cell transplantation.

†The median time from leukapheresis to product delivery.

INDICATION

YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA® is not indicated for the treatment of patients with primary central nervous system lymphoma.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®. Do not administer YESCARTA® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA®, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA®. Provide supportive care and/or corticosteroids as needed.**
- **YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS.**

Important Safety Information continued on adjacent page.

YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

IMPORTANT SAFETY INFORMATION (continued)

CYTOKINE RELEASE SYNDROME (CRS): CRS occurred in 94% of patients, including 13% with ≥ Grade 3. Among patients who died after receiving YESCARTA®, 4 had ongoing CRS at death. The median time to onset was 2 days (range: 1-12 days) and median duration was 7 days (range: 2-58 days). Key manifestations include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated.

NEUROLOGIC TOXICITIES: Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks, with a median time to onset of 4 days (range: 1-43 days) and a median duration of 17 days. Grade 3 or higher occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA®. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA®. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly.

YESCARTA® REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA® REMS. The required components of the YESCARTA® REMS are: Healthcare facilities that dispense and administer YESCARTA® must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA® infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA® are trained about the management of CRS and neurologic toxicities. Further information is available at www.YESCARTAREMS.com or 1-844-454-KITE (5483).

HYPERSENSITIVITY REACTIONS: Allergic reactions may occur. Serious hypersensitivity reactions including anaphylaxis may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA®.

SERIOUS INFECTIONS: Severe or life-threatening infections occurred. Infections (all grades) occurred in 38% of patients, and in 23% with ≥ Grade 3. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA® should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA® infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

PROLONGED CYTOPENIAS: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA® infusion. Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA® infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA® infusion.

HYPOGAMMAGLOBULINEMIA: B-cell aplasia and hypogammaglobulinemia can occur. Hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA® treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA® treatment, and until immune recovery following treatment.

SECONDARY MALIGNANCIES: Patients may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Due to the potential for neurologic events, including altered mental status or seizures, patients are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

ADVERSE REACTIONS: The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias.

Please see Brief Summary of Prescribing Information, including BOXED WARNING, on the following pages.

Reference: 1. YESCARTA™ [package insert]. Santa Monica, CA: Kite Pharma; 2017.

Kite
A GILEAD Company
Santa Monica, CA

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR YESCARTA®
(axicabtagene ciloleucel) suspension for intravenous infusion

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)]*.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)]*.**
- **YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

2 DOSAGE AND ADMINISTRATION

2.2 Administration: YESCARTA is for autologous use only. The patient's identity must match the patient identifiers on the YESCARTA cassette and infusion bag. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient *[see Dosage and Administration(2.2.3)]*.

Preparing Patient for YESCARTA Infusion: Confirm availability of YESCARTA prior to starting the lymphodepleting regimen. *Pre-treatment:* Administer a lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of YESCARTA. *Premedication:* Administer acetaminophen 650 mg PO and diphenhydramine 12.5 mg intravenously or PO approximately 1 hour before YESCARTA infusion. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of YESCARTA.

Preparation of YESCARTA for Infusion: Coordinate the timing of YESCARTA thaw and infusion. Confirm the infusion time in advance, and adjust the start time of YESCARTA thaw such that it will be available for infusion when the patient is ready. Confirm patient identity: Prior to YESCARTA preparation, match the patient's identity with the patient identifiers on the YESCARTA cassette. Do not remove the YESCARTA product bag from the cassette if the information on the patient-specific label does not match the intended patient. Once patient identification is confirmed, remove the YESCARTA product bag from the cassette and check that the patient information on the cassette label matches the bag label. Inspect the product bag for any breaches of container integrity such as breaks or cracks before thawing. If the bag is compromised, follow the local guidelines (or call Kite at 1-844-454-KITE). Place the infusion bag inside a second sterile bag per local guidelines. Thaw YESCARTA at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not wash, spin down, and/or re-suspend YESCARTA in new media prior to infusion. Once thawed, YESCARTA may be stored at room temperature (20°C to 25°C) for up to 3 hours.

Administration: For autologous use only. Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period. Do NOT use a leukodepleting filter. Central venous access is recommended for the infusion of YESCARTA. Confirm the patient's identity matches the patient identifiers on the YESCARTA product bag. Prime the tubing with normal saline prior to infusion. Infuse the entire contents of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw. Gently agitate the product bag during YESCARTA infusion to prevent cell clumping. After the entire content of the product bag is infused, rinse the tubing with normal saline at the same infusion rate to ensure all product is delivered. YESCARTA contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases.

Monitoring: Administer YESCARTA at a certified healthcare facility. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome (CRS): Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 1. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

Table 1. CRS Grading and Management Guidance

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity *(b)*.	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours). Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.

(a) Lee et al 2014, (b) Refer to Table 2 for management of neurologic toxicity, (c) Refer to tocilizumab Prescribing Information for details

Neurologic Toxicity: Monitor patients for signs and symptoms of neurologic toxicities (Table 2). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Table 2. Neurologic Toxicity Grading and Management Guidance

Grading Assessment	Concurrent CRS	No Concurrent CRS
Grade 2	Administer tocilizumab per Table 1 for management of Grade 2 CRS. If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above.	Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

4 CONTRAINDICATIONS: None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome (CRS): CRS,including fatal or life-threatening reactions, occurred following treatment with YESCARTA. In Study 1, CRS occurred in 94% (101/108) of patients receiving YESCARTA, including ≥ Grade 3 (Lee grading system) CRS in 13% (14/108) of patients. Among patients who died after receiving YESCARTA, four had ongoing CRS events at the time of death. The median time to onset was 2 days (range: 1 to 12 days) and the median duration of CRS was 7 days (range: 2 to 58 days). Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%). Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS) *[see Adverse Reactions (6)]*. Ensure that 2 doses of tocilizumab are available prior to infusion of YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for 4 weeks after infusion. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling Information (17)]*. At the first sign of CRS, institute treatment with supportive care, tocilizumab or tocilizumab and corticosteroids as indicated *[See Dosage and Administration (2.3)]*.

5.2 Neurologic Toxicities: Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA. Neurologic toxicities occurred in 87% of patients. Ninety-eight percent of all neurologic toxicities occurred within the first 8 weeks of YESCARTA infusion, with a median time to onset of 4 days (range: 1 to 43 days). The median duration of neurologic toxicities was 17 days. Grade 3 or higher neurologic toxicities occurred in 31% of patients. The most common neurologic toxicities included encephalopathy (57%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%) and anxiety (9%). Prolonged encephalopathy lasting up to 173 days was noted. Serious events including leukoencephalopathy and seizures occurred with YESCARTA. Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA. Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of neurologic toxicities. Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly *[see Management of Severe Adverse Reactions (2.3); Neurologic Toxicities]*.

5.3 YESCARTA REMS: Because of the risk of CRS and neurologic toxicities, YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA REMS *[see Boxed Warning and Warnings and Precautions (5.1 and 5.2)]*. The required components of the YESCARTA REMS are:

- Healthcare facilities that dispense and administer YESCARTA must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for infusion within 2 hours after YESCARTA infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer YESCARTA are trained about the management of CRS and neurologic toxicities.

Further information is available at www.YescartaREMS.com or 1-844-454-KITE (5483).

5.4 Hypersensitivity Reactions: Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

5.5 Serious Infections: Severe or life-threatening infections occurred in patients after YESCARTA infusion. In Study 1, infections (all grades) occurred in 38% of patients. Grade 3 or higher infections occurred in 23% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 16% of patients, bacterial infections in 9%, and viral infections in 4%. YESCARTA should not be administered to patients with clinically significant active systemic infections. Monitor patients for signs and symptoms of infection before and after YESCARTA infusion and treat appropriately. Administer prophylactic anti-microbials according to local guidelines. Febrile neutropenia was observed in 36% of patients after YESCARTA infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids and other supportive care as medically indicated. *Viral Reactivation:* Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing.

5.6 Prolonged Cytopenias: Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. In Study 1, Grade 3 or higher cytopenias not resolved by Day 30 following YESCARTA infusion occurred in 28% of patients and included thrombocytopenia (18%), neutropenia (15%), and anemia (3%). Monitor blood counts after YESCARTA infusion.

5.7 Hypogammaglobulinemia: B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with YESCARTA. In Study 1, hypogammaglobulinemia occurred in 15% of patients. Monitor immunoglobulin levels after treatment with YESCARTA and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement. The safety of immunization with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

5.8 Secondary Malignancies: Patients treated with YESCARTA may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Kite at 1-844-454-KITE (5483) to obtain instructions on patient samples to collect for testing.

5.9 Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including altered mental status or seizures, patients receiving YESCARTA are at risk for altered or decreased consciousness or coordination in the 8 weeks following YESCARTA infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, during this initial period.

6 ADVERSE REACTIONS: The following adverse reactions are described in Warnings and Precautions: Cytokine Release Syndrome, Neurologic Toxicities, Hypersensitivity Reactions, Serious Infections, Prolonged Cytopenias, Hypogammaglobulinemia.

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety data described in this section reflect exposure to YESCARTA in the clinical trial (Study 1) in which 108 patients with relapsed/refractory B-cell NHL received CAR-positive T cells based on a recommended dose which was weight-based *[see Clinical Trials (14)]* . Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia) or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 8.7 months. The median age of the study population was 58 years (range: 23 to 76 years); 68% were men. The baseline ECOG performance status was

43% with ECOG 0, and 57% with ECOG 1. The most common adverse reactions (incidence ≥ 20%) include CRS, fever, hypotension, encephalopathy, tachycardia, fatigue, headache, decreased appetite, chills, diarrhea, febrile neutropenia, infections-pathogen unspecified, nausea, hypoxia, tremor, cough, vomiting, dizziness, constipation, and cardiac arrhythmias. Serious adverse reactions occurred in 52% of patients. The most common serious adverse reactions (> 2%) include encephalopathy, fever, lung infection, febrile neutropenia, cardiac arrhythmia, cardiac failure, urinary tract infection, renal insufficiency, aphasia, cardiac arrest, *Clostridium difficile* infection, delirium, hypotension, and hypoxia. The most common (≥ 10%) Grade 3 or higher reactions include febrile neutropenia, fever, CRS, encephalopathy, infections-pathogen unspecified, hypotension, hypoxia, and lung infections. Forty-five percent (49/108) of patients received tocilizumab after infusion of YESCARTA.

Summary of Adverse Reactions Observed in at Least 10% of the Patients Treated with YESCARTA in Study 1

Adverse Reaction		Any Grade (%)	Grades 3 or Higher (%)
Cardiac disorders	Tachycardia	57	2
	Arrhythmia	23	7
Gastrointestinal disorders	Diarrhea	38	4
	Nausea	34	0
	Vomiting	26	1
	Constipation	23	0
	Abdominal pain	14	1
	Dry mouth	11	0
General disorders and administration site conditions	Fever	86	16
	Fatigue	46	3
	Chills	40	0
	Edema	19	1
Immune system disorders	Cytokine release syndrome	94	13
	Hypogammaglobulinemia	15	0
Infections and infestations	Infections-pathogen unspecified	26	16
	Viral infections	16	4
	Bacterial infections	13	9
Investigations	Decreased appetite	44	2
	Weight decreased	16	0
	Dehydration	11	3
Musculoskeletal and connective tissue disorders	Motor dysfunction	19	1
	Pain in extremity	17	2
	Back pain	15	1
	Muscle pain	14	1
	Arthralgia	10	0
Nervous system disorders	Encephalopathy	57	29
	Headache	45	1
	Tremor	31	2
	Dizziness	21	1
	Aphasia	18	6
Psychiatric disorders	Delirium	17	6
Respiratory, thoracic and mediastinal disorders	Hypoxia	32	11
	Cough	30	0
	Dyspnea	19	3
	Pleural effusion	13	2
Renal and urinary disorders	Renal insufficiency	12	5
Vascular disorders	Hypotension	57	15
	Hypertension	15	6
	Thrombosis	10	1

The following events were also counted in the incidence of CRS: tachycardia, arrhythmia, fever, chills, hypoxemia, renal insufficiency, and hypotension. For a complete list of events that contributed to the incidence of certain adverse reactions, please see footnote below Table 3 in Section 6.1 of the Full Prescribing Information.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with YESCARTA include the following: blood and lymphatic system disorders: coagulopathy (2%); cardiac disorders: cardiac failure (6%) and cardiac arrest (4%); immune system disorders: hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS) (1%), hypersensitivity (1%); infections and infestations disorders: fungal infections (5%); nervous system disorders: ataxia (6%), seizure (4%), dyscalculia (2%), and myoclonus (2%); respiratory, thoracic and mediastinal disorders: pulmonary edema (9%); skin and subcutaneous tissue disorders: rash (9%); vascular disorders: capillary leak syndrome (3%).

Grade 3 or 4 Laboratory Abnormalities Occurring in ≥ 10% of Patients in Study 1 Following Treatment with YESCARTA based on CTCAE (N=108)

Lymphopenia 100%, Leukopenia 96%, Neutropenia 93%, Anemia 66%, Thrombocytopenia 58%, Hypophosphatemia 50%, Hyponatremia 19%, Uric acid increased 13%, Direct Bilirubin increased 13%, Hypokalemia 10%, Alanine Aminotransferase increased 10%.

6.2 Immunogenicity: YESCARTA has the potential to induce anti-product antibodies. The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for pre-dose anti-FMC63 antibodies at baseline and Months 1, 3, or 6 in Study 1. There is no evidence that the kinetics of initial expansion and persistence of YESCARTA, or the safety or effectiveness of YESCARTA, was altered in these patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Risk Summary*: There are no available data with YESCARTA use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with YESCARTA to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if YESCARTA has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, and pregnancy after YESCARTA infusion should be discussed with the treating physician. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15% - 20%, respectively.

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

8.3 Females and Males of Reproductive Potential: *Pregnancy Testing*: Pregnancy status of females with reproductive potential should be verified. Sexually-active females of reproductive potential should have a pregnancy test prior to starting treatment with YESCARTA. *Contraception:* See the prescribing information for fludarabine and cyclophosphamide for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy. There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA. *Infertility:* There are no data on the effect of YESCARTA on fertility.

8.4 Pediatric Use: The safety and efficacy of YESCARTA have not been established in pediatric patients.

8.5 Geriatric Use: Clinical trials of YESCARTA did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently or have different safety outcomes as compared to younger patients.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Ensure that patients understand the risk of manufacturing failure (1% in clinical trial). In case of a manufacturing failure, a second manufacturing of YESCARTA may be attempted. In addition, while the patient awaits the product, additional chemotherapy (not the lymphodepletion) may be necessary and may increase the risk of adverse events during the pre-infusion period. Advise patients to seek immediate attention for any of the following: Cytokine Release Syndrome, Neurologic Toxicities, Serious Infections, Prolonged Cytopenia *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.5) and Adverse Reactions (6) for more information and signs and symptoms]*. Advise patients for the need to: Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA infusion until at least 8 weeks after infusion *[see Warnings and Precautions (5.2)]*, Have periodic monitoring of blood counts. Contact Kite at 1-844-454-KITE (5483) if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.8)]*.

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CV outcomes and will likely be the first agent chosen for addition. PCSK9 inhibitors have been evaluated in patients with FH, with high ASCVD risk and not at desirable LDL-C with maximally tolerated statins, and intolerant to statin therapy. In patients with known CV disease, PCSK9 inhibition with evolocumab significantly and safely decreased major CV events when added to statin therapy. The benefit with PCSK9 inhibition was achieved with lowering LDL-C well below current targets. Clinicians await the outcomes results with the long-term alirocumab trial. Overall, for LDL-C lowering, lower than traditional goals are better in terms of outcomes and appears to be safe.

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New Frontiers in Metastatic Melanoma: A Closer Look at the Role of Immunotherapy

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

There have been many advances in melanoma treatment with immunotherapy, but metastatic disease is still considered incurable. Ways to select the most appropriate patients for immunotherapy are needed to maximize the use of these agents.

Key Points

- The goal in treatment of metastatic melanoma with immunotherapy is to optimize efficacy and quality of life while minimizing toxicity and health care expenditures.
- Biomarkers for efficacy and toxicity are needed.
- Ways to overcome molecular and immune resistance mechanisms are needed.

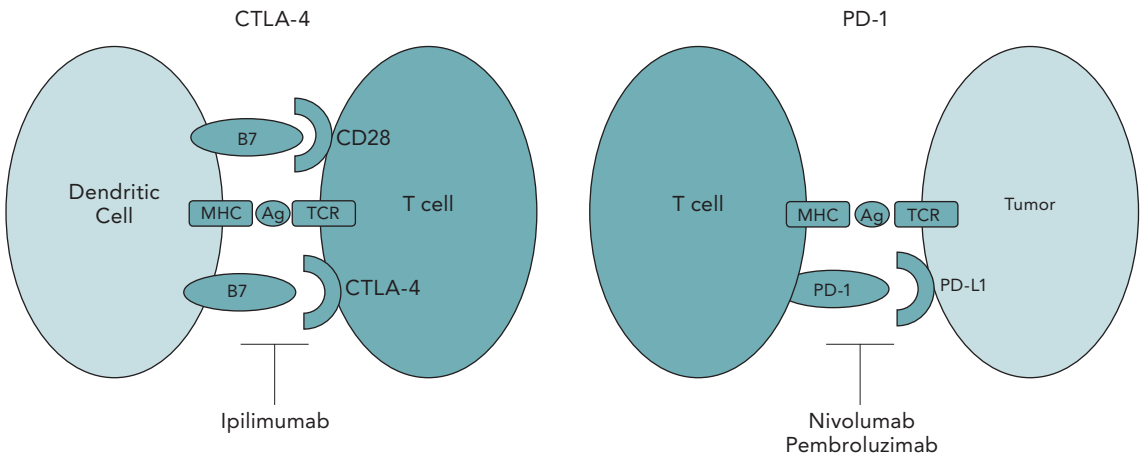
THE AMERICAN CANCER SOCIETY ESTIMATES there will be 91,270 new cases of melanoma diagnosed (about 55,150 in men and 36,120 in women) in the United States (U.S.) in 2018.[1] Approximately 9,320 people are expected to die from this cancer (about 5,990 men and 3,330 women). The rates of melanoma have been rising for the past 30 years, with the lifetime risk one in 34 for women and one in 53 for men. The median age at diagnosis is 59 years old.

It is very important that melanoma be diagnosed at an early stage when a greater than 90 percent cure rate is possible. The five- and 10-year survival rates depend on the stage at diagnosis. Five-year survival varies from 53 percent with Stage IIc (ulcerated lesion greater than 4 mm, no positive lymph nodes) to 15 percent with Stage IV (metastatic) disease. These survival rates are based on therapy with older agents for melanoma, - dacarbazine and interleukin 2 -, which do not provide an overall impact on survival.

Immunotherapy was investigated in melanoma because there have been rare spontaneous immune-based regressions of metastatic melanoma and lymphocytes commonly infiltrate the tumor. There is also evidence of activity of interleukin 2 in Stage IV melanoma and interferon alpha in deep Stage II b/c and Stage III melanoma. As researchers have learned more about how the immune system is regulated, additional agents have been developed which activate the immune system to target cancer cells.

A normal immune system has both activators and suppressors which are in balance. The suppressors have been termed checkpoints, and they prevent the immune system from becoming overactive and attacking self rather than foreign substances. Two clinically relevant immune checkpoints are cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1). Exhibit 1 illustrates how CTLA-4 binds to T cells to dampen T-cell activation and proliferation in order to prevent autoimmune reactions against healthy tissue while the immune system is activated against a pathogen.

Exhibit 1: Clinically Relevant Immune Checkpoints



PD-1 is a cell surface receptor that suppresses T-cell inflammatory activity. It has a dual mechanism of promoting apoptosis (programmed cell death) in antigen-specific T cells in lymph nodes while simultaneously reducing apoptosis in regulatory T cells (anti-inflammatory, suppressive T cells). Blocking the activity of immune checkpoint proteins releases the brakes on the immune system, increasing its ability to destroy cancer cells.

Ipilimumab (Yervoy®), an anti-CTLA-4 antibody, improves survival in patients with metastatic melanoma. Based on 10 prospective and two retrospective ipilimumab melanoma studies, ipilimumab improved median overall survival (OS) by 9.5 months in metastatic disease.[2] With ipilimumab treatment, the survival curve increased from 14 percent of patients surviving three years to 24 percent.[3] This agent is improving the tail end of the survival curve in a subset of patients.

Pembrolizumab (Keytruda®) and nivolumab (Opdivo®) target PD-1. Many melanoma tumor cells express programmed death ligand-1 (PDL-1) on their surface, which binds PD-1 on the T cells and shuts them off. Both pembrolizumab and nivolumab are effective in increasing progression-free survival (PFS) and OS in metastatic melanoma. Pembrolizumab has been compared to ipilimumab in one trial resulting in a better response rate, improved PFS, improved one-year survival, and less high grade toxicity with pembrolizumab.[4] Overall, PD-1 inhibitors appear to be more efficacious than ipilimumab as initial immunotherapy in metastatic melanoma.

It is important to note that immune cell infiltration into tumors occurs with immunotherapy treatment and this appears as tumor enlargement on imaging. Thus, response to immunotherapy cannot be assessed purely based on the size of tumors on imaging. Response measurement needs to incorporate symptomatic response and serial imaging.

The durability of benefit with immunotherapy is not yet known. Five-year survival with nivolumab improves from 15 percent to 34 percent. Longer term survival data will not be available for several years. While PD-1 inhibitor monotherapy is a significant treatment advance, these agents are still only effective in a subset of patients.

There is a scientific rationale for combining checkpoint inhibitors to improve OS. The combination of nivolumab and ipilimumab has been studied.[5] The median PFS was 11.5 months with the combination, 6.9 months with nivolumab, and 2.9 months with ipilimumab. The response rate and median PFS with combination therapy is higher in those with PD-L1 expression, but there is some benefit in those without expression. The combination also improves OS at two years (64% vs 59% and 49%, respectively). Although the combination is more effective than either agent alone, the rate of significant adverse effects is very high.

Immunotherapy causes significant immune-related adverse effects where the immune system begins attacking the body. These include rash, colitis, diarrhea, hepatotoxicity, pneumonitis, hypothyroidism, and hypophysitis. Management of these adverse effects, when moderate to high grade, can be intensive and typically requires high-dose corticosteroids. Hypothyroidism and hypophysitis can be irreversible and will require lifetime hormone replacement.

Exhibit 2: Key Factors to Assess Immunotherapy[2-8]

	Efficacy			Toxicity		Cost	
	RR	12m PFS	Survival	Any AE	Grade 3/4	Wholesale cost per dose*	Estimated Cost per Typical Patient**
Ipilimumab	12%	18%	58% 12m 21% 3yr	86%	27%	$47,238	$158,252
Nivolumab	40%	42%	73% 12m 34% 5yr	82%	16%	$8,634	$103,220
Pembrolizumab	33%	46% 6m	68% 12m	73%	10%	$10,358	Not available
Ipilimumab + Nivolumab	58%	49%	Not available	96%	55%	$50,116	$295,566

RR = response rate; PFS = progression free survival; AE = adverse effect
*100 kg person, 2015 costs
** Using Checkmate 067 study data

Pembrolizumab appears to be the best tolerated of the three available agents.

Overall, immunotherapy has proven benefits in terms of efficacy. A PD-1 inhibitor has higher efficacy and lower rates of toxicity over ipilimumab and thus likely should be the first immunotherapy agent chosen. As this point, combination therapy is not recommended until longer term survival data becomes available.

The hope is that immunotherapy will prevent morbidity of cancer and therefore reduce admissions to the hospital, subsequent systemic therapy or localized therapy such as surgery or radiation procedures, and other interventions that have financial costs. However, there are costs to immunotherapy beyond just the acquisition and administration costs, including the cost of managing treatment-related toxicity and costs related to lack of efficacy in all patients. Exhibit 2 provides an overview of the efficacy, toxicity, wholesale costs, and estimated total yearly costs related to immunotherapy for metastatic melanoma.[6-8] The estimated total yearly costs are derived from clinical trial data on the amounts given and does not include any treatments for adverse events. These therapies are very costly financially for insurers and for patients with high insurance copays. If a patient has a 20 percent insurance copay, they could potentially be paying $60,000 per year for ipilimumab/nivolumab treatment.

Given the enormous costs of immunotherapy, there are two possible strategies to decrease overall costs and improve efficacy. First is to develop effective adjuvant treatment for earlier stage melanoma to prevent recurrence and the development of Stage IV disease. Second is to identify biomarkers predictive of response so that only those likely to respond to immunotherapy receive it.

High-dose interferon is one option for adjuvant treatment in early stage melanoma which appears to improve recurrence-free survival(RFS) and overall survival.[9] Ipilimumab has also been studied as adjuvant therapy in resected Stage III melanoma for up to three years.[10] Significant prolongation of RFS, five-year survival, and median distant metastasis-free survival have been shown over placebo. Of course, this is a costly intervention in terms of adverse effects and overall financial costs (estimated at $629,840 for 12 weeks of therapy).

Talimogene laherparepvec (TVEC, Imlygic®) is another adjuvant option. It is an intratumorally delivered oncolytic immunotherapy. In this case, it is a herpes virus that has the gene for granulocyte-macrophage colony-stimulating factor (GM-CSF) production inserted into the viral genome. The virus has also been modified to selectively replicate in solid tumors. It has a dual mechanism of action of direct oncolytic effect by viral replication in the tumor leading to tumor cell lysis and an antitumor response in producing GM-CSF in the tumor micro-environment leading to a systemic immune response. It improved survival in patients with Stage III unresectable melanoma.[11] This agent is FDA indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Combination therapy may also be an option in

earlier disease to prevent Stage IV disease. Combinations of checkpoint inhibitors, checkpoint inhibitors with TVEC, checkpoint inhibitors with tumor microenvironment modulators (anti-vascular agents; indoleamine 2,3 dioxygenase inhibitors), or checkpoint inhibitors and targeted therapy are all possibilities that are being studied.

Biomarkers of immunotherapy efficacy can be used to ensure that only those who are likely to respond will receive this expensive therapy. Biomarkers can be used to optimize treatment planning, limit toxicity risk, and improve health care expenditures. The ideal biomarker would be easily obtained with minimal risk to the patient and obtained pretreatment. Biomarkers can be blood or tumor based. Blood biomarkers include neutrophil/lymphocyte ratio, effector to suppressor T-cell ratio, and CTLA-4 polymorphisms. PD-L1 expression, tumor infiltrating lymphocytes (TILs), and mutation burden are tumor-based biomarkers. At this time, PD-L1 expression is being measured and used as a biomarker for PD-1 immunotherapy. No biomarker is widely in use for ipilimumab therapy.

Conclusion

Immunotherapy is leading to dramatic advances in managing metastatic melanoma. Biomarkers for efficacy and toxicity are needed and so are ways to overcome molecular and immune resistance mechanisms in order that more patients can benefit. The goal in treatment of metastatic melanoma with immunotherapy is to optimize efficacy and quality of life while minimizing toxicity and health care expenditure.

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Understanding Appropriate Treatments to Prevent and Manage Chemotherapy-Induced Nausea and Vomiting.

Aminah Jatoi, MD

For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title.
This activity is supported by educational grants from Eisai and Merck & Co.

Summary

Although therapies are available to manage chemotherapy-induced nausea and vomiting (CINV), they are not effective in everyone. Following the CINV prevention and management guidelines can improve management; however, better medications are needed.

Key Points

- Antiemetic combinations are effective in 80 percent of patients, if used appropriately.
- The 80 percent ceiling effect can be improved upon by better drugs but also, importantly, by better guideline adherence.
- NEPA, olanzapine, and sustained-release granisetron are newer agents.
- Improving adherence to guidelines appears to improve outcomes.

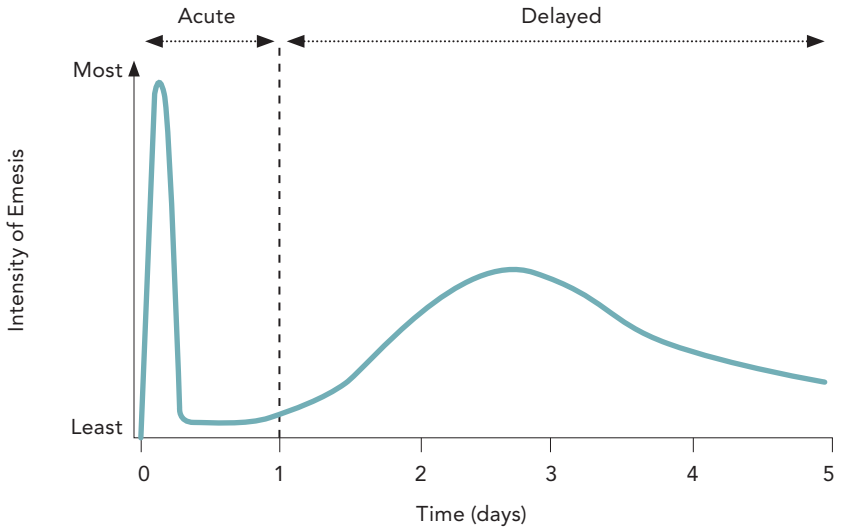
CHEMOTHERAPY, WHICH IS STILL COMmonly used to treat cancer, commonly causes nausea and vomiting. Chemotherapy-induced nausea and vomiting (CINV) is a major concern for patients.

Chemotherapy can be divided into emetic risk groups, ranging from high where 90 percent or more of patients given this agent will have CINV to minimal where less than 10 percent of patients are at risk. This classification system serves as a framework for antiemetic treatment guidelines. Cisplatin is an example of a high-risk agent. Moderate-risk agents (30-90% rates of CINV) include oxaliplatin and ifosfamide. Low-risk (10-30%) agents include paclitaxel and 5-fluorouracil. Minimal-risk agents (< 10%) include vincristine and bleomycin. It is important to classify the emetogenic potential of the chemotherapy regimen that a patient will receive and then to choose an appropriate regimen to control CINV.

The time development of CINV is also important. CINV may be classified as acute (beginning within the first 24 hours after chemotherapy), delayed (beginning more than 24 hours after chemotherapy), or anticipatory (beginning before acute chemotherapy-related symptoms would be expected to occur). Exhibit 1 shows the time course of CINV with cisplatin.[1] Anticipatory CINV tends to occur in patients who have not had adequate CINV control upfront. Adequate prevention and treatment of CINV with the very first chemotherapy cycle is important for preventing the development of anticipatory CINV. Regimens for CINV have to cover both acute and delayed phases. Patients need to understand that medications need to be taken for several days to prevent the delayed phase.

CINV appears to occur via two different mechanisms—one is located in the central nervous system

Exhibit 1: Time Course of CINV with Cisplatin[1]



(central), and the other is mediated in the GI tract (peripheral) (Exhibit 2).[2] The central mechanism is hypothesized to occur by activation of the chemotherapy trigger zone (CTZ) by a chemotherapeutic agent.. Once activated, the CTZ releases multiple neurotransmitters (serotonin, substance P, dopamine), which in turn activate the brainstem vomiting center. The peripheral mechanism is postulated to occur by a chemotherapeutic agent causing release of serotonin or substance P from the enterochromaffin cells. This then activates receptors in the GI tract, which are mediated by afferent fibers of the vagus nerve. The activated vagal afferent fibers send signals to the brainstem vomiting center. In both instances, the neurotransmitters may act independently or in combination to induce vomiting. Some chemotherapeutic agents activate both the central and peripheral mechanisms.

The main categories of antiemetic agents used are serotonin (5-HT3) antagonists (ondansetron, granisetron, palonosetron), neurokinin 1 (NK1) receptor antagonists (aprepitant, fosaprepitant), and corticosteroids (dexamethasone) (Exhibit 3). The serotonin antagonists are effective for both acute and delayed CINV, with palonosetron being the most effective for delayed CINV. The NK1 receptor antagonists block the binding of substance P in the brain and are effective for delayed CINV. The mechanism by which corticosteroids work in preventing nausea and vomiting are unknown, but studies have shown dexamethasone to be very effective for acute, delayed, and breakthrough CINV. Dexamethasone has a potentiating effect with 5-HT3 and NK1 agents. Dopamine antagonists are also used for breakthrough CINV.

The National Comprehensive Cancer Care Network (NCCN) publishes guidelines on managing CINV based on evidence and emetogenic potential of regimens.[3] For highly emetogenic chemotherapy, a 5-HT3 receptor antagonist, a NK1R antagonist, and dexamethasone is best. For moderately emetogenic chemotherapy, a 5-HT3 receptor antagonist and dexamethasone provides control. For patients receiving low-risk chemotherapy, dexamethasone as a single 8 mg dose provides control. An alternative is prochlorperazine. For high-risk patients who do not receive adequate control, the addition of olanzapine can be considered. Anticipatory nausea and vomiting is best prevented by effectively preventing chemotherapy-induced nausea; benzodiazepines can be used if it occurs. Palonosetron is better than other 5-HT3 receptor antagonists for delayed nausea and vomiting.[4]

A patient with a history of nausea and vomiting from other sources has a higher risk of CINV.[5] These patients may need more aggressive regimens than what is recommended by the guidelines.

Antiemetic guideline adherence leads to better symptom control, so adherence is very important.[6] System-based changes, which automatically order the appropriate antiemetic regimens based on a given chemotherapy regimen, can go a long way to increasing guideline adherence. Unfortunately, the antiemetic regimens currently available have a ceiling effect; only 80 percent of patients will

Exhibit 2: How CINV Occurs

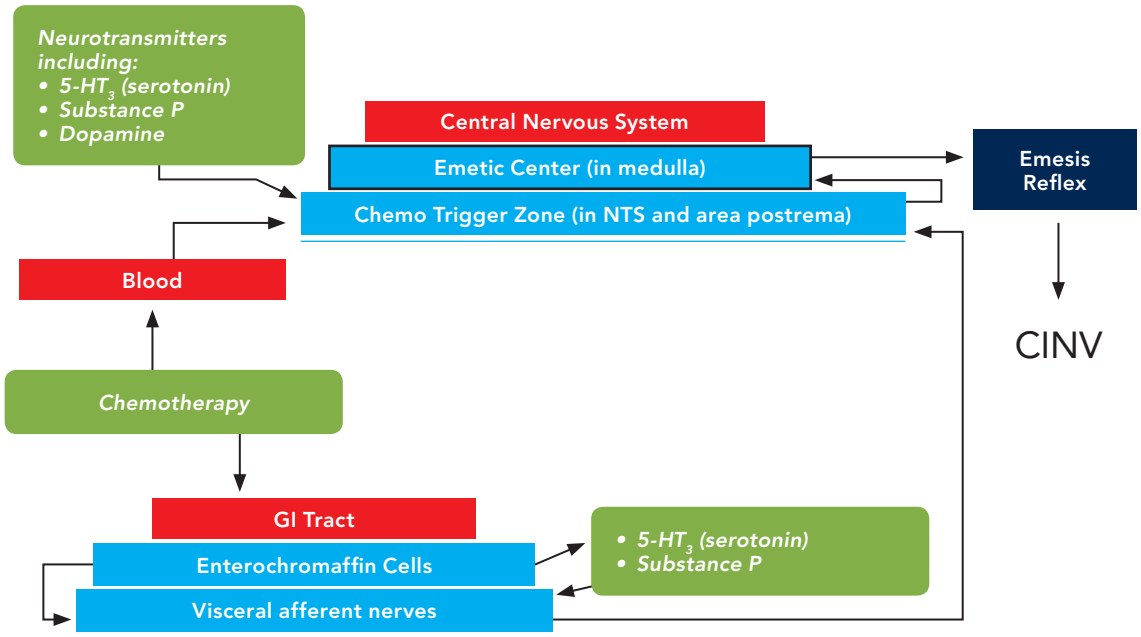


Exhibit 3

Class (Drugs)	Target/MOA	Primary Role in CINV
5-HT_3 receptor agonists (dolasetron/ondansetron/granisetron/ palonosetron	Blocks binding of serotonin	Acute CINV (day 1) Delayed CINV (days 2 - 5) palonosetron only
NK_1 receptor argonists (aprepitant/fosaprepitant) ADD netupitant, rolipitant	Blocks binding of substance P	Delayed
Dopamine antagonists • Phenothiazines (prochlorperazine[b]) • Substituted benzamides (e.g. metoclopramide[a]) • Butyrophenones (e.g. halopendol[a])	Blocks binding of dopamine	Breakthrough
Corticosteroids (e.g. dexamethasone)	Unknown	Acute[a] and delayed[b]

have adequate control, even when guidelines are followed. Better control of nausea and vomiting hinges on further drug development leading to better medications.

Newer agents for CINV are NEPA, olanzapine, and extended-release granisetron. NEPA (Akynzeo®) is an oral combination of netupitant (NK1 receptor antagonist) and palonosetron. Because these two agents have a very long duration of activity, NEPA is only given once on the day of chemotherapy. NEPA combined with dexamethasone is better than oral palonosetron and dexamethasone.[7] Key findings from three pivotal trials of fixed-dose NEPA showed the novel combination to be more effective than oral palonosetron alone in patients receiving moderately and highly

emetogenic chemotherapy. NEPA is consistently effective across multiple cycles of chemotherapy and effective in preventing CINV in patients receiving cisplatin and regardless of which agent is partnered with cisplatin.[8]

Olanzapine, an antipsychotic that blocks multiple neurotransmitters (dopaminergic, serotonergic, muscarinic, and other receptors), has been investigated for CINV because of its effect on increasing appetite. Olanzapine 10 mg is more effective than placebo in reducing CINV from highly emetogenic chemotherapy.[9] Efficacy results suggest this agent could be added to standard antiemetic regimens to augment palliation and is included in the guidelines as an option. With short-term use for CINV, the major adverse effect of olanzapine is sedation, with about 20 percent of patients having moderate to severe sedation. Importantly, it has been recognized that acute benzodiazepine toxicity can be exacerbated by olanzapine.[10]

Extended-release granisetron (Sustol®) is a newer formulation of an older agent. It has been compared to palonosetron injection and was found to be comparable based on the proportion of patients with complete response (no vomiting and no use of rescue medication during the acute phase (0 to 24 hours) and the delayed phase (> 24 to 120 hours) following the administration of chemotherapy in cycle 1) of moderate and highly emetogenic chemotherapy. The issue with using granisetron is prolongation of the QT interval.

Conclusion

If used appropriately, antiemetic combinations are effective in 80 percent of patients. The 80 percent ceiling effect can be improved upon by better medications but also, importantly, by better guideline adherence. NEPA, olanzapine, and sustained-release granisetron are newer treatment options. Improving adherence to guidelines is important for improving outcomes in CINV prevention.

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Recent Barriers and Future Insights of Biosimilars

Steven R. Feldman, MD, PhD

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

Biologics have revolutionized treatment of many diseases and now biosimilars for various biologics have been approved by the FDA. The approval process of these agents is rigorous and produces biologically similar products, which clinicians can prescribe with confidence.

Key Points

- Biologics cannot be duplicated.
- Innovator biologics change over time with changes in the manufacturing process.
- Biosimilars undergo a rigorous approval process.

BIOLOGICS ARE VERY EFFECTIVE AND SAFE, but they are very costly. They have revolutionized the treatment of rheumatoid arthritis, psoriasis, and many other diseases. In the search for reducing costs, manufacturers have sought to produce "generic" biologics or biosimilars. Compared with traditional small molecules, biologic monoclonal antibodies are very large complex molecules that cannot be duplicated exactly (Exhibit 1) and have a complicated production process (Exhibit 2).

A biosimilar is a biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product (innovator product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biologic activity, safety, and efficacy based on a comprehensive comparability exercise. Biosimilarity means "that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product".

Biosimilars will reduce costs, but there is still uncertainty about these products. This uncertainty can be summarized with the questions in Exhibit 3. Some of concerns with biosimilars come from cases of red cell aplasia from erythropoietin, when minor changes in production and storage in one brand occurred.

To address the concerns outlined in Exhibit 3, some facts about biologics and biosimilars should be reviewed. The manufacturing process of bio-

Exhibit 1: Complexity of Biologics

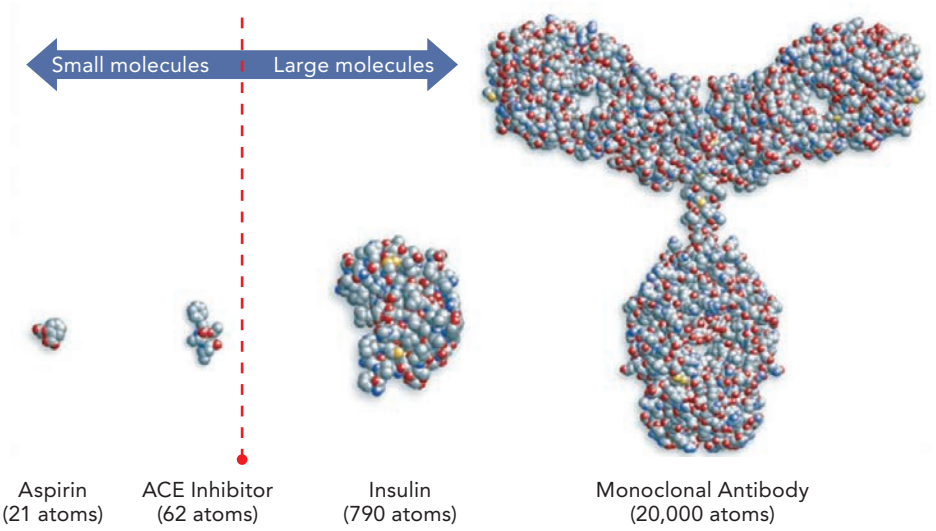
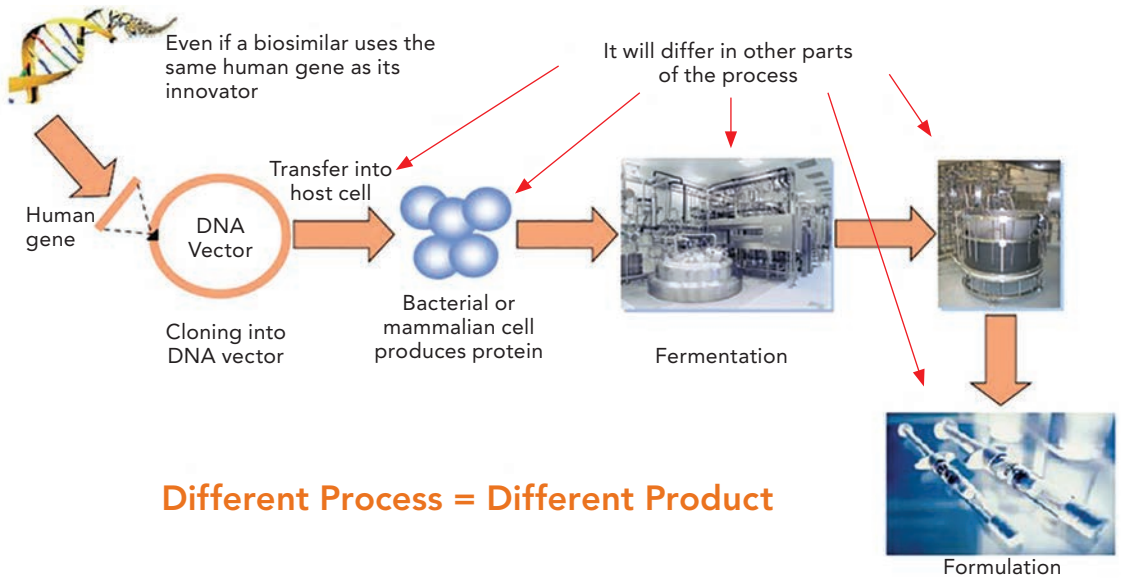


Exhibit 2: Process of Making Biologics



logics changes over time. Multiple process changes over time have occurred for adalimumab (15), etanercept (20), and infliximab (35). A small variation with each one may not matter much, but it is unknown how much effect there is after many changes. Additionally, innovator products have been shown to change from batch-to-batch and so will biosimilars. For example, significant variation in etanercept (Enbrel®) and adalimumab (Humira®) have been shown from batch-to-batch.[1,2]

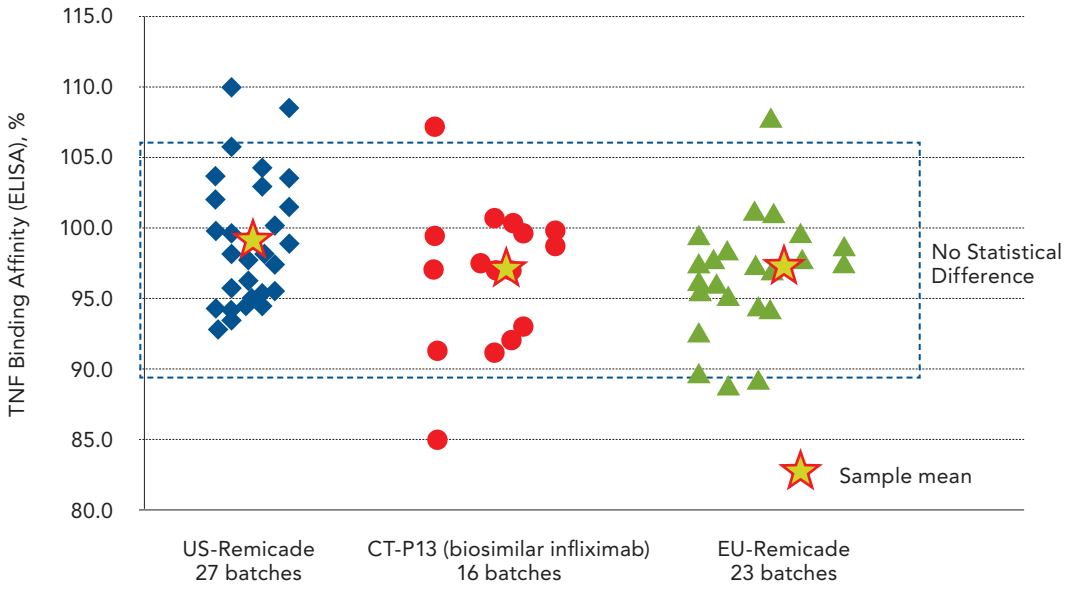
FDA approved biosimilars have statistically equivalent primary structure. This has been of the innovator and biosimilar have been shown to be with infliximab (Remicade®) and the biosimilar infliximab (Exhibit 4).[3]

Overall, the innovator is composed of many different variations of the same molecule and varies over time. There are no head-to-head clinical trials

Exhibit 3: Questions and Answers

- Will clinicians be comfortable prescribing a biosimilar that is not identical to the original drug?
  - "The innovator" has changed from what was originally FDA approved. Clinicians need to understand both are similar enough.
- Will clinicians accept patients being switched from originator to biosimilar without direct approval?
  - Patients switch from one batch of innovator to another, and no one cares.
- Will clinicians be satisfied if biosimilars are tested in patients with one disease but not all for which a product is FDA approved?
  - We are satisfied with even less, as new versions of the innovator have not been studied in clinical trials at all.
- Will clinicians be comfortable with potential differences in immunogenicity, safety and efficacy?
  - There is uncertainty about changes in the innovator, but clinicians don't pay it any mind at all.
  - Biosimilars are shown to not be different in these areas.
- Will clinicians be comfortable with the biosimilar using the same generic name that the originator drug uses?
  - We don't require or expect different batches of the innovator to have different names.

Exhibit 4: Statistical Equivalence in Biological Activity TNFα Binding Affinity[3]



showing equivalency of the various batches of innovators over time, but they still seem to be effective and clinicians are comfortable with this. The same is expected for biosimilars.

The pathway to FDA biosimilar approval is extensive. Extensive studies of analytics for biochemical and structural similarity, in vitro binding/potency, pharmacokinetics, pharmacodynamics, immunogenicity, and clinical trials for safety/efficacy are required. Numerous preclinical studies are required to show remarkable similarity and equivalent functional effects. At least one clinical trial for efficacy within an equivalence margin comparing the biosimilar to the innovator must be done. For example, the adalimumab biosimilar has been shown to have an overlapping pharmacokinetic profile with the innovator and equivalent efficacy in rheumatoid arthritis and plaque psoriasis.[4] Biosimilar infliximab has been shown to be equivalent to Remicade for anti-drug antibody development and efficacy.[5]

There may only be a clinical trial done for one disease indication for a given biosimilar. Clinicians should expect the biosimilar to work in all the indications for which the innovator is FDA approved because of the structural similarity and equivalent potency and pharmacokinetics. It is important that the clinical trial be done in the most sensitive disease in order to identify any real differences. The variants in the innovator do not provide even that much evidence because they have not actually been studied. As shown in Exhibit 3, all of the clinicians' concerns about biosimilars can be shown to not be an issue and that biosimilars are safe and effective.

The most important issue when using a biologic or a biosimilar is what the patient is doing with the agent at home. There are many things that the patient may do with the product that has more impact on the product than whether it is a biosimilar. They may be storing it incorrectly, shaking it, freezing it, or it was delivered to their hot mail box in the summer. Nonadherence is also a major issue in the use of biologic/biosimilars that trumps any variation between the two products.

Conclusion

Biologics are effective, safe, and cannot be duplicated. Current innovator products are not the same as the originals and clinicians should be comfortable with that. Biosimilars will give clinicians even more data – far more data – to support being more comfortable than they are now.

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Advanced Insights into the Prevention, Treatment and Management of Alzheimer's Disease

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For a CME/CNE version of this article, please go to http://namcp.org/home/education, and then click the activity title.
This activity is supported by educational grants from Avanir and Biogen.

Summary

Although there are medications approved for managing Alzheimer's disease (AD), none of these alter the destruction caused by the disease. The best way to reduce the burden of dementia overall is to prevent it from occurring. Managing cardiovascular disease risk factors is the most important for prevention.

Key Points

- Diagnosis of AD is still difficult.
- Nonpharmacologic interventions and medications can be used to manage behavioral issues.
- The medications approved for AD treatment are modestly beneficial before the last stages of the disease.
- Managing cardiovascular disease risk factors is important in AD prevention.
- A great deal of research is ongoing into noninvasive diagnostic tests and biomarkers and preventive treatments.

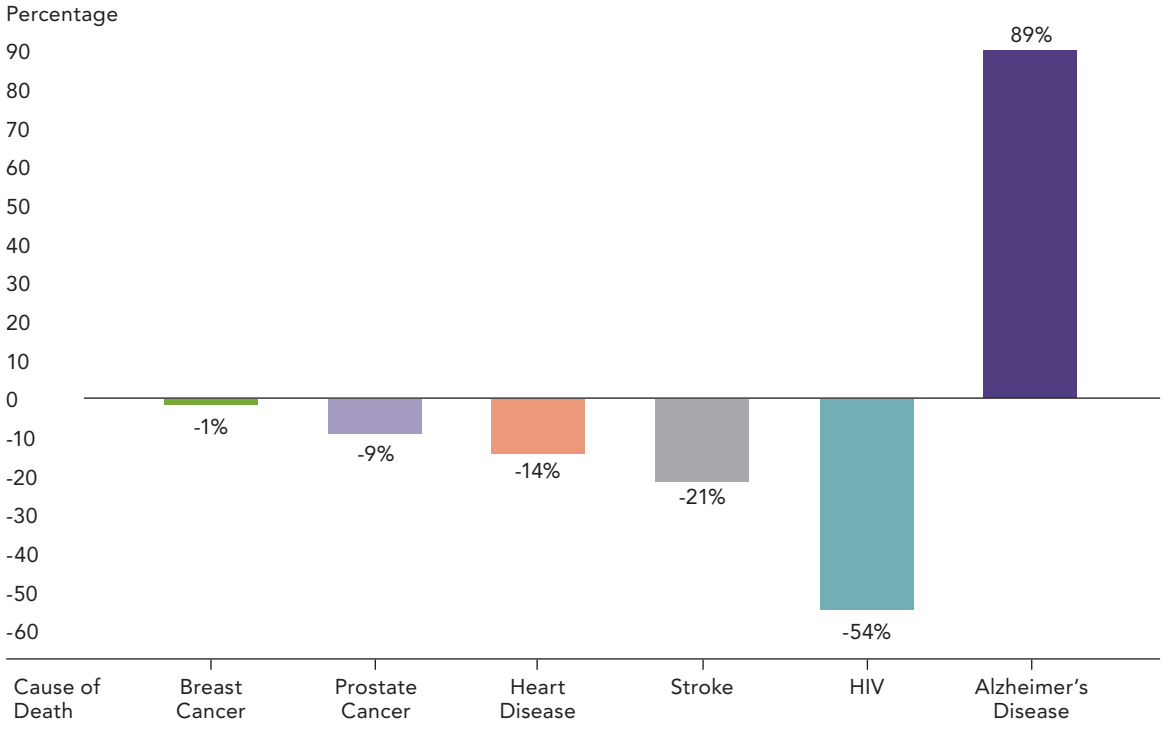
ALZHEIMER'S DISEASE (AD) IS AN ENORmous public health issue. The number of people projected to have Alzheimer's disease (AD) in the United States (U.S.) is expected to increase from 5.6 million currently to 13.8 million by 2050 because of our aging population.[1] From the time of diagnosis, those affected can live four to eight years or more. With the increasing prevalence of this disease, there is also an increasing death rate from AD. Between 2000 and 2014, the death rate from Alzheimer's disease rose 89 percent, whereas deaths from other common diseases declined (Exhibit 1).[2,3]

The cost of caring for someone with Alzheimer's disease is tremendous. In 2017, the total health care costs were estimated to be $259 billion, with 68 percent of these costs paid for by public money (Medicare and Medicaid).[1] Caring for someone with AD, who also has other chronic diseases such as heart failure or diabetes, is also more expensive than caring for someone without AD. As a country, we are not ready to manage the exploding AD population in terms of health care, housing, cost, and social impact.

Dementia generally begins with memory issues. Many people may have subjective memory complaints but they have no cognitive or functional deficits, and this is not a disease. In mild cognitive impairment (MCI), there are memory complaints and some cognitive deficits, but no functional deficits. Dementia, including AD, is a combination of cognitive and functional deficits.

The Alzheimer's Association recommends incorporating assessment of cognition during annual

Exhibit 1: Percentage Changes in Selected Causes of Death (all ages) Between 2000 and 2014[2,3]



wellness visits, which are paid for by Medicare in the over 65 population, in order to detect changes as soon as possible.[4] Annual unstructured (patient and informant based) and structured cognitive assessments can be used to monitor for significant changes in cognition. Observation by clinicians and associated staff are also important in detecting changes. This annual assessment can potentially lead to a new diagnosis of dementia for those with MCI or new recommendations for medical and overall care for those with dementia. Clinicians can explain to patients that this is something they do for all older patients as part of their annual visit.

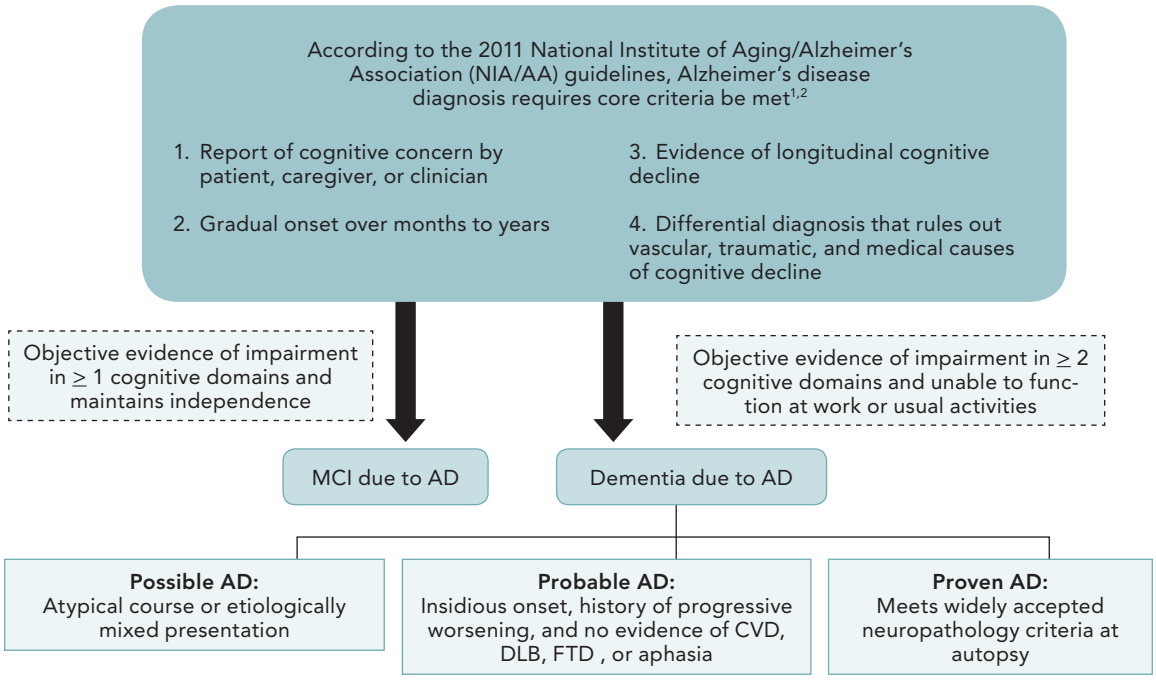
Dementia can be diagnosed in primary care. A two-visit approach is a time-effective process to evaluate suspected dementia in primary care. The first visit can include a complete medical history, a physical and neurological exam, an assessment for depression which can masquerade as cognitive impairment, exclusion of delirium, and a review for medications that affect cognition. The second visit includes assessment of multiple cognitive domains, activities of daily living (ADL) and independent ADL (IADL) functioning, and standard laboratory tests. Standard laboratory tests include thyroid-stimulating hormone, complete blood count, serum B12 and folate, complete metabolic panel, and testing for sexually transmitted diseases (HIV, syphilis) if at risk. Referral for structural brain imaging and neuropsychological testing may also be indicated. Structural brain imaging, including MRI or CT, is a supplemental aid in the differential diagnosis of

Exhibit 2: Causes of Cognitive Impairment[5,6]

Causes of cognitive impairment include

- Depression
- Delirium (e.g., infection)
- Thyroid dysfunction/ B12 deficiency
- Vascular dementia/stroke
- Parkinson's disease
- Lewy body dementia
- Frontotemporal dementia
- Alzheimer's disease
- Normal pressure hydrocephalus
- Substance or alcohol abuse
- Wernicke-Korsakoff's syndrome
- Creutzfeld-Jakob's disease
- Tumor
- HIV related dementia
- Sleep deprivation/disorder

Exhibit 3: NIA/AA Core Clinical Criteria of Alzheimer's Disease Diagnosis[10,11]



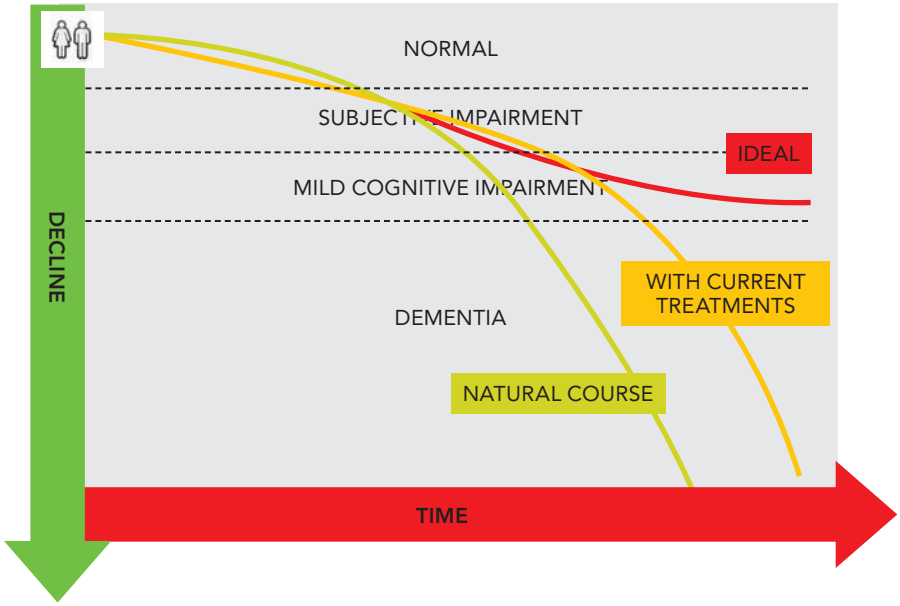
dementia, especially if abnormal neurologic findings are noted. These imaging studies are especially informative in dementia of recent onset and in progressive, younger onset dementia (<65 years of age), history of head trauma, or neurologic symptoms suggesting focal disease.[4]

Differentiating AD from other causes of cognitive impairment is challenging. Exhibit 2 lists the various causes of cognitive impairment.[5,6] MCI can be confused with normal aging.[5] Differentiating degenerative or vascular etiologies from reversible ones such as vitamin deficiency is important.[6] Patients often present with multiple comorbidities, which can contribute to confusion about their diagnoses.[5] About one in five patients with AD dementia diagnoses by experts do not actually have AD.[7-9]

The National Institute of Aging/Alzheimer's Association core criteria for diagnosis of all-cause dementia requires cognitive or neuropsychiatric symptoms that interfere with the ability to function at work or at usual activities, represent a decline in patient's level of functioning, cannot be explained by delirium or a major psychiatric disorder, and involve a minimum of two of the following domains: ability to acquire and remember new information; reasoning and handling of complex tasks, and judgment; visuospatial abilities; language functions; and changes in personality or behavior (Exhibit 3).[10, 11] Examples of problems with ability to acquire and remember new information includes misplacing items, forgetting appointments, and getting lost on a familiar route. Issues with reasoning and handling of complex tasks, and judgment can be demonstrated by poor decision-making ability and poor understanding of safety risks. Visuospatial ability difficulties include the inability to recognize faces or objects and inability to orient clothing on the body. Language difficulties include problems thinking of common words while speaking, along with speech, spelling, and writing errors. Changes in personality and behavior are demonstrated by uncharacteristic mood fluctuations, apathy, social withdrawal, and socially unacceptable behaviors. Specifically for AD, the onset of symptoms is gradual and occurs over years. A rapid decline in cognitive function is not AD. AD diagnosis is divided into MCI due to AD, possible AD, probable AD, and proven AD. Unfortunately, proven AD can only be diagnosed on autopsy.

The goals of treatment of AD are to improve or preserve ADL function; reduce caregiver burden; enhance quality of life, create a safe environment and increase social engagement; improve or preserve cognitive function; enhance mood and behavior; slow deterioration; and manage psychiatric and behavioral symptoms. Exhibit 4 illustrates the natural course of dementia and where we are today with current treatments. Current treatments are

Exhibit 4: Treatment



not ideal because they only slow the decline and do not slow neuronal loss or destruction.

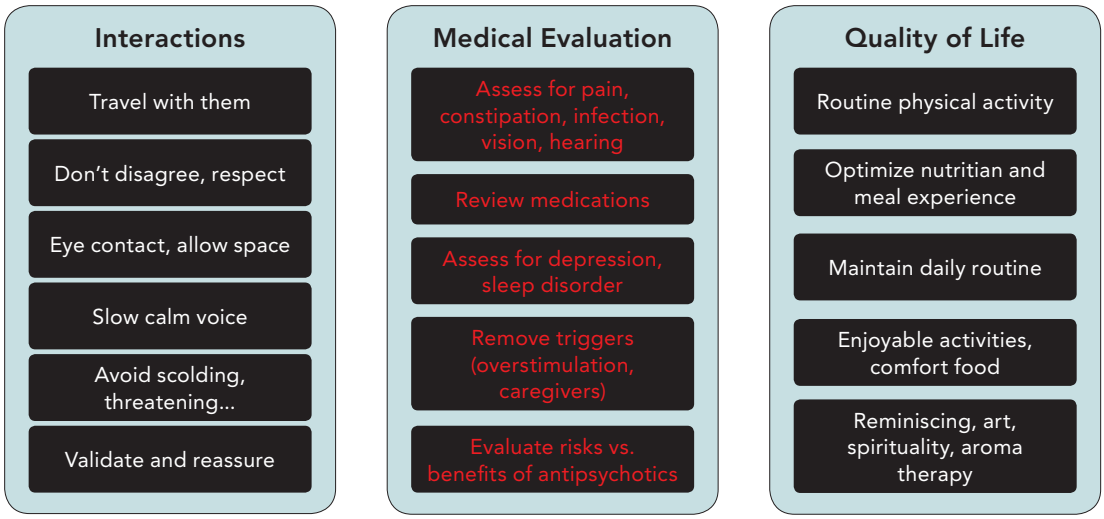
Four agents are FDA approved for AD including three cholinesterase inhibitors [donepezil (Aricept®), galantamine (Razadyne®), and rivastigmine (Exelon®)] and a NMDA receptor antagonist [memantine (Namenda®)]. These all have different indications for various stages of the disease and a combination of memantine/donepezil (Namzaric®) is available. These medications modestly improve cognitive function. Some studies have shown that they can delay the time to nursing home placement. Generally, in the late stages of disease, these medications should be stopped.

Ninety percent of individuals with dementia will develop at least one behavioral and psychological symptoms of dementia (BPSD). These symptoms include depression, hallucinations, agitation, aggression, wandering, and "sun-downing" and they are commonly manifested in moderate to severe disease. These symptoms lead to significant caregiver stress and frustration and are often the breaking point, leading to institutionalization. BPSDs are also often the impetus for weight loss, falls, infection, and incontinence. Exhibit 5 lists the various nonpharmacologic interventions which can be utilized before resorting to medication to treat BPSD

There are no FDA approved treatments for BPSD, but antipsychotics, antidepressants and anticonvulsants are used off label. There is benefit with antipsychotics for aggression, but this has to be balanced against the adverse effects. Seventeen placebo-controlled trials with antipsychotics showed significant benefit in aggression at 12 weeks, but also showed a 1.6 to 1.7-fold increased risk for mortality, primarily secondary to infections and cardiovascular causes.[12,13] Other adverse effects include neuroleptic malignant syndrome, extrapyramidal symptoms, cerebral adverse events, falls, sedation, QTc prolongation, and sudden death. First-generation antipsychotics such as haloperidol are felt to have equivalent risks as second-generation agents. The FDA weighed in that treatment of behavioral disorders with antipsychotics is associated with increased mortality and all antipsychotics have a black box warning about this. Benzodiazepines are sometimes used instead, but they also cause significant adverse effects, including depression, confusion, stroke/cerebral adverse events, falls/fractures, sleep disturbance, and delirium. Medication can be considered if BPSD poses a greater risk to individuals and families than the adverse effects to the patient. The lowest possible dose of any medication for BPSD should be prescribed. Nursing home antipsychotic use can be reduced using a large-scale communication training program.[14]

Prevention of dementia is an important intervention for the general population. Managing cardiovascular risk and stroke prevention throughout one's lifespan is the most effective intervention. Many factors that increase the risk of cardiovascular disease

Exhibit 5: Non-Pharmacological Approaches for Behavioral and Psychotic Symptoms of Dementia



are also associated with a higher risk of dementia including smoking, obesity in midlife, and diabetes.[15,16] Hypertension and high cholesterol in midlife are also implicated as risk factors.

Diabetes is an especially important risk factor. Overall, the incidence of dementia is increased by 50 to 100 percent, relative to people without diabetes (CV factors were not controlled in all trials).[17] There was an increased risk of AD by 50 to 100 percent and an increased risk of vascular dementia by 100 to 150 percent in those with diabetes. Diabetes likely increases risk through multiple mechanisms including macrovascular disease leading to vascular dementia, microvascular disease and direct damage to CNS from hyperglycemia leading to mixed dementia, and inflammation secondary to insulin resistance leading to Alzheimer's disease.[18] There is some evidence that impaired glucose tolerance (a precursor to diabetes) may also result in an increased risk.

Conversely, factors that protect the heart may also protect the brain and reduce the risk of developing AD or other dementias. These include weight loss, physical activity, and consuming a diet lower in saturated fats.

The characteristic pathologic finding in the brain with AD are plaques (clumped beta-amyloid protein) and tangles (collapsed tau protein). Brain changes associated with AD may begin up to 20 years before symptoms are evident.[19] Researchers are searching for a noninvasive method to identify the pathology to ease the diagnosis and identify earlier disease. AD is associated with reduced glucose uptake in brain areas important for memory, learning and problem solving, which can be seen with PET scanning with fluorodeoxyglucose (FDG –PET). However, patterns of reduced activity have not been shown to provide diagnostic information in a given individual.

Molecular imaging is the most active area of research and may provide biological clues to disease before changes in brain structure and function affect memory. Four compounds are currently approved for highlighting deposits of beta-amyloid (PiB, Florbetaben, Florbetapir, and Flutemetamol). This imaging may help monitor disease progression and effectiveness of next generation disease-modifying treatments. Beta-amyloid imaging is indicated for select patients including those with persistent or progressive unexplained MCI, those satisfying core clinical criteria for possible AD, and those with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age).[20] Amyloid imaging is inappropriate in the following situations: patients with core clinical criteria for probable AD with typical age of onset, to determine dementia severity, based solely on a positive family history of dementia or presence of apolipoprotein E (APOE) mutations, patients with a cognitive complaint that is unconfirmed on clinical examination, and in lieu of genotyping for suspected autosomal mutation carriers.

Cerebral spinal fluid (CSF) biomarkers may eventually be used to complement the diagnosis of AD; however, at this time, these are primarily used in research trials. Overall, the accuracy is greatest when CSF biomarkers are used to discriminate AD from normal controls. Biomarker ratios have higher ac-

curacy than single biomarkers. Phosphorylated Tau (pTau) was significantly more accurate than 42-residue isoform of beta amyloid (Ab42) and Tau, in discriminating AD from non-AD dementias. The consensus of a meta-analysis of the trials found that changes in Ab42, Tau, and pTau allow diagnosis of AD in its prodromal stage; if all three are normal, AD is ruled out.[21] The problem with CSF biomarkers is measurement variability. The Alzheimer's Association has funded a quality control program for these biomarkers.

There are a large number of ongoing trials that are continuing to look for effective treatments and prevention. A few are highlighted here. A trial is studying the effectiveness of solanezumab, a monoclonal antibody targeting beta-amyloid, in asymptomatic individuals with high levels of amyloid on PET scans. Another trail will explore use of pioglitazone to reduce insulin resistance in 3,500 asymptomatic individuals with genetic mutations for AD. The Alzheimer's Prevention Initiative (API) will be testing the treatment of gene mutation positive people with crenezumab, an antibody against beta-amyloid. The Alzheimer's Association Trail Match can be used to connect patients with available clinical trials.

Conclusion

Alzheimer's disease will almost triple in people over 65 by 2050. A structured clinical and laboratory evaluation can be performed in the primary care setting to make an appropriate diagnosis. Currently, there is no cure; good medical care and nonpharmacological management of mood and behavior are the most important treatments. Optimizing cardiovascular risks can reduce the development of dementia. Studies focusing on treatment of asymptomatic individuals may be the next frontier.

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Novel Therapies in the Management of Advanced Renal Cell Carcinoma (RCC): New Strategies and Options for Improved Patient Outcomes

M. Dror Michaelson, MD, PhD

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

The treatment of advanced renal cell carcinoma has changed dramatically since the early 2000s, with the introduction of targeted treatments and immunotherapy. The treatments recommended for first- and second-line therapy continue to evolve and will likely change when several studies currently underway are published.

Key Points

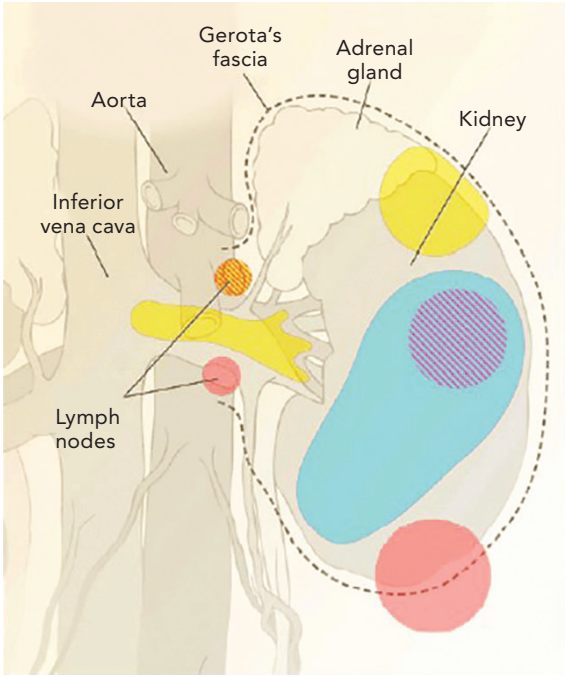
- Targeted therapy has dramatically revolutionized treatment of RCC.
- Both VEGF and mTOR are important therapeutic targets in RCC.
- Standard front-line therapy for most patients is sunitinib or pazopanib.
- Nivolumab and cabozantinib are preferred second-line options.
- Further immunotherapy approaches are under active investigation with aim toward substantial survival improvement.

THE STAGE AT WHICH SOMEONE IS DIAGnosed with renal cell carcinoma (RCC) will determine their prognosis and treatment plan. Exhibit 1 shows the American Joint Committee on Cancer Criteria staging criteria and prognosis by stage for renal cell carcinoma.[1] Stage I and II disease can be cured in the majority of patients. Stage III disease can be cured in the majority of patients but there are recurrences. Stage IV disease (metastatic RCC, mRCC) has the worst prognosis and is incurable in most.

Treatment of early localized disease (Stages I-III) is nephrectomy. Surgical advances in recent years include partial nephrectomy to preserve kidney tissue and minimally invasive laparoscopic nephrectomy. For patients who cannot have surgery, there is the option of percutaneous ablation, which includes radiofrequency/microwave ablation and cryotherapy.

Numerous adjuvant trials of anti-angiogenic therapy for reducing risk of recurrence have been conducted. Kidney cancer spreads by growing new blood vessels to invade existing vessels. Sunitinib and sorafenib, oral tyrosine kinase inhibitors taken for one year, have been compared to placebo in the adjuvant setting.[2] Median disease free survival (DFS) with sunitinib was 70 months (5.83 yr.), 69.7 months (5.81 yr.) with sorafenib, and 72.4 months (6.03 yr.) with placebo. Overall, there was no benefit in reducing recurrence. Another trial of sunitinib found a different result. The median duration of DFS was 6.8 years (95% confidence interval [CI], 5.8 to not

Exhibit 1: Clinical Staging and Prognosis in RCC[1]



Stage I
Tumor < 7 cm in greatest dimension and limited to kidney; 5-year survival - 95%

Stage II
Tumor > 7 cm in greatest dimension and limited to kidney; 5-year survival - 88%

Stage III
Tumor in major veins or adrenal gland, tumor within Gerota's fascia, or 1 regional lymph node involved; 5-year survival - 59%

Stage IV
Tumor beyond Gerota's fascia or > 1 regional lymph node involved; 5-year survival - 20%

Exhibit 2: Approved Therapies for mRCC[6]

TKI

Sunitinib (Sutent®)*
- Inhibits VEGFR(1, 2, 3), PDGFR(α,β), KIT, RET, Flt-3, and c-fms

Sorafenib (Nexavar®)
- Inhibits VEGFR, PDGFRβ, c-KIT, RET, and Raf

Pazopanib (Votrient®)*
- Inhibits VEGFR2-3, PDGFR, FGFR, c-Kit, c-Fms

Axitinib (Inlyta®)
- Inhibits VEGFR1-3, PDGFRβ and c-Kit

Cabozantinib (Cabometyx®)**
- Inhibits VEGFR2, c-Met, Axl, Ret, c-Kit, Flt-1/3/4, and Tie2

Lenvatinib (Lenvima®)
- Inhibits VEGF and FGF

Anti-VEGF

Bevacizumab (Avastin®)
- Binds VEGF and prevents receptorbinding

mTOR Inhibitor

Temsirolimus (Torisel®)*
- Inhibits mTOR through FKBP binding

Everolimus (Afinitor®)
- Inhibits mTOR through FKBP binding

Immunotherapy

Nivolumab (Opdivo®)**
- Anti-PD1 antibody

* Preferred first line therapy
** Preferred second line therapy

reached) in the sunitinib group and 5.6 years (95% CI, 3.8 to 6.6) in the placebo group.[3] At the time of data cutoff, an event of disease recurrence, a second cancer, or death had occurred in 113 of 309 patients (36.6%) in the sunitinib group and in 144 of 306 patients (47.1%) in the placebo group. At this point, clinicians are still unsure whether to utilize adjuvant therapy in Stage I to III disease. Results of several other trials with agents targeting angiogenesis are expected shortly and may resolve this issue.

Adjuvant immunotherapy trials, studying whether activating the immune system against the cancer has benefit, are being launched. These include trials of nivolumab, atezolizumab, pembrolizumab,

Exhibit 3: Common Adverse Events with Targeted Agents[8]

VEGF Inhibitors	VEGF TKIs	mTOR Inhibitors
Hypertension	Fatigue	Hypercholesterolemia
Proteinuria	Hypertension	Hyperglycemia
Diarrhea	Diarrhea	Treatment-related infections
Headache	HFSR	Pneumonitis
Cardiovascular events	Rash	Fatigue
Hemorrhage	Nausea/Vomiting	Asthenia
GI perforation	Stomatitis	Rash
	Constipation	Anemia
	Liver Toxicity	Diarrha
	Hypothyroidism	Nausea/Vomiting
	Cardiovascular events	Stomatitis

Exhibit 4: Second-line Treatment Options for mRCC[11-16]

	Lenvatinib/ Everolimus	Nivolumab	Carbozantinib	Axitinib
Median PFS, mos	14.6	4.6	7.4	6.7
ORR, %	43	25	17	19
Median OS, mos	25.5	25.0	21.4	20.1

mRCC = metastatic renal cell carcinoma
PFS = progression-free survival
mos = months
ORR = overall response rate
OS = overall survival

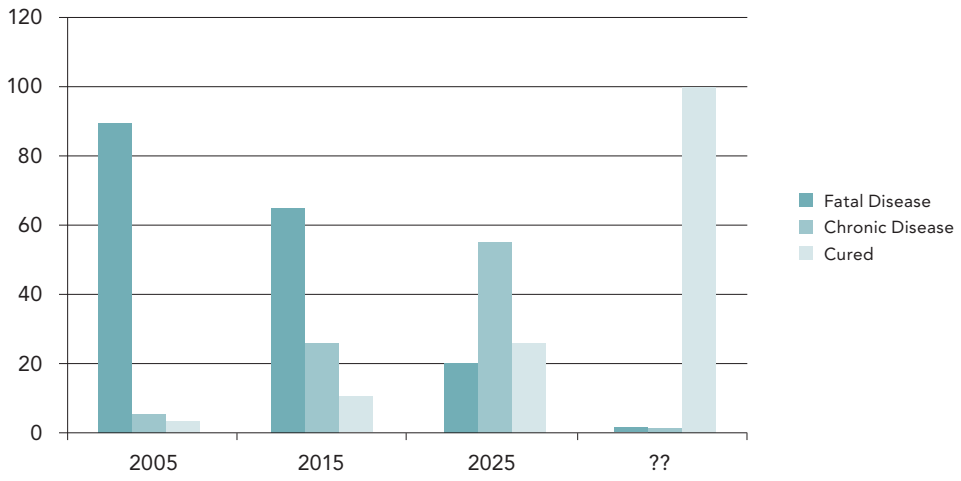
and nivolumab plus ipilimumab. The results of these trials are not expected for a minimum of five years. The current standard of care for early stage RCC is surveillance or clinical trial participation after nephrectomy.

The real advances in therapy have been for mRCC. Stage IV disease is very heterogeneous; patients have different outcomes independent of therapy. For example, some patients will only live for a few months compared with others who live for several years. Patients with Stage IV disease can be grouped into prognostic groups of high risk, intermediate risk, and low risk based on the time from diagnosis to treatment, hemoglobin, serum calcium, performance status, neutrophil count, and platelet count.[4,5]

Until the early 2000s, there were no specific treatments for mRCC; then high-dose interleukin 2 (IL-2) and interferon (IFN) became available. Unfortunately, only a small percentage of patients (5-10%) have a durable response with these older immunotherapies and they cause substantial toxicity. Many patients choose no treatment over the potential toxicities of these two treatments. Overall, the median survival with either IL-2 or IFN was 13 months.

It was discovered that the majority of cases of clear cell RCC are characterized by biallelic von Hippel-Lindau (VHL) gene function loss. The VHL gene product is an oxygen sensor in renal tubular cells. Loss of function leads to upregulation of downstream targets, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and others which promote metastasis. Thus, anti-angiogenic therapies were studied

Exhibit 5: Evolution of mRCC – from Fatal to Cured



in RCC and they improve progression free-survival (PFS) in mRCC. Exhibit 2 lists the FDA approved therapies for mRCC.[6]

Bevacizumab, an anti-VEGF agent, combined with IFN was the first anti-angiogenic therapy studied in mRCC. It improved median PFS to 10.2 months compared with 5.4 months for IFN alone.[7] Like all the agents used in mRCC, bevacizumab does cause significant adverse effects (Exhibit 3).[8]

Sunitinib, a small-molecule receptor tyrosine kinase inhibitor (TKI), inhibits all VEGF receptors, PDGF receptors, and others. It is given by oral administration and has both antitumor and antiangiogenic activity. Compared with IFN as first-line treatment of mRCC, sunitinib produces a longer median PFS (11.0 vs 5.1 months).[9] Those with favorable risk factor status do the best on sunitinib. It has been the standard of care for first line treatment of mRCC for several years. Pazopanib, another TKI approved for mRCC which has equivalent efficacy to sunitinib, is an alternative.[10]

Other TKIs have been studied for and are FDA approved for second-line therapy in mRCC. These include axitinib, sorafenib, cabozantinib, and lenvatinib. Lenvatinib is used in combination with everolimus, a mammalian target of rapamycin (mTOR) inhibitor.

Another option in second-line therapy is now second-generation immunotherapy. Nivolumab is a checkpoint inhibitor that activates the immune system against the tumor. Nivolumab was compared to everolimus in pretreated mRCC and found to improve median overall survival by 4.4 months.[11] This trial had a median OS of 25.0 months compared to 13 months with the older immunotherapies. Everolimus monotherapy used to be second-line therapy but has been supplanted largely by immunotherapy and TKIs based on efficacy. Exhibit 4 compares the efficacy of the second-line therapies.[11-16]

Indications for immunotherapy in mRCC are likely to expand and may include first-line therapy. Several Phase III trials are ongoing with combination therapy immunotherapy and immunotherapy and anti-angiogenesis therapy. The standard of care will continue to evolve as results of these trials are published.

Exhibit 5 illustrates the improvements in RCC treatment with the progression from fatal disease to chronic or cured disease. The hope is that survival can be extended in many more patients with immunotherapy and targeted therapy. Future priorities in RCC treatment are to identify individual predictive biomarkers for response, increase the complete response rate of therapy, and evaluate immunotherapy approaches in front-line treatment. Another priority is to explore new combinations, including immunotherapy combined with radiation and immunotherapy combined with targeted therapy

Conclusion

Standard of care for advanced RCC has dramatically changed in the era of targeted therapy and immunotherapy. Standard front-line therapy for most patients is sunitinib or pazopanib. Nivolumab and cabozantinib are now proven effective post-TKI with overall survival benefit in Phase III trials.

Axitinib and lenvatinib/everolimus are additional treatment options post-TKI failure. Further immunotherapy approaches are under active investigation, with aim toward substantial survival improvement.

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Effective Strategies and Clinical Updates in Pulmonary Arterial Hypertension

Hap Farber, MD

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

The standard medication regimens for pulmonary arterial hypertension, a fatal disease, continue to evolve. Instead of monotherapy, combination therapy should be started at the time of diagnosis. Aggressive combination therapy should also be used in those patients who are not clinically optimized.

Key Points

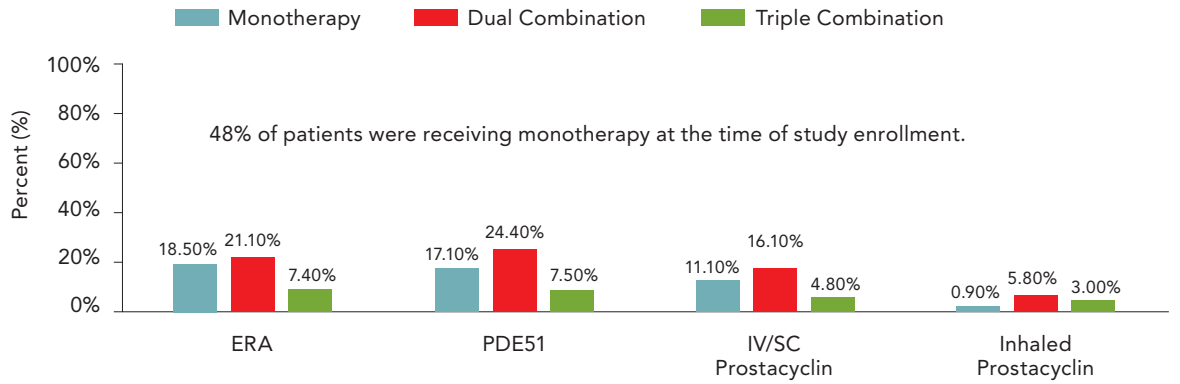
- The availability of oral, inhaled, and parenteral PAH therapies provides multiple treatment strategies for patients with PAH.
- The current evidence supports multi-drug therapy.
- Long-term data on the choice of initial medical therapy, de novo combination therapy, or therapy sequencing, are still incomplete.
- Considerations for initial therapy selection and for combining therapies should take into account consensus recommendations/guidelines, long-term efficacy and safety data, future treatment options, and patient characteristics for an individualized approach for each patient.
- Patients with severe disease or in those failing medical therapy should be referred to PAH centers early for advanced therapy.

PULMONARY ARTERIAL HYPERTENSION (PAH) is a fatal type of pulmonary hypertension (PH) that affects about 100,000 people in the United States (U.S.). It is characterized by the presence of precapillary PH, including an end-expiratory pulmonary arterial wedge pressure (PAWP) less than or equal to 15 mm Hg and pulmonary vascular resistance (PVR) greater than 3 Woods units.[1] PAH can be idiopathic, heritable, drug- and toxin-induced, persistent PH of the newborn, or associated with connective tissue disease (e.g., scleroderma), HIV infection, portal hypertension, congenital heart disease or schistosomiasis. Methamphetamine and cocaine are the two major causes of drug-induced PAH.

Patients with dyspnea and an estimated right ventricular systolic pressure (RVSP) of 40 mm Hg or higher by echocardiography (Echo) should have further evaluation. Echo-estimated measurements of PH, although the screening tool of choice, are not diagnostic and should never be the basis for the prescription of PAH-specific agents. Echo-based estimates greater than 60 mm Hg and/or right ventricular enlargement/dysfunction are cause for significant concern and an expedited evaluation by an expert team.[2,3] Echo compared to right heart catheterization has a false negative rate estimated at less than 1 percent and a false positive rate of 30 to 40 percent. Diagnosis requires a right heart catheterization.

The availability of oral, inhaled, and parenteral PAH therapies provides multiple treatment strategies for patients with PAH. The available treatment classes include endothelin receptor antagonists (ERA), phosphodiesterase 5 inhibitors (PDE5i), and prostacyclins (oral, inhaled, and intravenous).

Exhibit 1: Monotherapy and Combination Therapy in Patients with PAH[6]



ERA = endothelin receptor antagonists
PDE5i = phosphodiesterase five inhibitor

N = 2,438. Treatment reported at time of enrollment in REVEAL

Treatment issues in PAH are numerous. First is whether to treat with monotherapy, dual combination therapy, or triple combination therapy. Second is when to treat; this can be upfront at the time of diagnosis or as add-on (stable vs. failing). The third issue is which drugs should be given and in what order.

A small subset (<10%) of patients with idiopathic PAH have favorable long-term response to high-dose calcium channel blockers (CCBs).[4,5] Potential patients are identified by vasoreactivity testing. Slow up-titration with the CCBs is required with high-level maintenance doses (i.e., diltiazem, 240–720mg; nifedipine, 120–240mg). The patients who respond to CCBs are likely a unique subset of PAH; typically they do well on CCBs with lower morbidity and mortality compared with other patients with PAH.

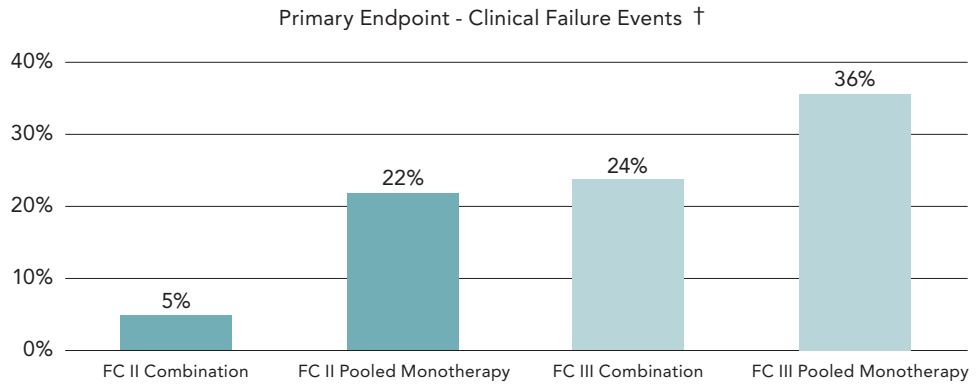
The REVEAL database is a multicenter, U.S.-based observational cohort of all patients with PAH at 50 centers of excellence. Of the 2,438 patients under therapy in the registry, a total of 47.7 percent were receiving monotherapy at the time of enrollment (Exhibit 1).[6] The remainder were receiving combination therapy using PAH-specific agents. Most were not receiving parenteral prostacyclins, which is the most potent class and should be used in the later stages of the disease. Only 43 percent of those in the registry were receiving parenteral prostanoids at the time of their death.[7] The 50 centers that report data to the REVEAL database are supposedly the best places in the U.S. to receive care for PAH and should be following guidelines; yet, the data suggest they are not. If the PAH centers are not following guidelines, then those without expertise in the field are likely doing even worse. It is not clear why the centers were not following the guidelines.

There are some caveats to the data on using PAH-specific monotherapy. The data with PAH monotherapy typically comes from 12-week trials which gives no data about durability of response. Most long-term data of PAH monotherapy come from open-label extensions of placebo-controlled trials and thus has no comparator arm. These trials allowed add-on therapy after the initial blinded treatment phase; thus, some or all of the efficacy seen in the open-label phase could be due to the add-on therapy and not the "primary" study medication. Results of the monotherapy trials cannot be compared across studies because each trial was unique, with fundamental protocol differences (study size, outcomes definitions, use of additional medications without reaching trial endpoint, etc.).

Likewise, the PAH combination therapy trials also have issues. Only the AMBITION trial prospectively studied the question of monotherapy versus de novo combination therapy.[8] All other currently reported trials featured "add-on" protocols; therefore, the relative contribution of individual agents to treatment success is difficult to assess. Combination therapy trials often have only a short-term component, with no long-term follow-up.

The results from a combination trial of ambrisentan and tadalafil changed the treatment paradigm in PAH from monotherapy to combination therapy. In this trial, combination therapy significantly improved the primary endpoint of time to clinical

Exhibit 2: Comparison of Initial Combination Therapy in Functional Class II and III Patients[6]



FC = Functional Class

failure (TcF) compared to monotherapy, with a reduction in risk of 50 percent.[8] Most of the decrease in risk was a decrease in hospitalization for worsening PAH. This trial found that an upfront combination of ambrisentan and tadalafil consistently outperformed pooled monotherapy on the endpoint of TcF across a variety of subgroups, including functional class. The only group that did not benefit from combination therapy was men. PAH is primarily a disease of women; when men have the disease they do worse.

This trial also dispelled the common notion that more aggressive therapy would benefit the sicker patients compared to those not as sick and that therapy could be postponed until later in the disease course. As shown in Exhibit 2, those with functional Class II had a 17 percent reduction in clinical events, whereas those with functional Class III disease had a 12 percent reduction.[9]

Studies with macitentan and selexipag added onto other therapy showed a 40 percent reduction in events.[10,11] Thus, anyone who is diagnosed with PAH likely needs aggressive combination therapy. The current treatment paradigm is to start two drugs at the time of diagnosis, unless the patient is going into a clinical trial. For patients already on some type of therapy who are not doing well clinically another therapy should be added to their regimen.

Not all agents in combination provide benefit. Bosentan in combination with sildenafil was not effective in one trial.[12] At this point, it is unknown which combination is best to use and in which order the various agents should be used.

Upfront triple combination therapy in PAH has been studied in one pilot study in a very sick, ICU population.[13] This small trial showed remarkable improvement in hemodynamics and the six-minute walk distance. This regimen of an intravenous prostanoid, a PDE5 inhibitor, and an ERA is very expensive. At this point, triple therapy is not the norm, but it is a possible treatment choice for those who match the entry criteria of this trial. A trial with three oral agents is ongoing.

Conclusion

Diagnosis of PAH requires a right heart cauterization. The availability of oral, inhaled, and parenteral PAH therapies provides multiple treatment strategies for patients with PAH. The current trend is toward use of multi-drug therapy which appears more efficacious than monotherapy. Long-term data on the choice of initial medical therapy, de novo combination therapy, or therapy sequencing, are still incomplete. Considerations for initial therapy selection and for combining therapies should take into account consensus recommendations/guidelines, long-term efficacy and safety data, second-line choices, and patient characteristics, with an individualized approach for each patient. In patients with severe disease or in those failing medical therapy, early referral to PAH centers for advanced therapy is important.

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