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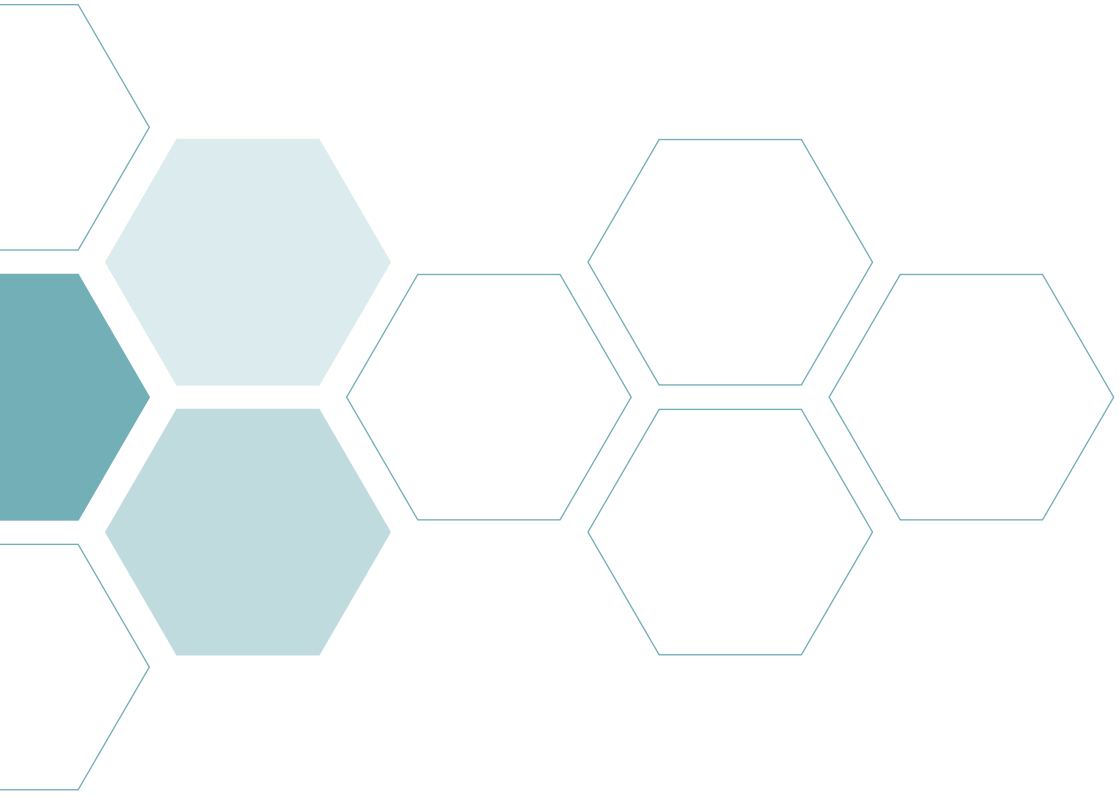

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Recent Advances in the Treatment and Management of Metastatic Breast Cancer: Expert Perspectives in an Evolving Treatment Paradigm

Lee Schwartzberg MD, FACP

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

Summary

Targeting how cells repair DNA damage with PARP inhibitors is leading to improvements in progression-free survival in those with metastatic breast cancer (MBC). These agents are better tolerated and lead to better quality of life than treatment with chemotherapy.

Key Points

- Germline BRCA testing should be done for all patients with MBC.
- Olaparib and talazoparib improved progression free-survival in MBC.
- There are FDA-approved companion assays for both agents to detect germline BRCA mutations.
- The indications for these agents are likely to expand significantly.

IN 2021, AN ESTIMATED 284,200 WOMEN will be diagnosed with breast cancer.[1] Approximately 65,000 will be diagnosed with metastatic breast cancer (MBC) and 43,600 women will die from breast cancer. Median survival for MBC is four years with hormone receptor (HR) positive human epidermal growth factor receptor two (HER2) negative, five years for HER2 positive, and two years for triple negative breast cancer (TNBC). MBC is the costliest disease stage.[2] Using data from the Vector Oncology Data Warehouse, one study found the annual cost for treating TNBC was $212,275 and $204,780 for HR+ disease.[3]

Progress against MBC has been made by the discovery of the role of DNA repair mechanisms in breast cancer and the subsequent development of therapies targeting these mechanisms. As shown in Exhibit 1, cells in the body can sustain DNA damage through various mechanisms.[4] This damage can lead to cell death if the DNA damage is not repaired. Important repair pathways in breast cancer are double-strand break DNA repair through homologous recombination through breast cancer one and two (BRCA1, BRCA2) proteins and base excision repair by poly (ADP-ribose) polymerase one (PARP1). BRCA1 and BRCA2 are very large proteins involved in maintaining genome integrity. Patients with genetic mutations in the BRCA1/2 genes have homologous recombination repair deficiency (HRD) but can repair DNA through other pathways such as PARP1.

BRCA mutations occur in about 0.25 percent of the general population (excluding those of Ashkenazi Jewish descent).[5] In the Ashkenazi Jewish (AJ) population, they occur in 2.5 percent in the overall population and in 10 percent of those with breast cancer. Two percent of women with breast cancer at any age and 10 percent of women with breast cancer who are younger than 40 years of age have BRCA mutations. They also occur in about 5 percent of men with breast cancer at any age.

The PARP inhibitors were developed to break down DNA repair in the PARP pathway to cause cell death in cells with HRD (Exhibit 2).[6] These agents

Exhibit 1: Mechanisms of DNA Repair[4]

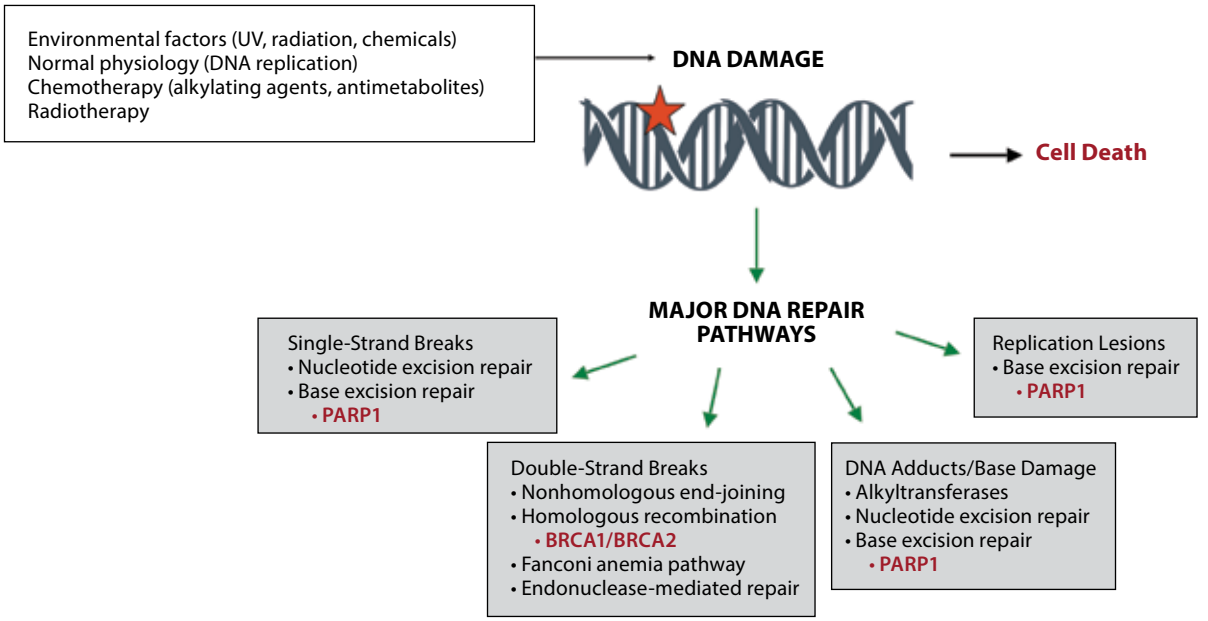
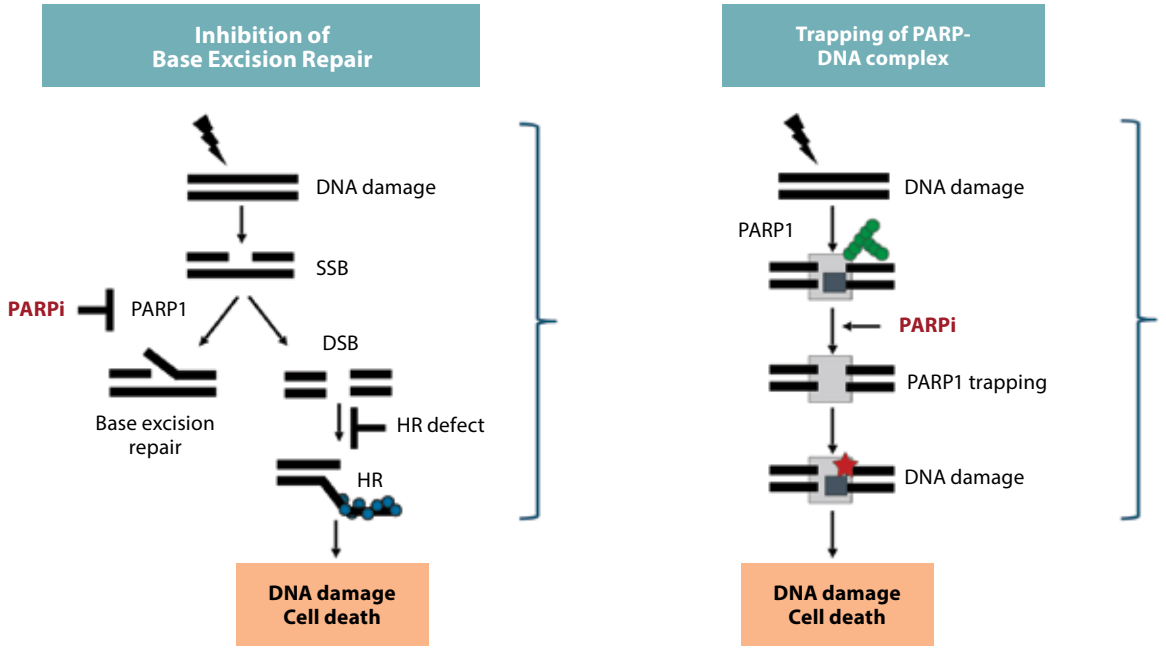


Exhibit 2: How Do PARP Inhibitors Kill Tumor Cells with Homologous Recombination Deficiency?[6]



DSB = double-strand break; HR = homologous recombination; SSB = single-strand break

work by both PARP inhibition and PARP1 trapping. Olaparib, talazoparib, niraparib, and rucaparib are all FDA-approved PARP inhibitors, but only olaparib and talazoparib are indicated for MBC. Talazoparib is a more potent PARP1 trapper than olaparib, but the clinical significance of this is unknown.[7]

The Phase III trial (OlympiAD) that lead to olaparib (Lynparza®) approval in germline BRCA-mutated (gBRCAm) MBC included subjects who had HER2-negative, gBRCAm MBC treated with no more than two prior lines of chemotherapy. The trial compared olaparib 300mg twice a day to standard of care chemotherapy (capecitabine, eribulin, or vinorelbine). Median progression-free survival (PFS) was significantly longer in the olaparib group than in the standard-therapy group (7.0 months versus 4.2 months; $p < 0.001$).[8] At 64 percent data maturity, median overall-survival (OS) was 19.3 months with olaparib versus 17.1 months with chemotherapy, which was not statistically different.[9] The response rate was 59.9 percent in the olaparib group and 28.8 percent in the standard-therapy group. The rate of Grade 3 or higher adverse events was 36.6 percent in the olaparib group and 50.5 percent in the standard-therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9 percent and 7.7 percent, respectively. Overall, olaparib monotherapy provided a significant benefit over standard therapy. Better median PFS and the risk of disease progression or death was 42 percent lower with olaparib monotherapy than with standard chemotherapy.

Talazoparib (Talzenna®) was evaluated in the Phase III Embraca trial. Subjects had no more than three prior lines of chemotherapy but had to have been treated with a taxane and anthracycline. This trial compared talazoparib 1 mg once a day to standard of care chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Median PFS was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months versus 5.6 months; $p < 0.001$).[10] Median OS was 19.3 months with talazoparib versus 19.5 months which was similar with olaparib but again was not statistically significant.[11] The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% versus 27.2%; $p < 0.001$). Hematologic Grade 3 and 4 adverse events (primarily anemia) occurred in 55 percent of the patients who received talazoparib and in 38 percent of the patients who received standard therapy. Nonhematologic Grade 3 adverse events occurred in 32 percent and 38 percent of the patients, respectively. Alopecia appears more common with talazoparib compared to olaparib. In this trial, patient-reported outcomes favored talazoparib over chemotherapy; significant overall improvements and significant delays in the time to clinically meaningful deterioration according to both the global health status-quality-of-life and breast symptoms scales were observed. As with olaparib, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to PFS.

Both olaparib and talazoparib are FDA-approved for gBRCAm HER2-negative MBC. The National Comprehensive Cancer Network guidelines recommend these agents as additional targeted therapy for any recurrent or MBC subtype with gBRCAm including HER2-positive disease.[12] The guidelines recommend BRCA testing for all patients with recurrent or MBC to identify candidates for PARP inhibitor therapy.[12] There are FDA-approved companion assays for both agents which should be used for the testing.

In addition, the guidelines also recommend olaparib as adjuvant therapy for one year for those with gBRCAs and TNBC if there is residual disease after adjuvant or preoperative chemotherapy. One year of adjuvant therapy is also an option for those with gBRCAm, HR-negative, and HER2-negative if there are four or more positive lymph nodes after adjuvant chemotherapy or residual disease after preoperative therapy and a clinical stage score of three or more. BRCA mutation testing is recommended at any age to aid in adjuvant treatment decisions for olaparib use in high-risk HER2-negative breast cancer.[13]

At the West Cancer Center, all patients with MBC are recommended for testing. The testing is discussed during care planning. Pathology annotates and recommends testing during the diagnostic process. Once testing is completed, the genetic counselor proactively communicates with patients who have positive results.

PARP inhibitors are being studied in combination with programmed death one (PD-1) checkpoint inhibition immunotherapy, in combination with chemotherapy, in MBC with other DNA repair gene mutations other than BRCA, and in combination with radiation in inflammatory breast cancer. Niraparib, another PARP inhibitor approved for other BRCA-mutated cancers, in combination with pembrolizumab produced good results in patients with metastatic TNBC who had somatic BRCA mutations and PD-ligand one (PD-L1) expression.[14] This trial showed that this combination may be a desirable choice for treating patients with both HRD and PD-L1 expression. Other trials of PARP

inhibitors and immunotherapy are ongoing. Veliparib, an investigational PARP inhibitor, has been studied with and without carboplatin and paclitaxel chemotherapy in HER2-negative MBC with BRCA mutations (BROCADE-3).[15] Median progression-free survival was 14.5 months in the veliparib/chemotherapy group versus 12.6 months in the chemotherapy group (p = 0.0016). Final OS data have not yet been published. Based on the data from ongoing studies, the use of PARP inhibitors is likely to expand, especially into the earlier stages of breast cancer treatment.

Conclusion

BRCA mutation testing should be done for all patients with MBC. Olaparib and talazoparib are approved in gBRCAm, HER2-negative MBC, but the National Comprehensive Cancer Network guidelines support use in any subtype. There are FDA-approved companion assays for both agents to detect BRCA mutations. The PARP inhibitors provide meaningful clinical benefit with overall less toxicity and improved quality of life compared to standard single-agent chemotherapy. There are active research programs in other settings including earlier stage breast cancer and in combination with other classes of agents.

Lee Schwartzberg MD, FACP is a Professor of Medicine at The University of Tennessee Health Science Center, Chief Medical Officer at OneOncology, and Medical Director of the West Cancer Center, as well as a practicing medical oncologist in Memphis, TN.

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Recent Advances in the Management of ALS: What Managed Care Needs to Know in an Evolving Treatment Paradigm

Senda Ajroud-Driss, MD

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Summary

Amyotrophic lateral sclerosis is a complex devastating neurogenerative disease that is costly to manage. Although significant improvements in care have been made in the past 20 years, it is still a fatal disease.

Key Points

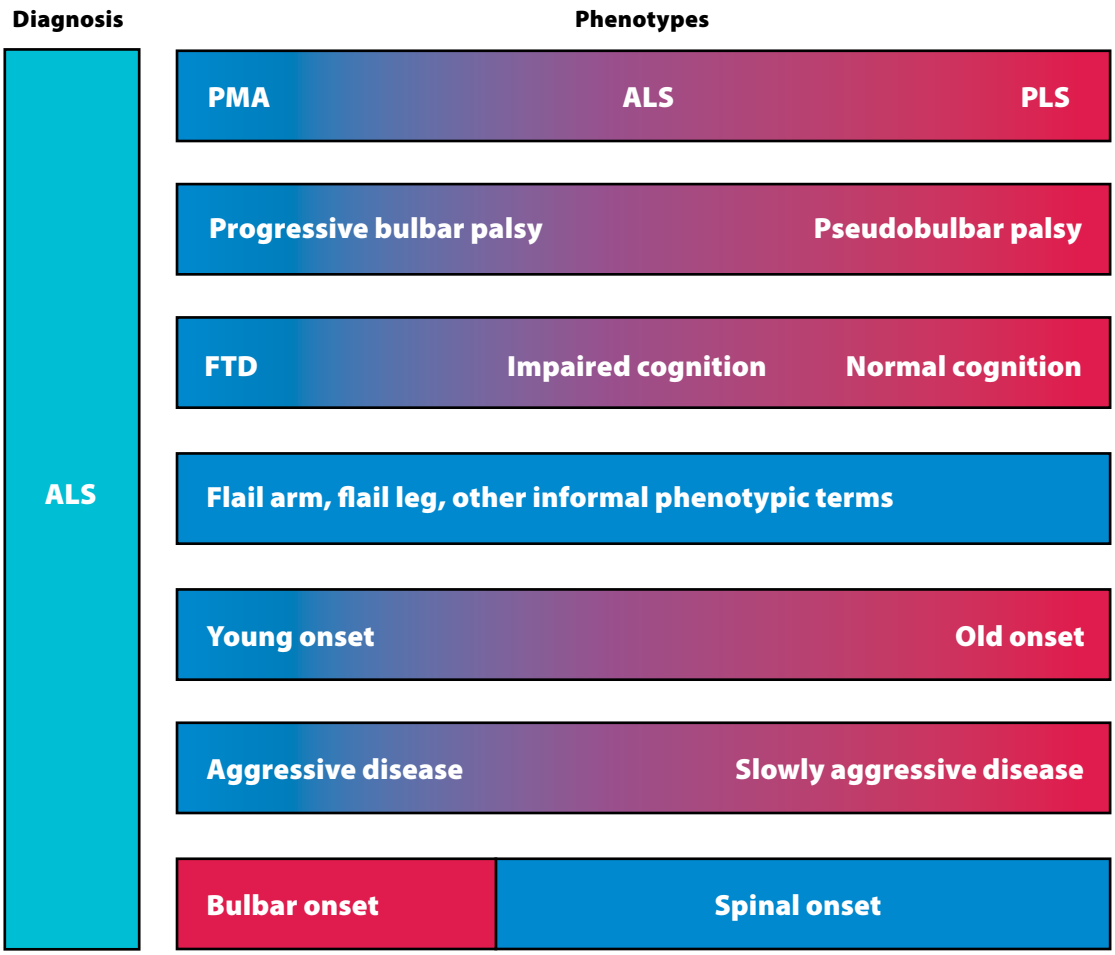
- Disease-modifying therapies (DMTs) are available and should be used as early as possible in the disease process.
- In addition, nutritional interventions, respiratory care interventions, and aggressive symptomatic management improve quality of life and prolong survival.
- Multidisciplinary care is also important for achieving good outcomes.

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a rare incurable progressive neurodegenerative disorder affecting upper and lower motor neurons and bulbar neurons.[1] The incidence of ALS in the United States (U.S.) is between one and two cases per 100,000 people and prevalence is between four and six per 100,000. Approximately 30,000 Americans have ALS, with cases in males slightly predominate (1.5 to1.0).

Genetic factors cause approximately 10 percent of cases [familial ALS (fALS)], and the rest are considered sporadic (sALS).[1] The average age of onset in fALS is 46 years and 56 years in sALS. More than 30 ALS-specific genetic mutations have been identified to date. The most common is chromosome 9 open reading frame 72 (C9orf72) gene mutation, which accounts for approximately 30 to 40 percent of all fALS cases.[2,3] Superoxide dismutase 1 (SOD1) mutations account for about 20 percent of fALS cases. Many of the same gene mutations have been identified in sporadic onset patients. Common genes altered in sALS include the paraoxonase family (PON), Ataxin-2, NEK1, and DPP6. Certain environmental factors are associated with development of sALS. These include male gender, geographic clusters (Guam), β-N-methylamino-L-alanine (BMAA, natural non-proteinogenic diamino acid produced by several species of both prokaryotic and eukaryotic microorganisms), smoking, military service, intense physical activity, lead, head trauma, low magnetic fields, and pesticides.

The clinical presentation of this disease is complex and can include upper extremity weakness, lower extremity weakness (which leads to tripping and falls), speech change, swallowing issues, unexplained weight loss, difficulty breathing, and head drop. ALS is a clinical diagnosis supported by characteristic electrophysiological features, and there are no biomarkers to help with the diagnosis. Various tests are needed to support the diagnosis and rule out ALS mimics, including cerebrospinal fluid analysis, nerve conduction studies, electromyography, and MRI of the brain, cervical spine, and lumbar spine. In addition to testing, physical examination and symptoms can help exclude mimics. There are various ALS subtypes, depending on motor involvement, age of onset, and other factors (Exhibit 1).[4]

Exhibit 1: The Spectrum of ALS[4]



ALS = amyotrophic lateral sclerosis; PMA = progressive muscular atrophy; PLS = primary lateral sclerosis; FTD = frontotemporal dementia

Because treatments are now available and seem to work better in early disease, early diagnosis is important. Diagnostic delay is a predictor of poor prognosis. Older age, bulbar onset, respiratory function, concomitant frontal temporal dementia, and others are also related to ALS outcome.[5]

Treatment of ALS requires many different aspects of care and is best accomplished in a multidisciplinary manner in a specialty clinic. Because multidisciplinary care has been shown to improve patient survival and quality of life, it is recommended in the American Academy of Neurology (AAN) guidelines.[6]

Patients with ALS require a great deal of symptomatic care. The AAN guidelines provide recommendations for managing various symptoms, but it should be noted that many of the medications recommended by the guidelines are not FDA-approved for these specific indications.[7] Cramps, spasticity, and sialorrhea can all have a significant impact on quality of life. Cramps can be treated with gabapentin, baclofen, muscle relaxants, and mexiletine. Spasticity is managed with baclofen (including via intrathecal pump), tizanidine, and benzodiazepines. Sialorrhea is treated with atropine, glycopyrrolate, anticholinergic antidepressants, hyoscyamine, and botulinum toxin injections. Pseudobulbar affect is common in those with ALS and can be managed with dextromethorphan/quinidine (Neudexta®) and various antidepressants. Mobility and activities of daily living are two other major areas where patients will need increasing

levels of care and adaptive devices as the disease progresses. Mobility devices will help patients maintain their independence as long as possible. Speech devices will also become necessary.

Two important survival interventions in ALS are feeding tubes for maintaining nutrition and noninvasive ventilation (NIV). Weight loss is a negative prognostic factor, and a 10 percent weight loss is an indicator of faster progression. Early use of feeding tubes should be encouraged in order to maintain weight and nutrition. NIV should be considered to treat respiratory insufficiency in ALS, both to lengthen survival and to slow the rate of lung function decline.[7] It also improves quality of life, sleep quality, and comfort in those with respiratory insufficiency. With continued respiratory function decline, tracheostomy and invasive ventilation have to be considered.

Riluzole (Rilutek®, Tiglutik®) and edaravone (Radicava®) are the two FDA-approved DMTs approved for ALS treatment. Riluzole is given orally and blocks release of glutamate and modulates sodium channels. Riluzole prolongs median tracheostomy-free survival by two to three months compared to placebo in patients younger than 75 years with definite or probable ALS who have had the disease for less than five years and who have a forced vital capacity (FVC) of greater than 60 percent.[8,9] Data from real-world use has shown improvements in median survival times of more than 19 months.[10] This is a well-tolerated agent with minimal adverse events. The AAN practice parameter states that riluzole should be offered to slow disease progression in patients with ALS (Level A evidence).[7]

Edaravone was approved by the FDA in 2017 to slow the functional decline in patients with ALS. One trial in patients within three years of symptom onset showed no benefit over placebo, but a post-hoc analysis suggested that a subset of patients with a more rapid rate of progression benefitted from treatment with edaravone.[11] Another trial in 137 people with some degree of impairment in each of the ALS Functional Rating Scale-revised (ALSFRS-R) domains had good lung function, within two years of symptom onset, and had a further decline of –1 to –4 ALSFRS-R points during a 12-week observation period found that edaravone slowed the rate of disease progression, as measured by a decrease in ALSFRS-R score, by 33 percent at six months compared to patients in the placebo group.[12] Many insurers restrict this agent to only those patients who would have met the inclusion criteria of this trial despite edaravone being FDA-approved for all patients with ALS. Strict inclusion criteria are needed for ALS trials because this is a heterogenous disease and researchers want to compare like groups in order to show benefit—just because a group of ALS patients were not included in the trial does not mean they will not respond. This agent is well tolerated but has to be given by an intravenous infusion for 10 days out of every 28 days. Because of the need for multiple intravenous doses per month, patients require implantation of an intravenous port. The cost of edaravone is estimated to be around $148,000 per year. When this agent first became available, patients all wanted to be on it. Now, fewer patients seek it out because of the difficulty in showing benefit on disease progression.

There are many different challenges in study treatments in ALS. It is a heterogenous disease with an unknown pathogenesis and many times has delayed diagnosis. There is an absence of biomarkers which can be used for diagnosis and measurement of treatment efficacy. Platform trials are an option for improving and speeding up clinical trials in this disease. Some interesting trials are ongoing in testing some new therapies. A Phase III trial was recently completed with repeated injections of autologous bone marrow-derived mesenchymal stromal cells which have been altered to be neurotropic factor-secreting (NurOwn®), but the results have not yet been published. Arimoclomol, an amplifier of heat shock protein expression involved in cellular stress response in ALS, is under investigation. Tofersen is an investigational molecule for superoxide dismutase 1 (SOD1) ALS, the second most common genetic form.

A combination of sodium phenylbutyrate and taurursodiol (PB-TURSO) is also under investigation. The combination has been found to reduce neuronal death in experimental models, and in ALS it simultaneously mitigates endoplasmic reticulum stress and mitochondrial dysfunction. This oral combination (3 g of sodium phenylbutyrate and 1 g of taurursodiol, administered once a day for 3 weeks and then twice a day) has been compared to placebo in patients with definite ALS in a Phase II trial. In a modified intention-to-treat analysis, the mean rate of change in the ALSFRS-R score was −1.24 points per month with the active drug and −1.66 points per month with the placebo (difference, 0.42 points per month; 95% confidence interval, 0.03 to 0.81; $p = 0.03$) over 24 weeks.[13] In a long-term survival analysis of the open label phase of the trial, median overall survival was 25.0 months among participants originally randomized to PB-TURSO and 18.5 months among those originally randomized to placebo (hazard ratio, 0.56; 95%

confidence interval, 0.34 to 0.92; $p = .023$).[14] These results suggest that PB-TURSO has both functional and survival benefits in ALS. Clinicians are waiting to see if this combination will be approved by the FDA based on the Phase II trials or whether it will require a Phase III trial.

Conclusion

Although still a fatal disease, improvements in care and therapeutics are leading to longer-term survival in those with ALS. Two disease DMTs are available, and more are under investigation. DMTs, nutritional interventions, respiratory care interventions, and aggressive symptomatic management improve quality of life and prolong survival.

Senda Ajroud-Driss, MD is an Associate Professor of Neurology and Director at the Les Turner ALS Center at Northwestern University Feinberg School of Medicine in Chicago, IL.

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Patient-Focused Treatment Decisions in the Management of Type 2 Diabetes Mellitus: Expert Perspectives on the Evolving Role of SGLT2 Inhibitors in Cardiovascular and Renal Outcomes

Silvio E. Inzucchi, MD

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

Summary

In recent years, substantial benefits of the sodium-glucose co-transporter two (SGLT2) inhibitors have been shown beyond simple glucose lowering. These benefits include reductions in various cardiovascular and renal outcomes. These agents are now recommended for many with diabetes and those with heart failure whether they have diabetes or not.

Key Points

- SGLT2 inhibitors have significant benefit in reducing risk of cardiorenal outcomes.
- These agents are recommended for certain patient groups, regardless of the need for additional glucose lowering or presence of diabetes.

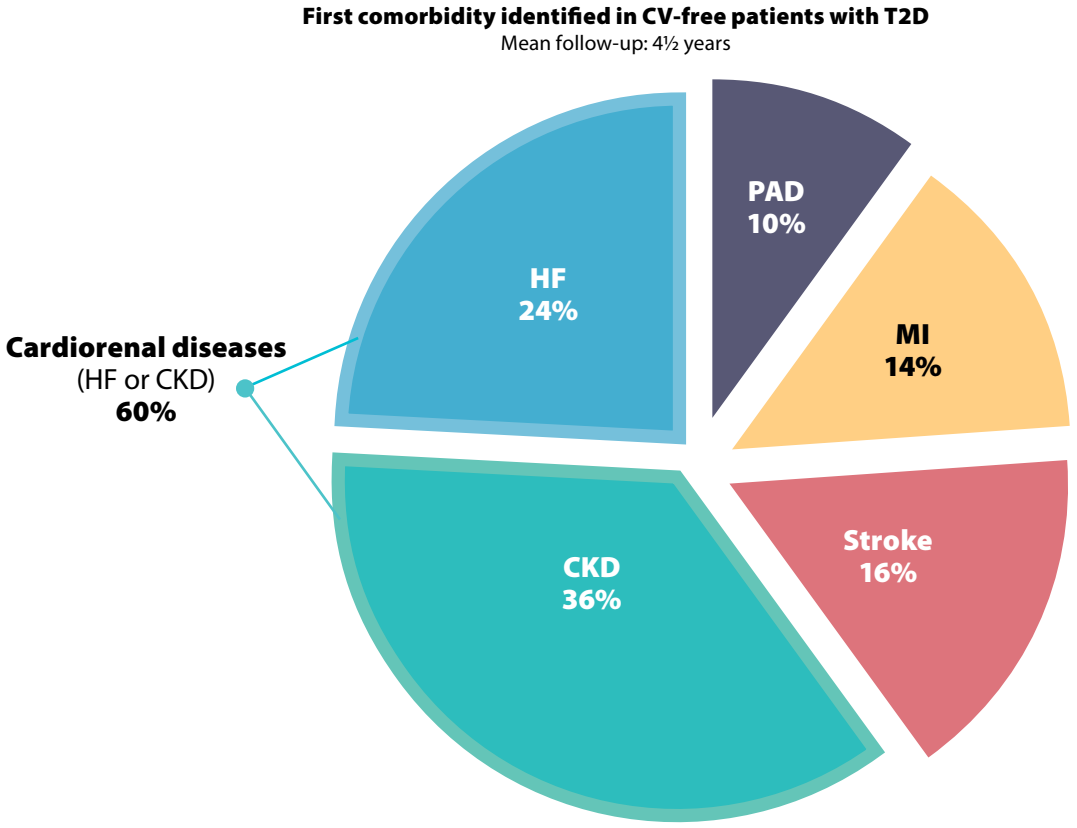
PATIENTS WITH TYPE 2 DIABETES MELLITUS (T2DM) are at higher risk of developing heart failure (HF) and chronic kidney disease (CKD) compared with the general population.[1,2] CKD and HF are the first clinical consequences typically seen in T2DM. In a retrospective analysis of data from over 1.1 million patients with T2DM, CKD and HF occurred before other consequences such as peripheral arterial disease, heart attack and stroke in 60 percent of patients (Exhibit 1).[3]

HF and CKD drive poor clinical outcomes such as hospitalization and end-stage renal disease (ESRD), which further increase the risk of death.[4,5] The combination of T2DM and HF is a recipe for death, especially in those over 65. In one trial, incident HF among older adults with T2DM was associated with a high mortality rate of 32.7 per 100 person-years compared with 3.7 per 100 person-years among those with T2DM who remained HF free.[6] Moreover, HF increases the risk of renal function decline and adverse renal outcomes (incident CKD, ESRD, and mortality) in those with normal kidney function.[7] Similarly, declining estimated glomerular filtration rate (eGFR) and worsening albuminuria in CKD increase the risk of developing HF.[8]

Importantly, glucose control alone, even when intensive, has failed to reduce the risk of adverse HF outcomes in T2DM (Exhibit 2).[9] It is also well known that there are multiple metabolic abnormalities in T2DM which are all contributing to the development of HF and CKD (Exhibit 3).

The sodium glucose co-transporter two (SGLT2) inhibitors are the most recent medication class for T2DM, exerting their hemoglobin A1C (A1C) lowering effect through glucosuria by lowering the renal threshold for glucose excretion.[10] SGLT2 is responsible for reabsorbing up to 90 percent of the glucose filtered at the glomerulus. The remaining 10 percent is reabsorbed by SGLT1 that is expressed on the luminal (brush border) surface of cells of the S3 segment of the proximal tubule. SGLT2 inhibitors increase urinary glucose excretion to 70 to 80 grams per day. In addition to glucose lowering, they are associated with modest reductions in blood pressure (-4 to -2 mm Hg), body weight (~ 2 kg), and triglycerides.[11] They also do not cause hypoglycemia

Exhibit 1: Chronic Kidney Disease and Heart Failure are the First Clinical Manifestations in T2D[3]



CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure;
MI = myocardial infarction; PAD = peripheral artery disease; T2D = Type 2 diabetes

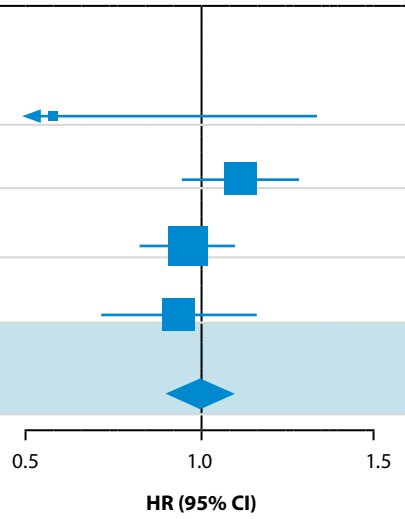
when used alone. Adverse events include polyuria, dehydration, genital mycotic infections, reversible decreases in GFR, small increases in low-density lipoprotein cholesterol (LDL-C), and diabetic ketoacidosis.[11-13]

This class of agents have become a significant focus in T2DM management because of their impact on cardiovascular disease (CVD) and renal disease development. Since 2008, manufacturers have to evaluate new antiglycemic products for their effects on CVD to primarily ensure they are doing no harm. Those that show benefit can carry specific labeling on CVD, renal, and HF benefits. Four agents – canagliflozin dapagliflozin, empagliflozin, and ertugliflozin – are available in the United States (U.S.), and each have different labeling based on the trials which have been completed (Exhibit 4).

Cardiorenal outcomes with SGLT2 inhibitors have been examined in four large scale trials – Dapagliflozin Effect On Cardiovascular Events (DECLARE-TIMI 58), Canagliflozin Cardiovascular Assessment Study (CANVAS), Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE).[14-17] From these trials, SGLT2 inhibitors have been shown to protect against CVD and death in diverse subsets of patients with T2DM regardless of CVD history. A recent systematic review and meta-analysis found no evidence that the effects of SGLT2 inhibitors varied across patient subgroups, defined by the presence of cardiovascular disease or heart failure at baseline (Exhibit 5).[18] All patient subgroups benefitted with respect to hospitalization for HF, cardiovascular death, and death from any cause. The only difference in effects across subgroups was for stroke, with protection observed among those with reduced kidney function but not those with preserved

Exhibit 2: Glucose Control Effect on Risk of Adverse HF Outcomes in T2DM[9]

Trial	Number of Events (annual event rate, %) More Intensive	Less Intensive	Change in A1C (%)	HR (95% CI)
Hospitalized/Fatal HF				
UKPDS	8 (0.06)	6 (0.11)	- 0.66	0.55 (0.19 to 1.60)
ACCORD	152 (0.90)	124 (0.75)	- 1.01	1.18 (0.93 to 1.49)
ADVANCE	220 (0.83)	231 (0.88)	- 0.72	0.95 (0.79 to 1.14)
VADT	79 (1.80)	85 (1.94)	- 1.16	0.92 (0.68 to 1.25)
Overall	459	446	- 0.88	1.00 (0.86–1.16) ($Q = 3.59$, $p = 0.31$, $I^2 = 16.4\%$)



ACCORD = Action to Control Cardiovascular Risk in Diabetes
ADVANCE = Action in Diabetes and Vascular Disease: Preterax® and Diamicron® Modified Release Controlled Evaluation
UKPDS = UK Prospective Diabetes Study
VADT = Veterans Affairs Diabetes Trial

Exhibit 3: Multiple Complex Pathophysiological Abnormalities in T2DM

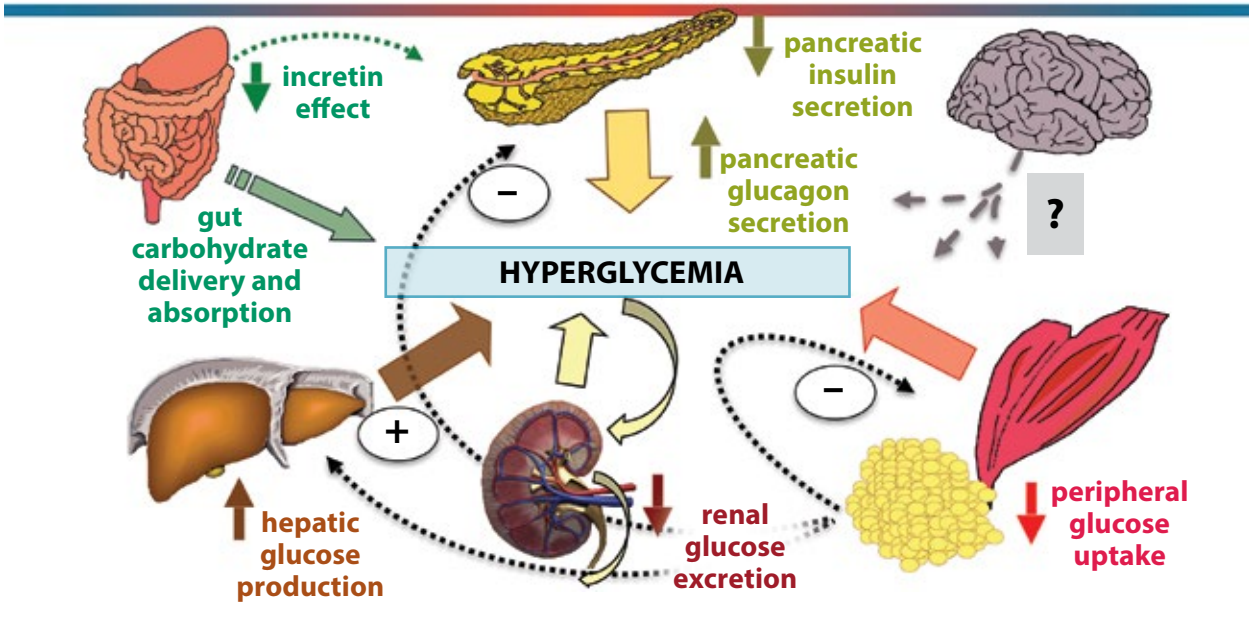


Exhibit 4: FDA-Approved Indications

Agent	Indications
Canagliflozin (Invokana®)	• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease. • to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria.
Dapagliflozin (Farxiga®)	• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors. • to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). • to reduce the risk of sustained eGFR decline, end-stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression
Empagliflozin (Jardiance®)	• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure and reduced ejection fraction.
Ertugliflozin (Steglatro®)	• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

kidney function. It is important to note that the one completed trial with ertugliflozin found it to be noninferior to placebo in terms of CVD outcomes, and it was not included in the meta-analysis.[19]

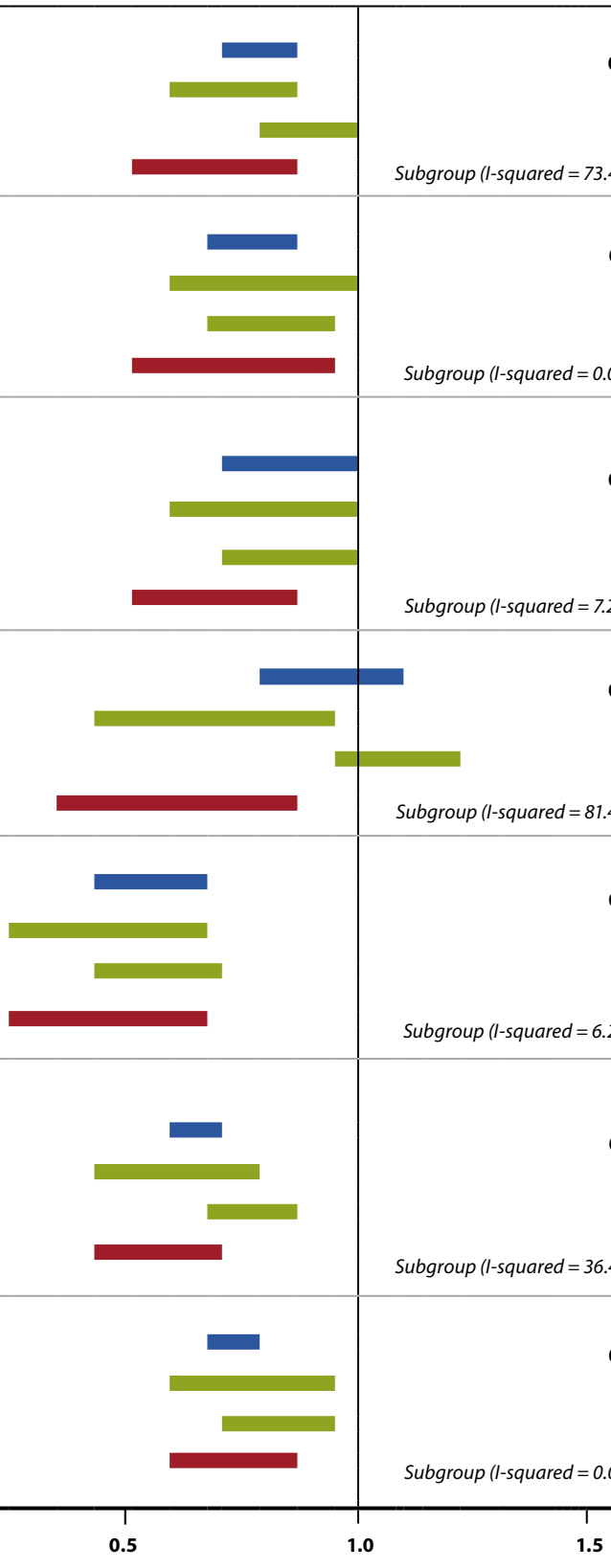
Additionally, all but the ertugliflozin trial showed benefit in reducing the progression of CKD. The benefit was a 24 to 40 percent relative-risk reduction. A meta-analysis of the four outcomes trials found that SGLT2 inhibitors reduce the need for dialysis, kidney transplantation, and death from kidney disease by 67 percent and the development of ESRD by 65 percent.[20] The benefits of SGLT2 inhibitors on kidney function are similar to what is seen with angiotensin- converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB). Additionally, dapagliflozin and canagliflozin have been shown to have renal benefits in those with CKD, with or without diabetes.[17,21]

Interestingly, benefits of this class are also being shown in nondiabetic individuals. DAPA HF was the first trial to assess clinical outcomes from a SGLT2 inhibitor in nondiabetic individuals. In this trial of patients with reduced ejection fraction HF, the primary outcome of worsening HF (composite of death from CV causes, hospitalization for HF, or urgent visit resulting in intravenous treatment for HF) occurred in a significantly lower percentage of patients in the dapagliflozin group (16.3%) compared to the placebo group (21.2%).[22] Similar benefits were seen in those with or without T2DM. A subsequent trial with empagliflozin found that it significantly improved CV and renal outcomes in patients with HF and a reduced ejection fraction, independent of baseline diabetes status and across the continuum of A1C levels.[23] A trial with each of these agents in those with HF and preserved ejection fraction is ongoing (EMPEROR-Preserved, DELIVER).

Potential mechanisms of SGLT2 inhibitors CV benefits include both metabolic and hemodynamic effects. Metabolic effects include decreased A1C, fasting glucose, post-prandial glucose, body weight, and waist circumference. These agents also increase

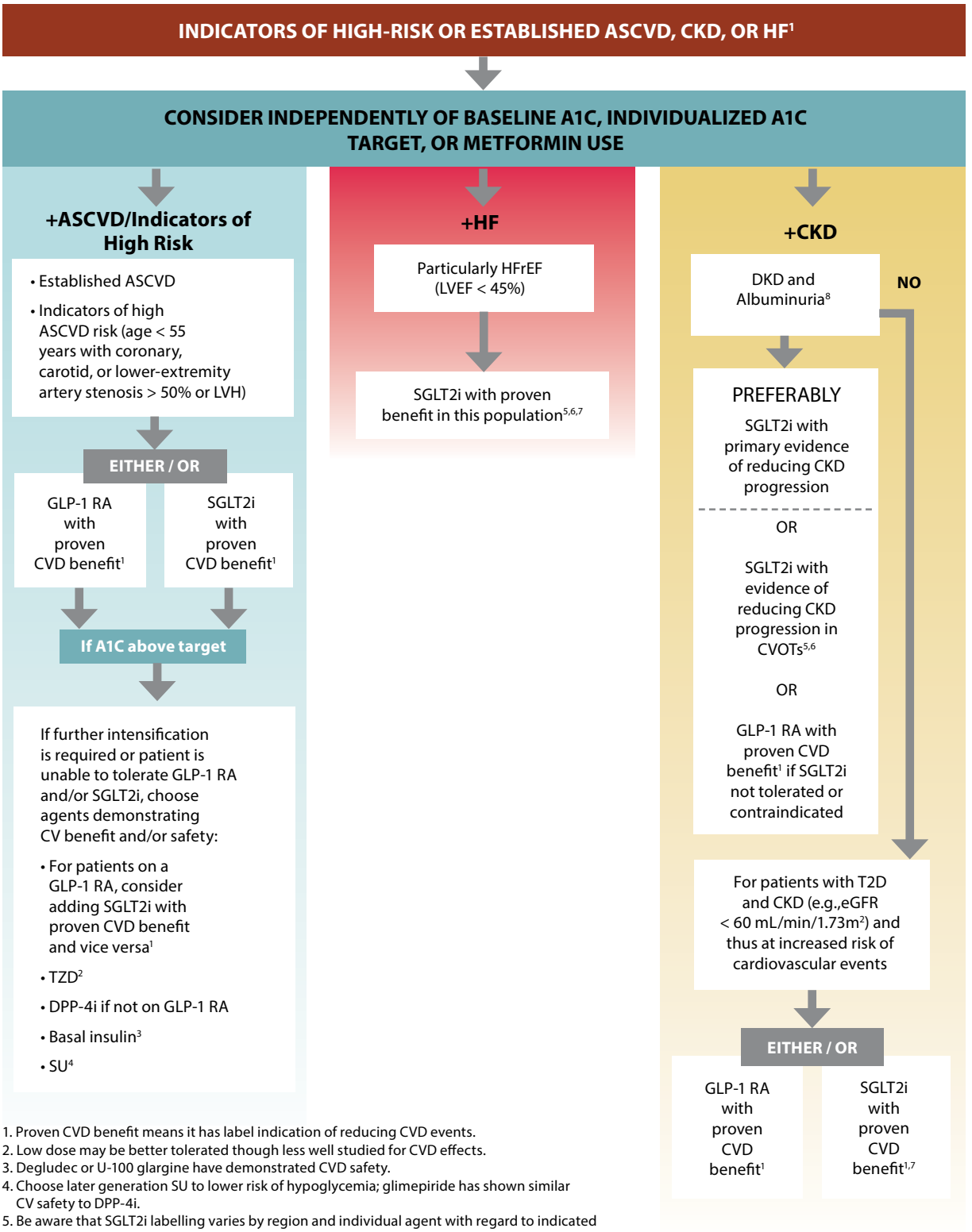
Exhibit 5: Benefits of SGLT2 Inhibitors[18]

Outcome by Groups	Events	Patients	Hazard Ratio (95% CI)	*p* value
MACE				
Overall	3,828	38,723	**0.88 (0.82 to 0.94)**	< 0.001
eGFR < 60 at baseline	1,051	7,754	0.80 (0.70 to 0.90)	
eGFR ≥ 60 at baseline	2,777	30,969	0.92 (0.85 to 0.99)	
			Subgroup (I-squared = 73.4% $p_{interaction}$ = 0.053)	
Cardiovascular Death				
Overall	1,506	38,723	**0.83 (0.75 to 0.92)**	< 0.001
eGFR < 60 at baseline	512	7,754	0.83 (0.70 to 0.99)	
eGFR ≥ 60 at baseline	994	30,969	0.83 (0.73 to 0.94)	
			Subgroup (I-squared = 0.0% $p_{interaction}$ = 0.983)	
Myocardial Infarction (fatal and non-fatal)				
Overall	1,782	38,723	**0.96 (0.86 to 1.09)**	0.01
eGFR < 60 at baseline	439	7,754	0.75 (0.59 to 0.96)	
eGFR ≥ 60 at baseline	1,343	30,969	1.05 (0.91 to 1.20)	
			Subgroup (I-squared = 7.2% $p_{interaction}$ = 0.299)	
Stroke (fatal and non-fatal)				
Overall	1,150	38,723	**0.96 (0.86 to 1.09)**	0.541
eGFR < 60 at baseline	279	7,754	0.75 (0.59 to 0.96)	
eGFR ≥ 60 at baseline	871	30,969	1.05 (0.91 to 1.20)	
			Subgroup (I-squared = 81.4% $p_{interaction}$ = 0.020)	
Heart Failure Hospitalization				
Overall	1,192	38,723	**0.68 (0.60 to 0.76)**	< 0.001
eGFR < 60 at baseline	431	7,754	0.62 (0.62 to 0.85)	
eGFR ≥ 60 at baseline	461	30,969	0.71 (0.61 to 0.82)	
			Subgroup (I-squared = 6.2% $p_{interaction}$ = 0.302)	
Cardiovascular Death/ Heart Failure Hospitalization				
Overall	1,997	31,703	**0.76 (0.70 to 0.82)**	< 0.001
eGFR < 60 at baseline	660	5,935	0.72 (0.62 to 0.85)	
eGFR ≥ 60 at baseline	1,337	25,768	0.82 (0.74 to 0.91)	
			Subgroup (I-squared = 36.4% $p_{interaction}$ = 0.210)	
All Cause Mortality				
Overall	2,612	38,723	**0.85 (0.79 to 0.92)**	< 0.001
eGFR < 60 at baseline	806	7,754	0.83 (0.72 to 0.96)	
eGFR ≥ 60 at baseline	1,806	30,969	0.86 (0.78 to 0.94)	
			Subgroup (I-squared = 0.0% $p_{interaction}$ = 0.732)	



Fixed effect models with inverse variance weighting. *P* values have not been adjusted for multiple comparisons.

Exhibit 6: American Diabetes Association Choice of Diabetes Medication[13]



1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Low dose may be better tolerated though less well studied for CVD effects.
3. Degludec or U-100 glargine have demonstrated CVD safety.
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i.
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of EGFR for initiation and continued use.
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population.

glucagon, decrease uric acid, and increase ketone bodies (b-hydroxybutyrate). Hemodynamic effects include osmotic diuresis and/or natriuresis-induced decongestion and decreased blood pressure, arterial stiffness, and sympathetic tone. An exploratory analysis from the EMPA-REG OUTCOME trial found that changes in markers of plasma volume were the most important mediators of the reduction in risk of CV death with empagliflozin.[24]

The use of a SGLT2 inhibitor is recommended by the American Diabetes Association guidelines for those with indicators of high-risk or current atherosclerotic CVD (ASCVD), HF, or CKD (Exhibit 6).[13] For these patient groups, a SGLT2 inhibitor or, in the case of high-risk for ASCVD, a glucagon-like peptide one (GLP-1) receptor antagonist should be considered regardless of A1C, glycemic goals, or metformin use. These agents are not being used primarily for glucose lowering in these cases but for risk reduction. The selection of a SGLT2 inhibitor should be one proven to provide benefits for the specific indication.

SGLT2 inhibitors are now included as part of guideline-directed medical therapy in the U.S. HF treatment guidelines.[25] Dapagliflozin and empagliflozin have non-diabetes indications to reduce the risk of CV death and hospitalization for HF in adults with heart failure with reduced ejection fraction. Use of the SGLT2 inhibitors is limited by kidney function, and in advanced disease this class of agents does not work well because their mechanism of action depends on kidney function. The package labeling for each agent has recommendations on kidney function levels where use is not recommended or contraindicated. Although these agents have been studied in patients with eGFR down to 30 mL/min and appear safe, only canagliflozin is labeled for use at this low level.

Conclusion

Some of the SGLT2 inhibitors have been associated with reductions in major cardiovascular events (MACE), CV death, and/or HF hospitalization in patients with T2DM as well as in patients with HF with reduced ejection fraction. These agents also reduce the progression of kidney disease in patients with or without diabetes. Large-scale outcome trials have recently shown that SGLT2 inhibitors reduce adverse HF outcomes in those with HF and reduced ejection fraction (with or without diabetes). The emerging positive results from these studies suggest that these drugs are not solely glucose-lowering medications. Careful patient selection is key, avoiding this class in those individuals at the highest risk of adverse events and complications.

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Navigating Current and Emerging Approaches in the Treatment and Management of Hemophilia

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

Summary

Appropriate prophylactic treatments for a patient's lifetime and adherence support are required to optimize outcomes for those with hemophilia. Various improvements in hemophilia treatment including extended half-life factors and non-factor products have been developed to address the major unmet needs in this devastating disease. Those with this disease who were started on therapy as children are now living normal lifespans with minimal disease consequences.

Key Points

- Hemophilic arthropathy is the most significant complication of hemophilia.
- Inhibitor development is the most serious complication of hemophilia treatment.
- Non-factor replacement therapies appear to be the future of hemophilia treatment.
- Clinical decision-making regarding treatment selection and optimization is complex and requires Hemophilia Treatment Center expertise and resources.
- Gene therapy is a potential cure for hemophilia and should be available within the next few years.

HEMOPHILIA IS A MONOGENETIC BLEEDING disorder due to deficiency or absence of a coagulation protein [Factor VIII (FVIII) or IX (FIX), Exhibit 1]. Hemophilia A and B have indistinguishable clinical features but must be distinguished by laboratory testing in order to choose the correct treatment. There are approximately 30,000 males with hemophilia in the United States (U.S.).[1] About one-third of patients have no family history of hemophilia and have the disease as a result of spontaneous genetic mutations. Lack of family history can lead to delays in diagnosis.

Without proper treatment, recurrent bleeding into joints results in crippling arthropathy. Hemophilic arthropathy is currently the most significant complication of hemophilia. Intramuscular, gastrointestinal, and intracranial bleeds can be limb- and life-threatening. The severity of bleeding tendency in a given patient depends on the factor level present (Exhibit 2). Frequent spontaneous bleeding occurs in those with severe hemophilia (< 1% factor levels); however, severe hemophilia is usually diagnosed at birth or in early childhood. Two-thirds of all those with hemophilia have severe disease. Those with moderate or mild disease may not be diagnosed until adulthood.

The current state-of-the-art care for hemophilia treatment includes prophylaxis with factor replacement for all with a severe bleeding phenotype, pharmacokinetic-tailored dosing regimens for factor

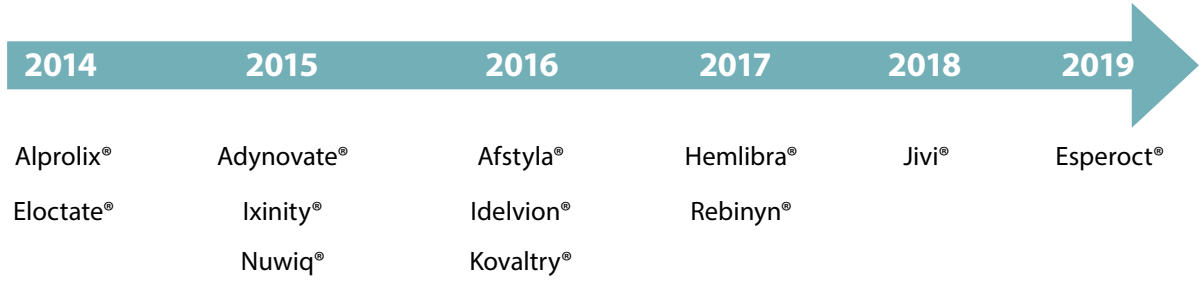
Exhibit 1: Phenotypes of Hemophilia

Hemophilia A	Hemophilia B
• Factor VIII deficiency	• Factor IX deficiency
• Classical hemophilia	• Christmas disease
• 1 in 5,000 - 10,000 male births	• 1 in 30,000 male births
• 80% of total cases	• 20% of total cases
• Spontaneous mutations = 30%	• Spontaneous mutations = 20%

Exhibit 2: Clinical Features of Hemophilia

Mild (> 5%)	Moderate (1% to 5%)	Severe (< 1 %)
• Bleed only after severe injury, trauma, or surgery	• Bleed after injury, surgery	• Frequent spontaneous bleeding
• May not be diagnosed until adulthood	• May have occasional spontaneous bleeding	• Diagnosis made in early childhood

Exhibit 3: Products Introduced Since 2014



prophylaxis with a goal of zero bleeds, adjustment of the treatment regimen for different life stages and activity levels, and care provided at a hemophilia treatment center (HTC). Bleed protection needs for children, teens, adults, and the elderly are different and thus require treatment adjustment. Treatment selection and optimization is complex and requires HTC expertise and resources. Thus, to receive state-of-the-art care, every patient with hemophilia should be cared for in a HTC.

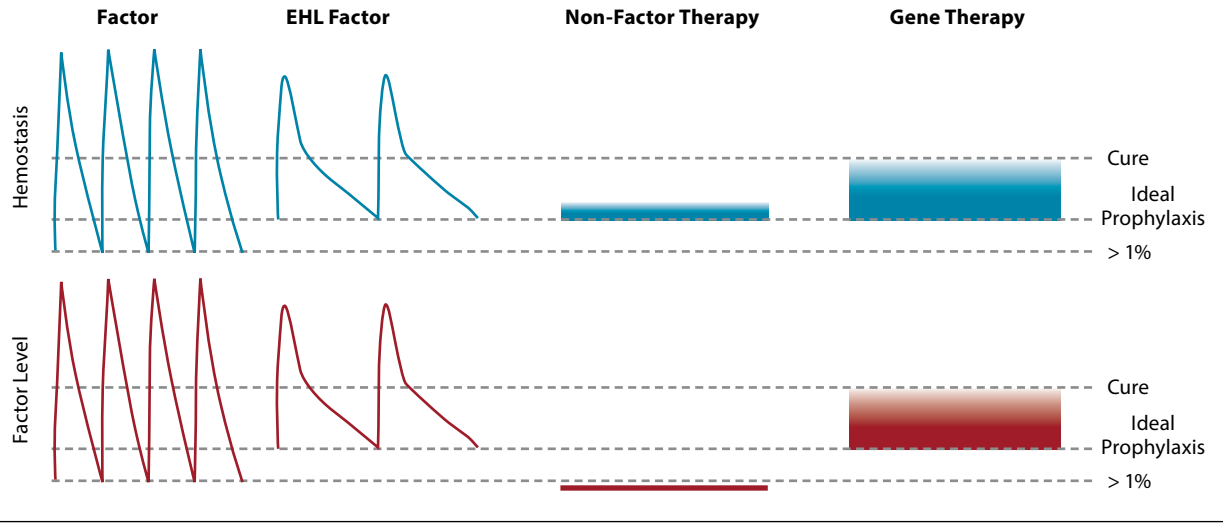
The primary treatment of hemophilia is factor replacement therapy. The benefits of adequate factor replacement include a proven decrease in bleeds, prevention of joint damage, improved functional status and quality of life, possible delay of arthropathy progression, if already present, and protection from traumatic and unexpected bleeds. Although factor replacement is expensive, the costs of not doing prophylaxis are much more, especially in terms of disability costs. Children with hemophilia today are started on prophylaxis at a very young age, are maintaining normal joints, living a normal life span, and many have never experienced a single bleed.

Plasma-derived concentrates were first developed in the 1960s, recombinant factor products were introduced in the 1990s, and extended half-life products became available in 2014. Each new generation of recombinant factor products have improved the removal of contaminants and decreased the infusion volumes. Since 2014, seven new FVIII products, four new FIX products, and one non-factor product have been approved (Exhibit 3).

Exhibit 4 compares standard half-life factor, extended half-life (EHL) factor, non-factor therapy, and gene therapy.[2] There are decades of experience with well-established efficacy and safety for the standard half-life factor replacement products, but there are issues. They require frequent intravenous infusions (3 to 4 times per week); it is difficult to maintain adequate trough levels; and long-term adherence is a major challenge.[2] Large inter-patient pharmacokinetic variability with the standard half-life factors also commonly occurs.[3] Young adults are the group sector with especially difficult adherence issues. Standard half-life products are still used in adult patients and subsequently have been doing well on them for many years.

EHL factor products have been modified in many ways to prolong the half-life. FVIII EHL products can be dosed every three to seven days compared with every two to three days with standard half-life products. There has been a biological barrier to extending the half-life of FVIII because its half-life is dependent on that of von Willebrand factor. FIX EHL products have a much more dramatic extension of dosing intervals (once every 1 to 2 weeks compared with 1 to 2 times per week). This is game changing for the patients with FIX deficiency, with some patients able to extend their dosing out to every 21 days. Unlike standard half-life factor products, EHL

Exhibit 4: Comparing Treatment Options[2]



products are not interchangeable, have clinically meaningful pharmacokinetic differences, and have more complex and varied dosing schedules. The EHL products are effective and safe, produce a high degree of patient satisfaction, and have improved adherence compared with standard half-life products. They are a viable choice for many, but not for all patients. Variables that affect decision-making in choosing an EHL product compared with standard factor products include age, adherence, venous access, activity type and pattern, pharmacokinetics, bleeding phenotype, and joint status.

The first EHL FVIII and FIX products were approved in 2014. These products pushed pharmacokinetic-guided dosing to the forefront of hemophilia care. Higher trough levels are achievable with realistic dosing schedules, resulting in better bleed protection, which is the main benefit of these products. The need for less frequent infusions results in better long-term adherence to prophylaxis. Exhibits 5 and 6 show the available EHL factor products. With proper patient selection and pharmacokinetic-tailored dosing, EHL factor prophylaxis is cost effective.

The development of inhibitors is the most serious complication of factor replacement therapy. When treated with factor replacement, the immune system of some hemophilia patients react to exogenous FVIII or FIX as a foreign protein and produce antibodies directed against the factor (inhibitors), which neutralizes their procoagulant effect, rendering factor replacement useless. Inhibitors are typically seen in those with severe hemophilia (hemophilia A, ~ 30%; hemophilia B, < 5%). Inhibitors may occur in those with mild or moderate hemophilia after intense factor exposure related to trauma or surgery. The end result of inhibitors is bleeding becomes more difficult to control, devastating joint disease and disability occur because bleeding is not well controlled, and therapy is even more expensive because alternative therapies must be used. A non-factor replacement therapy for those with hemophilia A and inhibitors is now available.

Non-factor replacement therapy includes two categories: FVIII mimetics and medications that "rebalance" coagulation by inhibiting regulatory proteins. The rebalancing agents are still investigational. Subcutaneous and less frequent administration with these agents will make treating small children much easier and may improve adherence in all age groups. Importantly, the non-factor replacement therapies are unaffected by the presence of inhibitors.

Emicizumab-kxwh (Hemlibra®) was FDA-approved in 2017 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with FVIII inhibitors. It is now approved for use in those without inhibitors. Emicizumab-kxwh is a bispecific humanized monoclonal antibody that restores the function of missing activated FVIII by bridging activated FIX and factor X to facilitate effective hemostasis in patients with hemophilia A.[3]

Rebalancing agents are under investigation. Fitusiran and at least three tissue factor pathway inhibitors (TFPIs) are under study in hemophilia

Exhibit 5: EHL Factor VIII Drugs

	Efmoroctocog alfa (Eloctate®)	Rurioctocog alfa pegol (Adynovate®)	Damoctocog alfa pegol (Jivi®)	Turoctocog alfa pegol (Esperoct®)
FDA-approval	2014 Adults and Children	2015 Adults and Children	2018 Adults and Adolescents, previously treated	2019 (n/a until after 2020) Adults and Children
rFVIII design	B domain deleted	Full length	B domain deleted	B domain truncated
Modification to extend half life	Fc fusion	PEG (20 kDa)	PEG (60 kDa)	PEG (40 kDa)
Half life (hours) (adult)	19.7 +/- 2.3	14.7 +/- 3.8	17.9 +/- 4.0	~ 19
Dosing (adult)	50 U/kg every 4 days ***Adjust:*** 25 to 65 U/kg every 3 to 5 days	40 to 50 U/kg 2x per week	30 to 40 U/kg 2x per week ***Adjust:*** 40 to 60 U/kg every 5 days; may be further adjusted to less or more frequent dosing	50 U/kg every 4 days ***Adjust:*** less or more frequent dosing based on bleeding episodes
Efficacy	• All highly effective when used as prophylaxis • Also effective for breakthrough bleeds and perioperative management			
Safety	• Generally well tolerated with no unexpected safety issues			

Dosing and half life data taken from U.S. Prescribing Information for each drug.

A and B, with and without inhibitors. Fitusiran lowers antithrombin levels, which inhibits blood clotting, while increasing production of thrombin to aid clotting. It would be used as prophylaxis and would be dosed monthly. Trials with this agent, at lower doses than initially used, have resumed after being put on hold because of non-fatal vascular thrombotic events in trial participants.[4]

Concizumab is a novel subcutaneous prophylactic therapy for hemophilia. It is a hemostatic rebalancing agent that binds to the Kunitz-2 domain of TFPI, one of the molecules that contribute to downregulation of coagulation thereby preventing TFPI from binding to and blocking the factor Xa (FXa) active site.[5] The research program for this agent was also halted for a period of time because of thrombotic adverse events.

Marstacimab is another investigational anti-TFPI for hemophilia. A Phase II study with this agent found decreased mean annualized bleeding rates compared with pre-study annualized bleeding rates in severe hemophilia A or B, with or without inhibitors.[6] No thrombotic adverse events were seen in this small, open-label trial. A Phase III study (ClinicalTrials.gov Identifier: NCT03938792) is currently recruiting to evaluate the safety and efficacy of marstacimab (300 mg loading dose and 150 mg weekly) in patients with severe hemophilia A or B.

Even with non-factor replacement therapies, there is a role for factor replacement. Factor replacement can achieve normal hemostasis, although temporarily,

Exhibit 6: EHL Factor IX Drugs

	Eftrenonacog alfa (Alprolix®)	Albutrepenonacog alfa (Idelvion®)	Nonacog beta pegol (Rebinyn®)
FDA-approval	2014 Adults and Children	2016 Adults and Children	2017 Adults and Children
rFIX design	Full length	Full length	Full length
Modification to extend half life	Fc fusion	Albumin fusion	PEG (40 kDa)
Half life (hours) (adult) [Mean (%CV)]	50 U/kg: 86 (37%) 100 U/kg: 97 (35%)	25 U/kg: 118 (38%) 50 U/kg: 104 (25%) 75 U/kg: 104 (18%)	40 U/kg: 114.9 (9.7%)
Dosing (adult)	50 U/kg once weekly, or 100 U/kg every 10 days; Adjust based on individual response	25 to 40 U/kg every 7 days; If well controlled, may switch to 50 to 75 U/kg every 14 days	40 to 80 U/kg (Not approved for prophylaxis in the U.S.)
Efficacy	• Highly effective when used as prophylaxis. • Also effective for breakthrough bleeds and perioperative management.		• Effective for on-demand treatment and perioperative management.
Safety	• Generally well tolerated with no unexpected safety issues		

Dosing and half life data taken from U.S. Prescribing Information for each drug.

and factor levels can be measured. All currently available factor replacement therapies still require repeated injections given over a lifetime. Trough levels achievable with realistic dosing regimens of currently available factor products do not provide complete bleed protection. Factor replacement is used for prevention and treatment of bleeds. Non-factor replacement therapies do not achieve normal hemostasis and a factor level equivalent cannot be measured. Hemostatic correction with non-factor replacement therapy provides better sustained trough coverage than factor replacement, but no peak coverage for intense physical activity, surgery, or bleeding episodes. The approved non-factor replacement agent and future agents are used for prevention of bleeds, but they cannot be used to treat bleeds.

Two additional factor products are under investigation. These are rFVIIIFc-vWF-XTEN (BIVV001) and dalcinonacog alfa (DalcA, FIX). BIVV001 is a B domain-deleted recombinant FVIII with an immunoglobulin-G1 Fc fusion to increase half-life.[7] It also has a von Willebrand factor D'D3 domain which allows for circulation independent of plasma von Willebrand factor and protein polymer insertions to increase half-life. Dalcinonacog alfa is a full-length FIX protein with greater potency (22-fold) and longer half-life than wild-type FIX. It has three amino acid substitutions that increase catalytic activity, increase resistance to antithrombin inhibition, and improve affinity for FVIII. It is different from current FIX products because it can be given subcutaneously, in small volumes, and has a prolonged half-life.

Gene therapy is the holy grail of hemophilia treatment. The goal of course is a cure, but a true cure will require sustained normal hemostasis, eliminating the need for any factor replacement or

non-factor therapies. Hemophilia is a good target for gene therapy for several reasons. Hemophilia A and B are monogenetic diseases, and the clinical manifestations are due to a single missing protein. Even a modest increase in factor level can have a dramatic clinical benefit. There are well-characterized mouse and larger animal models for preclinical studies of gene therapy. FVIII and IX can be made by cells other than those that normally make them. Lastly, lab and clinical endpoints (factor level and bleed rate) can be easily measured.

Gene editing, cell therapy, and gene transfer are all being investigated. Gene editing (e.g., CRISPR) seeks to repair or replace the broken gene. Cell therapy (e.g., CAR-T) introduces a functional gene into cells that are delivered into the body. Gene transfer (e.g., vector-based gene therapy) introduces copies of the functional gene into the body. There are 27 active gene therapy trials listed on clinicaltrials.gov.

Valoctocogene roxaparvovec (Valrox) for hemophilia A is currently the farthest along and is in Phase III trials. At three years, this gene therapy resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic FVIII use in all participants.[8] The subjects in this trial had severe hemophilia A, were 18 or older, and had no inhibitors and no antibodies to the vector that was used.

Conclusion

The therapeutic landscape for hemophilia has evolved rapidly since 2014. Clinicians now have better tools to address some long-standing unmet needs and continued improvement on the current treatment platforms is ongoing. Clinical decision-making regarding treatment selection and optimization is complex and requires HTC expertise and resources. Gene therapy is a potential cure for hemophilia and is currently under investigation.

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New Frontiers in the Treatment and Management of Chronic Cough: A Closer Look at the Role of Emerging Therapies

Michael S. Blaiss, MD

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

Summary

Patients with chronic cough have a significantly reduced health-related quality of life. For some patients, there is an explanation and effective treatment for their cough, whereas others have refractory or unexplained chronic cough. There are no FDA-approved agents for chronic cough, but several are under investigation.

Key Points

- Chronic cough significantly reduces quality of life.
- An extensive workup may be required to look for probable causes.
- Present treatments have minimal effect on refractory or unexplained chronic cough.
- Emerging therapies, especially P2X3 antagonists, show great promise.

COUGH SERVES TWO MAIN PURPOSES; clear the airways and protect the airway from irritates and foreign bodies. Cough can be classified as acute, subacute, and chronic (Exhibit 1).[1] The most common cause of acute cough is an upper respiratory tract infection. Post-viral infection cough is the most common cause of subacute cough. Chronic cough, which lasts eight weeks or longer, is a major issue to be dealt with because of the impact on the patient. About 11 percent of the population worldwide will have chronic cough.[2] In the 2018 National Health and Wellness Survey in the United States (U.S.,) the self-reported prevalence of chronic cough was 5 percent.[3] Those with chronic cough can

Exhibit 1: Classification of Cough[1]

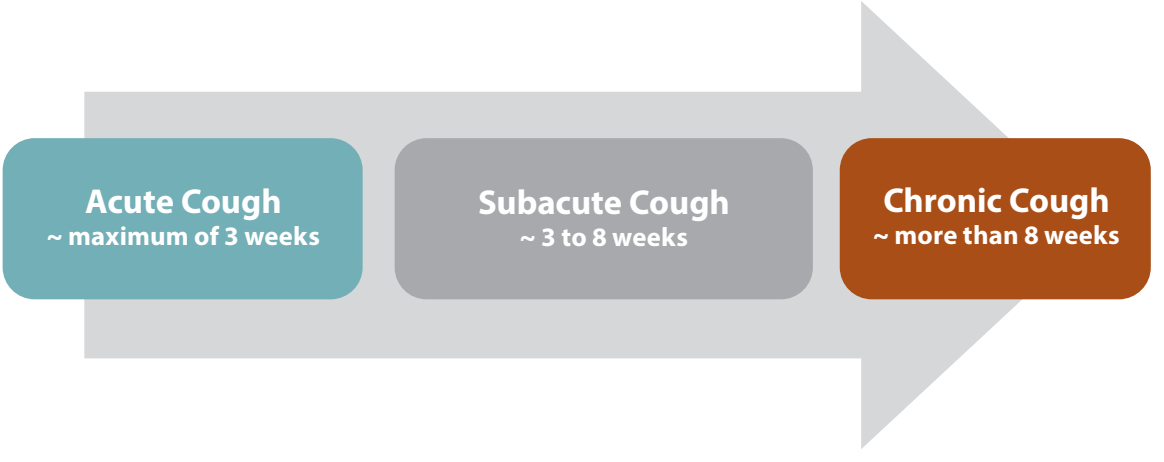


Exhibit 2: Evaluation and Management of Chronic Cough[4]

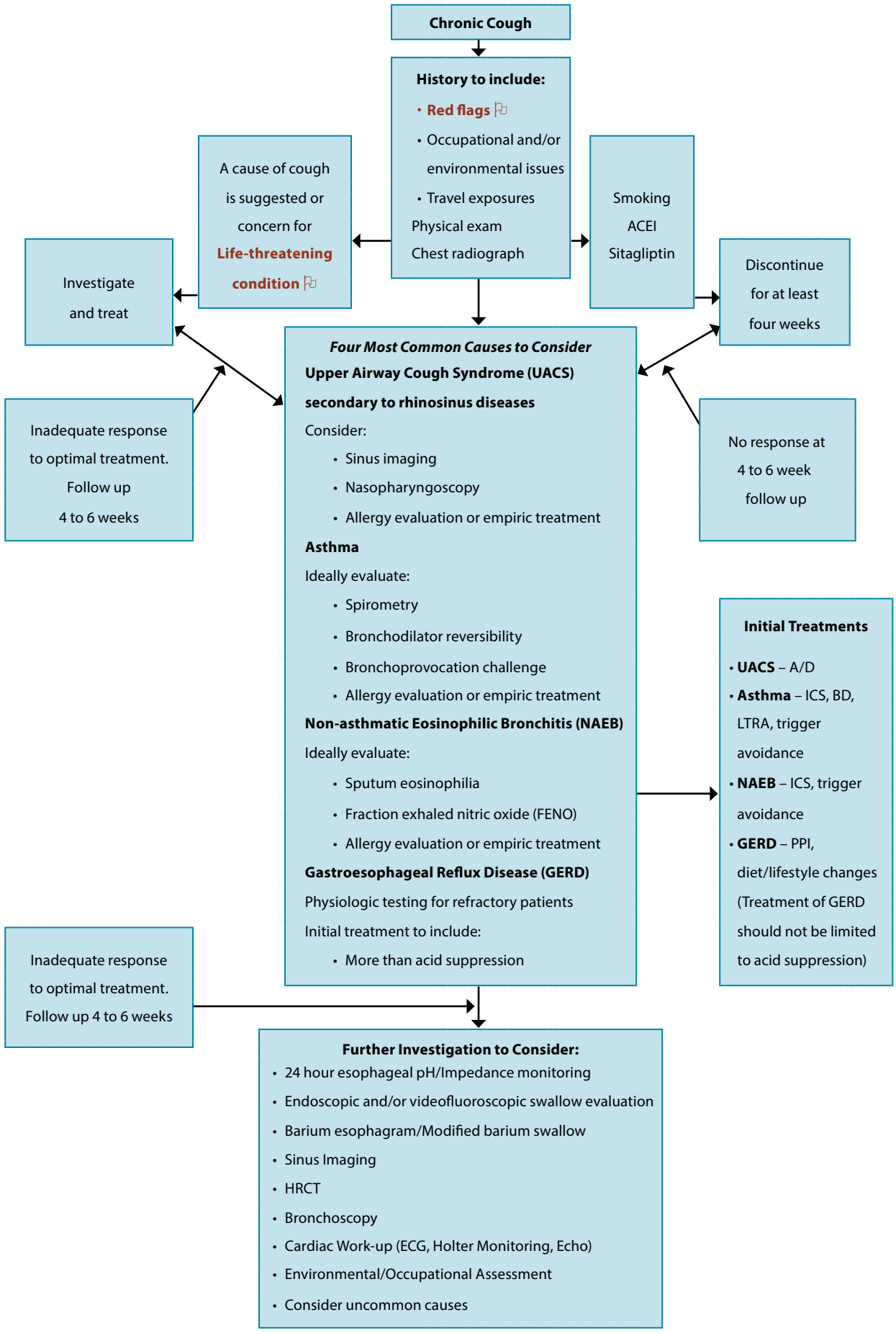


Exhibit 3: Red Flags[4]

Hemoptysis
Smoker 45 years of age or older with a new cough, change in cough, or coexisting voice disturbance.
Adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or whom have quit within the past 15 years.
Prominent dyspnea, especially at rest or at night.
Hoarseness
Systemic symptoms • Fever • Weight loss • Peripheral Edema with weight gain
Trouble swallowing when eating or drinking
Vomiting
Recurrent pneumonia
Abnormal respiratory exam and/or abnormal chest radiograph coinciding with duration of cough.

be difficult to treat because of the lack of effective cough suppressants.

Patients who seek medical care for cough cite the need for reassurance that nothing serious, such as lung cancer, is occurring as the most common motivator to seek care. Vomiting, exhaustion and chest pain from coughing, difficulty speaking, and embarrassment are also frequent reasons to seek care. Chronic cough is more common in women, in those older than 50 years of age, and in smokers.[3] Chronic cough has a tremendous impact on health-related quality of life, especially the physical and mental components.[3] The rates of depression and anxiety symptoms are 2.4 times higher in those with chronic cough. It also impacts work productivity.

The diagnosis and management guidelines for chronic cough suggest an initial workup which includes identifying the length of time of cough, triggers of cough (environmental exposures, occupational exposures), previous evaluations and treatments, and current medications (Exhibit 2).[4] Red flags for potentially life-threatening conditions also should be identified (Exhibit 3).[4]

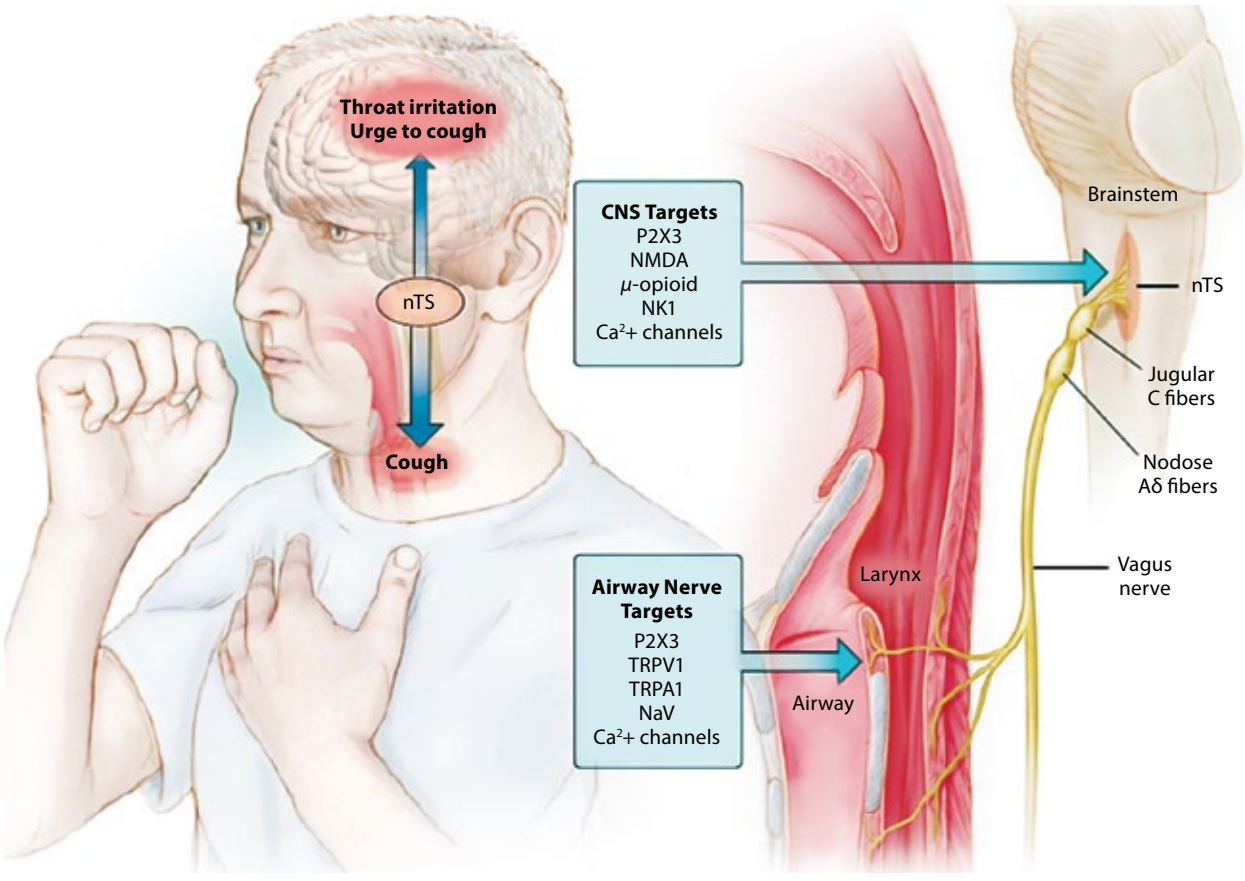
Four conditions cause most cases of chronic cough in immunocompetent, nonsmoking patients with normal chest radiographic findings. These are upper airway cough syndrome (UACS), asthma, non-asthmatic eosinophilic bronchitis, and gastroesophageal reflux disease (GERD). Each of these should be treated with standard guideline-directed therapy. If not associated or underlying medical conditions are identified as causing a chronic cough, the cough is considered to be unexplained chronic cough (UCC). When associated and/or underlying medical conditions are identified and treated per guidelines but cough persists, the cough is considered to be refractory chronic cough (RCC).[5]

The treatment of UCC and RCC may include speech pathology for cough control techniques and treatment of neuronal pathways of cough.[4,6] These patients should be referred to a cough specialist or a chronic cough center.

Gabapentin, which is not FDA-approved for cough, is the only medication recommended by the treatment guidelines; however, pregabalin, amitriptyline, and low-dose morphine have also been used.[4] In one randomized placebo controlled trial, in 62 patients with UCC/RCC, gabapentin (up to 1,800 mg daily dosage) significantly improved cough-specific quality of life compared with placebo (between-group difference in Leicester cough questionnaire score during treatment period 1.80, $p = 0.004$, number needed to treat of 3.58).[7] The adverse events of gabapentin included drowsiness, clumsiness, constipation, nausea, and dry mouth.

Better treatments for UCC/RCC, which are effective but do not cause sedation, are needed. Exhibit 4 shows some of the potential central

Exhibit 4: Potential Targets for Chronic Cough[5]



nTS = nucleus tractus solitarius; NMDA = N-methyl-D-aspartate; NK1 = neurokinin-1; TRPV1 = transient receptor potential vanilloid 1; TRPA1 = transient receptor potential Ankyrin 1; Ca = calcium

nervous system and airway nerve targets.[5] Trials with sodium-channel blockers and transient receptor potential vanilloid 1 (TRPV1) antagonists have failed so far. The two viable areas of investigation include neurokinin (NK-1) receptor antagonists and P2X3 antagonists.

Aprepitant, a commercially available NK-1 receptor antagonist for post-chemotherapy nausea, showed signs of efficacy for UCC/RCC in an open-label pilot study.[8] Orvepitant has shown efficacy in a preliminary study in 13 patients with 40 mg daily.[9] A Phase IIb study is planned. Extracellular adenosine triphosphate (ATP), released due to inflammation, shearing forces, or smooth muscle contraction in airways may be an important mechanism for patients with UCC/RCC.[10] Binding of extracellular ATP to P2X3 and P2X2/3 receptors on C-fiber creates an action potential.[11] C-fiber activation initiates pathologic cough.

Four P2X3 antagonists are under investigation for UCC/RCC; gefapixant, BLU-5937, eliapixant, and S-600918. Phase III studies with gefapixant have been completed, and the other agents are in Phase II studies. Phase II and Phase III studies have shown efficacy with gefapixant and it has been submitted to the FDA for approval for UCC/RCC.[12-16] In the Phase III COUGH-1 and COUGH-2 trials, the primary efficacy endpoints were met for the gefapixant 45mg twice daily treatment, but not with 15 mg twice daily.[15,16] There were over 2,000 patients in these two studies. In COUGH-1 with 45 mg twice daily, there was a statistically significant reduction in 24-hour cough frequency at week 12 versus placebo (geometric mean coughs/hour = 18.24 at baseline compared to 7.05 at primary endpoint, 32.9% relative reduction; $p = 0.041$). There was also a statistically significant reduction in 24-hour cough frequency at week 24 with 45 mg twice daily in COUGH-2 (baseline = 18.55 versus 6.83 at primary endpoint, 26.1% relative reduction; $p = 0.031$). Mild to moderate taste-related adverse events were the most common, 58.0 percent to 68.6 percent for 45 mg and 3.3 percent

to 8.3 percent for placebo The discontinuation rates for the 45 mg dose were 15 percent and 20 percent respectively, compared to 3 percent and 5 percent in the placebo arm, respectively.

Taste disturbance rates and cough reduction increased with increasing gefapixant dose.[17] Taste disturbances occur because there are P2X2 and P2X3 receptors on the taste buds. Gefapixant interacts with both P2X2 and P2X3.

The Phase II RELIEF trial of BLU-5937 did not achieve statistical significance for the primary endpoint of reduction in placebo-adjusted cough frequency at any dose tested.[18] A clinically meaningful and statistically significant placebo-adjusted reduction in cough frequency was achieved in a pre-specified sub-group of high cough count patients (all patients at or above the baseline median average of 32.4 coughs per hour).[18] This trial has not yet been published. Lower rates of taste disturbance have been seen with BLU-5937 compared with gefapixant.[17]

Eliapixant at 200 mg and 750 mg twice daily decreased 24-hour cough counts by 23 and 25 percent, respectively.[19] A taste-related adverse event was seen in 15 percent and 21 percent of patients. Again, results from this Phase IIb trial have not yet been published. S-600918, 150 mg once daily, reduced daytime coughs by 31.6 percent ($p = 0.0546$) relative to placebo in 31 patients, while 24-hour coughs, a secondary endpoint, were significantly reduced by 30.9 percent ($p = 0.0386$).[20] Taste change (3.2%) and taste injury (3.2%) were observed during S-600918 treatment.

Conclusion

Chronic cough is a frustrating clinical burden with reduced quality of life in the patient population. An extensive workup may be required to look for probable causes. Present treatments have minimal effect on refractory or unexplained chronic cough; however, emerging therapies, especially P2X3 antagonists, show great promise for patients.

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New Horizons in the Treatment and Management of Hepatocellular Carcinoma: Expert Perspectives on the Evolving Role of Immunotherapy

Richard S. Finn, MD

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

Summary

The preferred first-line treatment for advanced hepatocellular carcinoma (HCC) has recently changed based on a trial showing superiority over the previously preferred therapy of a tyrosine kinase inhibitor. With each new advance in therapy, median overall survival for this devastating disease is improving.

Key Points

- Atezolizumab in combination with bevacizumab is now the first-line systemic therapy choice for those with advanced HCC.
- Other novel combinations which include immunotherapy are likely to be approved for use in the future.

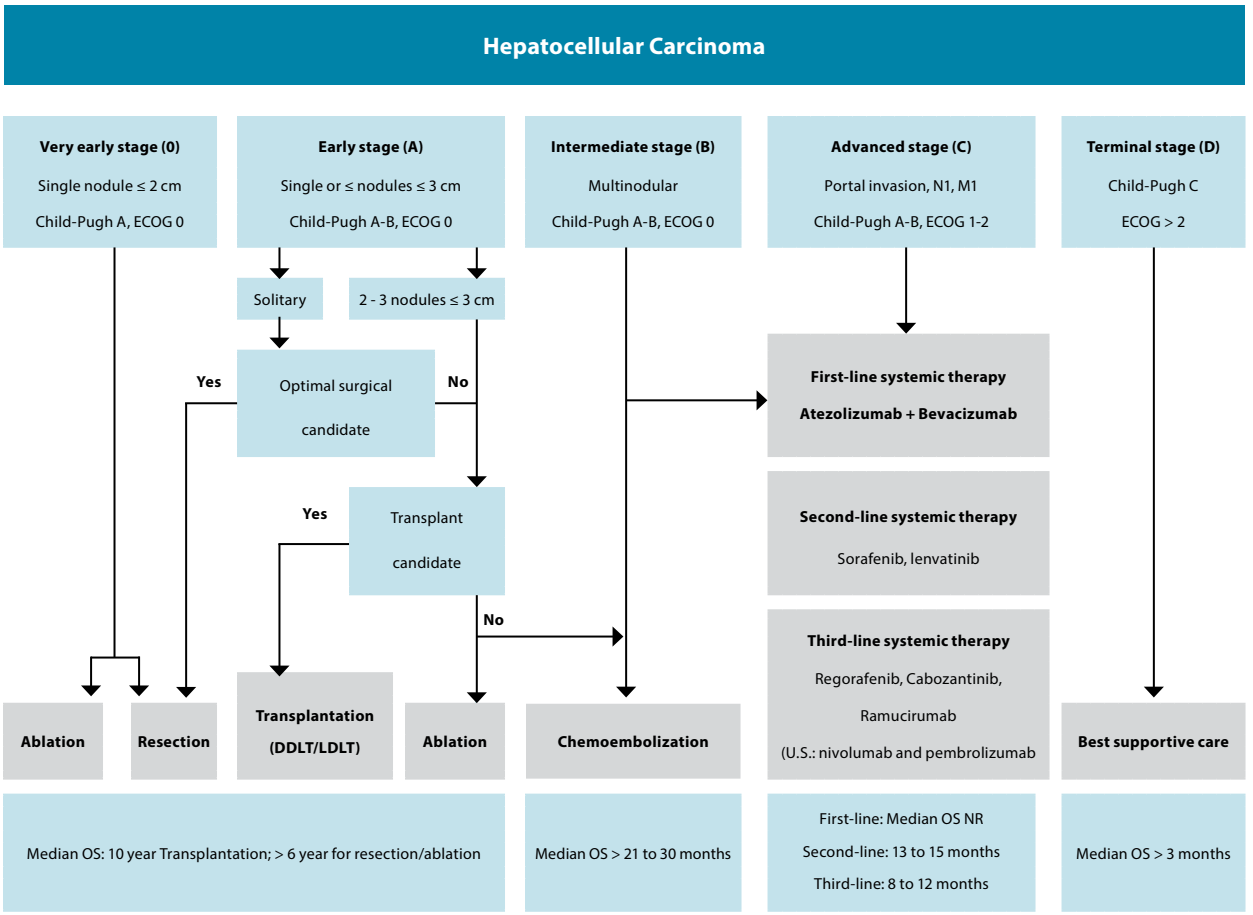
HEPATOCELLULAR CARCINOMA (HCC) IS the most common primary liver malignancy. It arises from transformed hepatocytes with 90 percent of cases associated with cirrhosis of all causes. HCC is asymptomatic until advanced, and it is incurable. Exhibit 1 shows the modified Barcelona Clinic Liver Cancer (BCLC) staging and an example treatment strategy.[1,2] Overall prognosis for survival is poor with HCC, with a five-year relative survival rate of 20 percent.[3] By stages, the relative five-year survival rate is 34 percent in patients diagnosed with localized disease, 12 percent with regional disease, and 3 percent with distant disease.

Treatments for advanced unresectable HCC are chemoembolization and palliative systemic therapies. An example of chemoembolization is transarterial radioembolization withYttrium-90. Systemic therapies include tyrosine kinase inhibitors (TKIs), anti-vascular endothelial growth factor (VEGF) agents, and immunotherapy. Sorafenib and lenvatinib are the primary TKIs which have been used, and both provide overall survival benefits.[4-6] In a trial where patients were treated with regorafenib, a second-line and later TKI, after sorafenib failure, there was a median overall survival (OS) of 26 months from the first sorafenib dose to death.[7] Thus, although incurable, survival with advanced HCC has been improving.

Immunotherapy has been investigated as a treatment for advanced HCC because this cancer is a classical inflammation-induced tumor type and spontaneous immune-induced regression has been observed. Immunotherapy was initially recommended as second-line treatment for advanced HCC after a TKI, but one combination (atezolizumab plus bevacizumab) is now the recommended first-line treatment.

The atezolizumab/bevacizumab combination was investigated because checkpoint immunotherapy and anti-VEGF therapies appear to work synergistically (Exhibit 2).[8-13] Bevacizumab is an antiangiogenic agent with additional immunomodulatory effects. In combination, bevacizumab appears to further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumor.

Exhibit 1: Treatment Strategy in the Management of HCC[1,2]

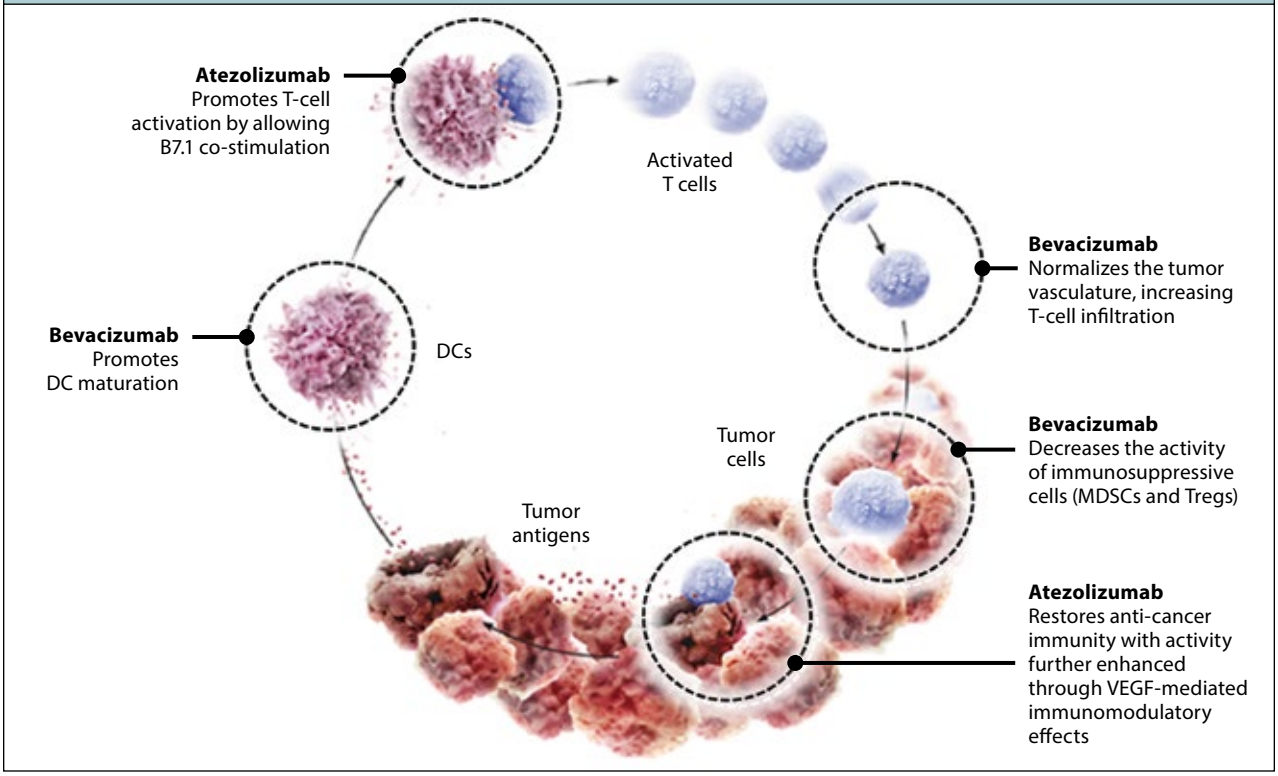


In patients with unresectable HCC, atezolizumab combined with bevacizumab resulted in better overall and progression-free survival (PFS) outcomes than sorafenib.[14] Overall survival at 12 months was 67.2 percent with atezolizumab/bevacizumab and 54.6 percent with sorafenib. Median PFS was 6.8 months and 4.3 months in the respective groups (hazard ratio for disease progression or death, 0.59; $p < 0.001$). Grade 3 or 4 adverse events occurred in 56.5 percent of those who received atezolizumab/bevacizumab and in 55.1 percent who received sorafenib. Grade 3 or 4 hypertension occurred in 15.2 percent of patients in the atezolizumab/bevacizumab group.

The recommended first- and subsequent-line systemic therapies for advanced HCC are shown in Exhibit 3.[15] The move away from sorafenib or lenvatinib as first-line therapy occurred with the publication of the previously discussed trial. Patients can go through many lines of therapy as long as their Child-Pugh score remains Class A. The Child-Pugh score is a measure of severity of the patient's underlying liver disease in addition to the HCC and includes total bilirubin, serum albumin, prothrombin time prolongation, ascites, and hepatic encephalopathy. There are few National Comprehensive Cancer Network recommended options beyond nivolumab and sorafenib if the patient's liver disease is worse than Class A.

Ongoing studies are looking at other novel combinations, and these will likely be approved in the next few years. Atezolizumab in combination with cabozantinib is being compared to sorafenib. Also, combination immunotherapy with tremelimumab {anti-cytotoxic T lymphocyte associated protein four (CTLA4)] and durvalumab [anti-programmed death ligand one (PD-L1)] is being studied. Early results from these trials look very promising.

Exhibit 2: Combining VEGF Inhibition and Immunotherapy[8-13]



VEGF = vascular endothelial growth factor; DC = dendritic cell; MDSCs = Myeloid-derived suppressor cells; Tregs = regulatory T cells

Conclusion

Advanced HCC is still a fatal disease; however, for the first time, there is now a highly active regimen (atezolizumab/bevacizumab) that is superior to sorafenib in the front-line setting. Other novel combinations which include immunotherapy are likely to be approved for use in the future.

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Exhibit 3: NCCN Recommended Therapy for Advanced HCC[15]

First-Line Systemic Therapy		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Atezolizumab + bevacizumab (Child-Pugh Class A only, category 1)	***Sorafenib*** (Child-Pugh Class A, category 1 or B7) *Lenvatinib* (Child-Pugh Class A only, category 1)	***Nivolumab*** (if ineligible for TKI or other anti-angiogenic agents, Child-Pugh Class A or B, category 2B) FOLFOX (category 2B)
Subsequent-Line Therapy if Disease Progression		
Options	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Regorafenib (Child-Pugh Class A only, category 1) ***Cabozantinib*** (Child-Pugh Class A only, category 1) ***Ramucirumab*** (AFP ≥ 400 ng/ml only, category 1) ***Lenvatinib*** (Child-Pugh Class A only) ***Sorafenib*** (Child-Pugh Class A or B7) ***Larotrectinib*** (NTRK gene fusion) ***Entrectinib*** (NTRK gene fusion)	***Nivolumab + ipilimumab*** (Child-Pugh Class A only) ***Pembrolizumab*** (Child-Pugh Class A only, category 2B)	***Nivolumab*** (Child-Pugh Class B only, category 2B) ***Dostarlimab-gxly*** (MSI-H/dMMR tumors, category 2B)

Implementing Expert Treatment Strategies in the Management of Inflammatory Bowel Disease

Miguel Regueiro, MD

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

Summary

Bowel healing is the goal of inflammatory bowel disease treatment to reduce the long-term complications of this disease, including cancer and surgical removal of parts of the bowel. There are effective, disease-modifying therapies which can induce bowel healing in moderate to severe disease; however, managing this complicated disease requires a specialist.

Key Points

- There are numerous treatment options for inflammatory bowel disease which are disease-modifying.
- Tumor necrosis factor (TNF) inhibitors may not be the best choice for all patients despite many managed care plans requiring use of these first.
- A specialist-based inflammatory bowel disease medical home model should be considered to improve outcomes.

INFLAMMATORY BOWEL DISEASE (IBD) is an autoimmune disease that has traditionally been divided into Crohn's disease (CD) and ulcerative colitis (UC) based on clinical patterns of disease on colonoscopy. UC is diffuse superficial inflammation of the colon, and CD is focal areas of deep inflammation interspersed with normal tissue throughout the GI tract. UC can lead to chronic changes in the colon lining which can lead to colon cancer. The deep inflammation of CD through the layers of the intestines leads to the complications of fistula, stricture, bowel obstruction, abscesses, and colon cancer.

The treatment of IBD has evolved dramatically since the first use of sulfasalazine in 1950. Recognition of various immune system targets and development of agents that work on these targets has led to anti-tumor necrosis factor (TNF), anti-cytokine, anti-integrin, and Janus kinase (JAK) inhibitor-based therapies.[1] Exhibit 1 shows the FDA-approved agents for CD and UC. The focus of this article is moderate to severe IBD.

Anti-TNF inhibitors are effective for induction and maintenance in moderate to severe IBD, with rapid onset of symptom control.[2] They are effective in achieving mucosal healing, improving health-related quality of life (HRQoL), reducing surgeries/hospitalizations, and in treating fistulizing disease.[2,3] Combination therapy with an immunomodulator like methotrexate is preferred due to the potential for immunogenicity and loss of response. Anti-TNF therapy does generate adverse events, including infection and malignancies such as lymphoma.

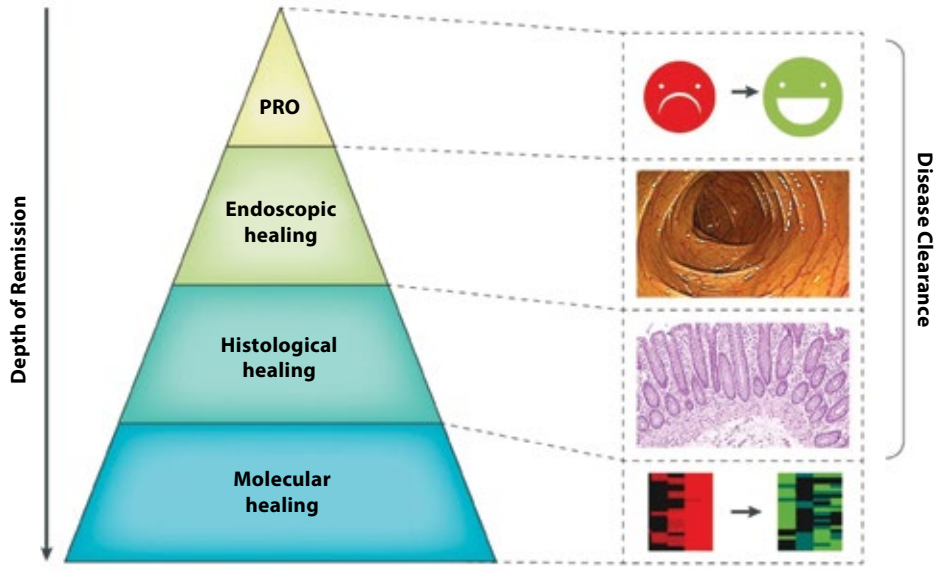
One-third of patients will not respond to induction therapy with anti-TNF inhibitors (primary nonresponse), and 50 percent of those who do respond will lose response within a few years.[4,5] It is not known what leads to primary nonresponse or loss of response. Theories include neutralizing anti-drug antibodies, low serum trough levels, and other immune pathways rather than TNF driving inflammation. Concomitant immunosuppressives, such as methotrexate and azathioprine, decrease clearance of TNF-inhibitors so they may help maintain higher levels to combat loss of efficacy. Anti-drug antibodies, low serum albumin, high baseline C-reactive protein (CRP), high baseline TNF concentration, high body mass index, and male gender all increase clearance and may increase risk of primary nonresponse or loss of response.[6] The

Exhibit 1: Biologics/Targeted Therapies in IBD

Mechanism	Agent	Route	Frequency*	Indication	
				CD	UC
Anti-TNFα	Infliximab (Remicade®)	IV	Every 8 weeks	✓	✓
	Adalimumab (Humira®)	SC	Every 2 weeks	✓	✓
	Certolizumab pegol (Cimzia®)	SC	Every 4 weeks	✓	
	Golimumab (Simponi®)	SC	Every 4 weeks		✓
Anti-integrin	Natalizumab (Tysabri®)	IV	Every 4 weeks	✓	
	Vedolizumab (Entyvio®)	IV	Every 8 weeks	✓	✓
IL-12/23	Ustekinumab (Stelara®)	SC	Every 8 weeks	✓	✓
JAK inhibitor	Tofacitinib (Xeljanz®)	Oral	Twice daily		✓

*Not including loading dose.

Exhibit 2: What Should Be the Target?



PRO = patient reported outcomes

American Gastroenterological Association supports the use of reactive therapeutic drug monitoring (TDM) to guide treatment changes in patients with active IBD who are being treated with anti-TNF agents or thiopurines.[7] Their guidelines state that there is insufficient evidence to inform on the use of routine proactive TDM with anti-TNF agents in patients with quiescent disease. The best evidence for TDM is with adalimumab and infliximab.

Natalizumab and vedolizumab (Entyvio®) are anti-integrin agents. Since the introduction of vedolizumab, natalizumab is not used as frequently because of cases of progressive multifocal leukoencephalopathy (PML). Vedolizumab, a humanized monoclonal antibody to α4β7 integrin that modulates gut lymphocyte trafficking, was approved in 2014 for moderate to severely active UC and CD. The gut specificity of this agent provides it

Exhibit 3: Personalizing the Choice of Therapy in Moderate to Severe IBD[19]

anti-TNFs (IFX, ADA, CTZ, GOL)	• Longest history • IV and SQ options • Rapid onset of action • Combination with immunomodulator best • Immunogenicity • Joints/perianal disease • Infection risk • Lymphoma risk (with IM)
Anti-IL12/23 (Ustekinumab)	• IV then SQ • Fast onset of action • Efficacy in anti-TNF naïve and failure • Low immunogenicity • Psoriasis • Excellent safety profile
Anti-Integrin (Vedolizumab)	• IV (soon SQ also) • Little slower • Better results in anti-TNF-naive patients • Low immunogenicity • Gut-selective with excellent safety profile
JAK inhibitors (Tofacitinib)	• Only for UC • New kid on the block • Oral • Rapid onset of action • Non-protein-based therapy • Joints • Risks not completely defined (e.g., blood clots)

an advantage over natalizumab. In UC, it is a first-line option for induction of remission in patients with moderately active disease who fail conventional therapy.[2] It produces superior outcomes in anti-TNF-naïve patients, but many times gets restricted to use after TNF inhibitor failure.[8] In CD, it is effective as induction therapy, but may have slow onset of action relative to anti-TNF agents.[2] It is recommended for maintenance in patients with vedolizumab-induced remission. Higher vedolizumab serum concentrations are associated with higher remission rates after induction; TDM with this agent is still under investigation.[9] Vedolizumab has demonstrated a favorable safety profile compared to TNF inhibitors and natalizumab because of its gut specificity. Autoimmune, infusion-related, and enteric infections are infrequent. Use is not associated with increased risk of serious or opportunistic infections and the rate of malignancy in those treated with this agent are consistent with that observed in IBD patients normally.[10]

Ustekinumab (Stelara®) is a fully human IgG1k monoclonal antibody that binds the p40 subunit of interleukin (IL)-12 and IL-23. By preventing the binding of IL-12 and IL-23 to an IL-12 receptor, it inhibits IL-12 and IL-23 mediated signaling, cellular activation, and cytokine production. Ustekinumab is FDA-approved for moderate to severe CD, UC, psoriasis, and psoriatic arthritis. In UC, it is effective in inducing and maintaining remission in moderate to severe UC. Ustekinumab is recommended for moderate to severe CD patients who have failed

Exhibit 4: Novel Therapies in Development

Anti-integrin	Etrolizumab (anti-β7) Anti-MAdCAM-1 (PF-00547,659) AMG181 (anti-α4β7) Abrilumab SHP647
Anti-interleukin	Brazikumab Risankizumab Mirikizumab Guselkumab Tildrakizumab Spesolimab (IL-36R) PF-04236921
JAK Inhibitors and TYK2	Filgotinib Upadacitinib Baricitinib TD-1473 Peficitinib BMS-986165
S1P Receptor Modulators	Ozanimod Etrasimod Amiselimod
TLR-9	DIMS0150
PDE4 Inhibitor	Apremilast
Microbial Therapies	Intestinal Microbiota Transfer (IMT) SER-287

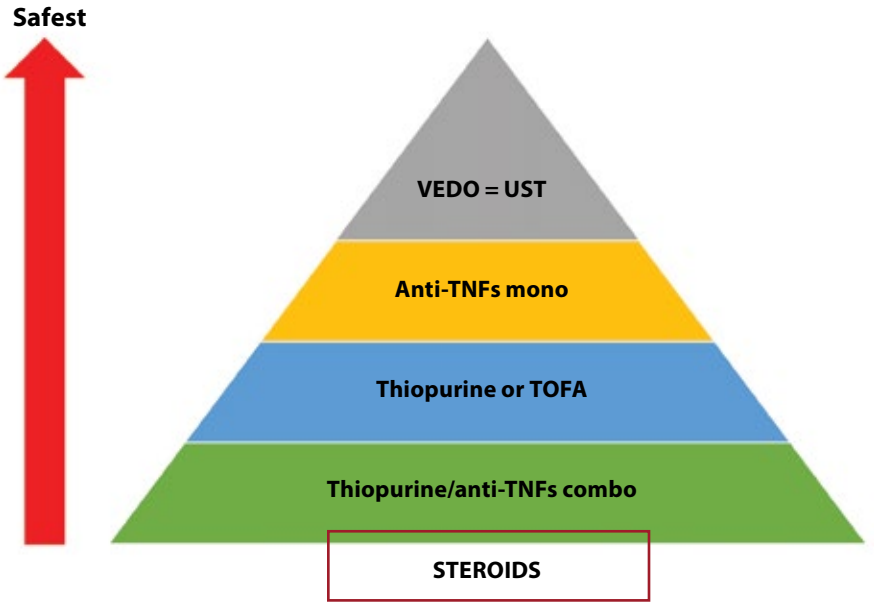
previous treatment with corticosteroids, thiopurines, methotrexate, and/or anti-TNF agents.[3] It produces similar induction success to anti-TNF agents in CD and has efficacy in anti-TNF-naïve and failure patients. Overall, it has superior safety to anti-TNF therapies, produces a low rate of immunogenicity, and is an excellent choice for concomitant IBD and psoriasis.[2]

Tofacitinib (Xeljanz®) is a small-molecule oral Janus kinase (JAK) inhibitor that blocks downstream activation by blocking JAK1, 2, and 3. These actions suppress production of pro-inflammatory cytokines IL-2, 4, 7, 9, 15, and 21. It was FDA-approved in 2018 for moderate to severely active UC and is the only oral therapy currently approved for UC. In UC, it rapidly induces remission and is effective as maintenance therapy.[2] It is effective in both anti-TNF-naïve and experienced patients. Importantly, combination therapy with other immunosuppressants appears to increase infection risk from potent immunosuppression and should not be used.[2] The study of tofacitinib for CD was stopped due to disappointing results in a Phase IIb trial. Other investigational JAK inhibitors continue to be studied in CD.

Herpes zoster risk is increased by JAK inhibitors, so patients should have vaccination prior to starting. Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, has been observed with tofacitinib in rheumatoid arthritis patients who were 50 years of age and older with at least one cardiovascular risk factor treated with tofacitinib 10 mg twice daily compared to tofacitinib 5 mg twice daily or TNF inhibitors in a large, ongoing post-marketing safety study. Many of these events were serious and some resulted in death. Thrombosis does not appear to be an issue in those with IBD, but clinicians typically avoid tofacitinib in patients at risk. Unfortunately, in IBD, the higher dose is commonly required to maintain remission, but most clinicians will try tapering to a lower dose once remission is achieved.

There are three pillars to IBD care — early intervention, a treat-to-target (T2T) approach aimed at blocking disease progression, and a tight control strategy based on therapeutic monitoring and subsequent adjustments of treatment. There is a window of opportunity in IBD when early effective treatment reduces inflammatory activity and bowel damage so therapy should be instituted as soon as possible after diagnosis. A T2T approach involves pre-defining a treatment target that is associated with optimal long-term outcomes (in consultation with the patient), continuously monitoring disease activity, and modifying treatment until the target is reached.[11] Currently, bowel healing by both histology and endoscopy is the primary treatment target; however, with continued advances in treatment, molecular healing may become an option (Exhibit 2).[12] Bowel healing is the goal rather than just symptom control because patients with no clinical symptoms have been shown to have ongoing bowel inflammation and damage. Endoscopic healing leads to better outcomes, including lower rates of CD-related surgery. Deep remission (defined as no symptoms, no corticosteroids, and endoscopic remission) has been shown to be disease-modifying in early CD. In the Effect of Tight Control Management on CD (CALM) study, deep remission was significantly associated with a lower risk of a major adverse outcome (fistula/abscess, stricture,

Exhibit 5: Safety Pyramid of Current IBD Meds[19]



VEDO = vedolizumab; UST = ustekinumab; TNF = tumor necrosis factor; TOFA = tofacitinib

perianal fistula/ abscess, CD hospitalization, or CD surgery).[13] Patients who are in endoscopic and/or deep remission are significantly less likely to have disease progression over a median of three years.

The success of the three-pillar strategy depends on patient commitment and involvement in the long-term management of their condition and their acceptance of this model of care. Improving patient-physician communication and supporting patients in their understanding of the evidence base is vital to ensure this happens. Adoption of this strategy could be the best way to change disease course (hospitalizations, surgeries, bowel damage, and disability) and improve patients' quality of life.[14,15]

There are IBD treatment guidelines from the American Gastroenterological Association and the American College of Gastroenterology.[3,16-18] These guidelines provide recommendations for identifying those with moderate to severe IBD who are at highest risk for complications of the disease and benefit the most from biologics and JAK inhibitors. Based on risk factors, many patients need these therapies, but they are required by managed care restrictions to step through other less effective or less safe therapies. Many patients are only treated with corticosteroids. While corticosteroids are highly effective for control of symptoms, they do not alter the course of IBD, do not consistently achieve mucosal healing, are not effective for maintenance of medically induced remission, and carry risk for well-known long-term adverse events.[3,13] Patients who are at risk of progression require treatment with more effective disease-modifying agents in order to change the course of their disease. Steroid-free remission is emerging as another treatment target in IBD.

Which therapy to select for induction and remission in moderate to severe IBD is a matter of debate. Exhibit 3 summarizes some of the considerations in personalizing therapy selection.[19] In a meta-analysis of 12 trials (no head-to-head comparisons) in biologic-naïve patients with UC, infliximab and vedolizumab were ranked highest for induction of clinical remission.[20] In patients with prior anti-TNF exposure (four trials, no head-to-head comparisons), tofacitinib was ranked highest for induction of clinical remission in UC. In a meta-analysis of moderate to severe CD trials in biologic-naïve patients, infliximab and adalimumab were ranked highest for induction of clinical remission.[21] In patients with prior anti-TNF exposure, adalimumab and ustekinumab were ranked highest for induction of clinical remission. In patients with response to induction therapy, adalimumab and infliximab were ranked highest for maintenance of remission. Ustekinumab had the lowest risk of serious adverse events and infection in maintenance trials. Exhibit 5 shows a safety ranking for the treatment options for IBD.[19]

Numerous agents including several new categories are under development for IBD. Exhibit 4 lists some

of these agents. Etrolizumab, an anti-integrin that targets β7, is the closest new agent to market. Several agents already approved for psoriasis or rheumatoid arthritis are also under investigation for IBD, including guselkumab, tildrakizumab, and upadacitinib.

A new model of patient care for IBD is needed because care of this disease has become increasingly complicated and fragmented. IBD is a complex disease. Patients have IBD at the peak of their lives and although IBD is their primary disease, it has many impacts (i.e., medically, physically, behaviorally, and potentially surgically).[22] In the traditional care model, the gastroenterologist serves as a consultant and works with other providers in the health care system, including primary care doctors and surgeons, so patients have to go from one stop to another on a fragmented journey of care. This siloed approach often falls short of seamless, efficient, high-quality, patient-centered care. In an IBD medical home model, the gastroenterologist is the principal provider for a cohort of IBD patients. The gastroenterologist is responsible for the coordination and management of health care of this population and places the IBD patient at the center of the medical universe.[23] The "secret sauce" of medical homes is care of patients by understanding the interactions between biological and environmental factors in the mind-body-illness interface. Implementing an IBD medical home should start with a small team and expand as demands or needs dictate. The team may include a gastroenterologist, a psychiatrist or behavioral health specialist, nurse practitioners, nurse coordinators, a social worker, a pharmacist, a dietitian, and health coaches.

An IBD medical home is based on the premise that providers and payers working together can achieve more efficient, high-quality care for patients than either party working alone.[23] Payers have essential resources for infrastructure support, preventive services delivery, marketing and engagement expertise, large databases for risk stratification and gap closure, and care management capacity to be a valuable partner.

Conclusion

There are numerous treatment options for IBD which are disease-modifying; however, TNF inhibitors may not be the best choice for all patients despite many managed care plans requiring use of these first. Numerous additional therapies are on the horizon which will continue to complicate the management of IBD. A specialist-based IBD medical home model should be considered to improve outcomes.

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Closing Gaps and Overcoming Barriers in Adolescent and Adult Immunizations: Expert Perspectives for Improved Patient Outcomes

Rachel Caskey, MD, MAPP

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

Summary

Immunization is one of the most effective preventive health measures. Despite safe and effective vaccine for numerous diseases and nationally accepted guidelines, the rates of vaccination for certain groups have significant room for improvement.

Key Points

- Vaccines are safe, effective, and cost effective.
- Adolescent and adult vaccination rates need to be improved.
- Clinicians and payers need to work to overcome barriers to vaccination.

VACCINATION PROGRAMS ARE AMONG the most widely used and cost-effective public health interventions. Mass vaccination has led to control of multiple infectious diseases, including measles, mumps, diphtheria, polio, and rubella (Exhibit 1).[1] The majority of mass vaccinations in the United States (U.S.) have been in the form of school mandates. Universal vaccination recommendations necessitate certain obligations to the public – vaccines work, are cost-effective to society, are safe, and are available.

Vaccinations have been shown to be cost effective. The U.S. childhood vaccine program costs approximately $7.5 billion, but the health care cost savings for this program are estimated to be over $76 billion (direct and indirect costs including potential rare adverse events).[2] Adult immunizations are also cost effective. For example, if the U.S. could immunize an additional 10 percent of adults 65 years and older with tetanus/diphtheria/pertussis (Tdap), more than 97,000 cases of pertussis in all age groups would be prevented at a cost of $4.7 million, but at a cost savings of $47.7 million (direct and indirect cost).[3] Multiple studies examining immunizing adults against influenza have nearly all shown cost savings, based on severity of disease and efficacy of vaccine. Overall, every dollar spent on vaccines results in approximately $10 in cost savings.

Vaccines are safe. No vaccine is 100 percent safe, but nothing is. Nearly all vaccine adverse events are very mild and include pain at the injection site, sore arm, redness, and fever. The risk of a serious adverse event from disease is far greater than the risk from vaccination. People are at far greater risk of an adverse outcome from riding in a car, crossing the street, or choking on food than from a vaccine. Vaccine safety is monitored carefully in the U.S. with a combination of post-licensure manufacturer monitoring, Vaccine Safety Datalink, and Vaccine Adverse Event Reporting System (VAERS). Overall, vaccines have been found to be extremely safe and most safety issues are of limited clinical significance.[4]

Adolescent vaccines are often neglected or overlooked by parents as not as important as those in early childhood. Universally recommended vaccines for adolescents include Tdap (tetanus, diphtheria, acellular pertussis), human papillomavirus (HPV, Gardasil9®), meningitis (MenACWY and meningitis B), and annual influenza.[5] Because adolescents often have fewer opportunities for well visits (or no well visits), vaccinations may lag behind compared to infants and young children. Exhibit 2 shows 2018 rates of some of the universally recommended adolescent vaccines.[6] Failure by health care providers, parents, and other caregivers to adhere to the recommended immunization schedules, including the timing of immunizations, leaves adolescents susceptible to life-threatening vaccine-preventable diseases. Adolescence is also a suitable

Exhibit 1: Comparison of Annual Morbidity and Morbidity for Vaccine-Preventable Diseases[1]

Disease	20th Century Annual Morbidity	2017 Reported Cases	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	122	> 99%
Mumps	162,344	5,629	97%
Pertussis	200,752	15,808	92%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	9	> 99%
Congenital Rubella Syndrome	152	2	99%
Tetanus	580	31	95%
Haemophilus influenzae	20,000	22	> 99%

time to "catch up" on necessary immunizations that may have been missed at an earlier age. The Centers for Disease Control and Prevention (CDC) publishes specific guidance on catch up vaccinations.

Of the universally recommended vaccines for adolescents, the HPV vaccine is the first and only cancer preventing vaccine. HPV infection with oncogenic subtypes is responsible for a tremendous number of cancers, including more than 99 percent of cervical cancer cases, but in order to be most effective vaccination needs to occur before any exposure to HPV occurs.[7] Although typically thought of as sexually transmitted, HPV can spread through the anogenital region via skin-to-skin contact and condoms are only partially effective in preventing transmission. Some female adolescents have been found to test positive for vaginal HPV prior to first vaginal sexual intercourse.[8]

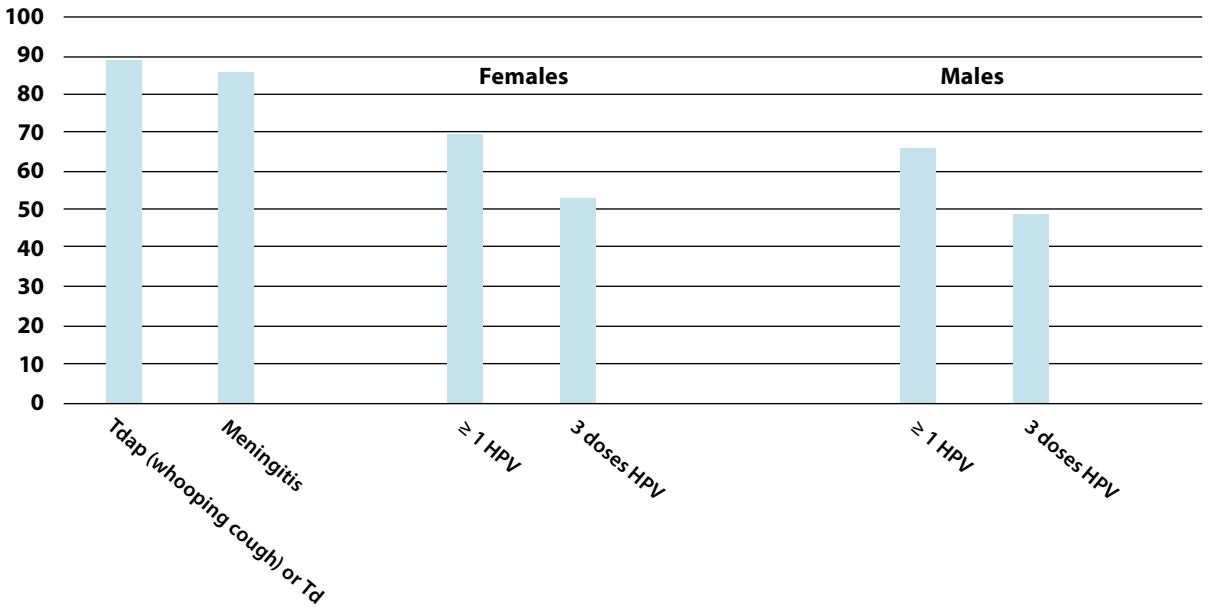
Adolescents and young adult males should be a major target for HPV vaccination campaigns. Genital HPV prevalence is higher in males than in females and does not decrease with age like it does in females.[9,10] Additionally, the incidence of HPV-related oral pharyngeal carcinomas are increasing, and these are twice more common in men. HPV vaccination, along with cervical cancer screening programs, are reducing the incidence of cervical cancer in the U.S. In a 12-year follow-up on the long-term efficacy of the earlier 4-valent HPV vaccine in females aged 16 to 23 years, the vaccine was 100 percent effective in preventing cervical, vulvar, and vaginal cancer.[11] HPV vaccination is recommended for both males and females from age 9 or 11 through age 26 years. Those 27 to 45 years, who were not vaccinated in the past, can make a decision to be vaccinated based on shared decision-making.

In addition to parents being reluctant to vaccinate their children against a sexually transmitted disease, clinicians can be a barrier to HPV vaccination. In a survey of physicians, only 73 percent reported recommending HPV vaccine as highly important and only 13 percent of physicians perceived HPV vaccine as being highly important to parents compared with 74 percent for Tdap and 62 percent for meningococcal vaccine.[12] Among physicians with a preferred order for discussing adolescent vaccines, 70 percent discussed HPV vaccine last.

The essential vaccines for all adults include annual influenza and Tdap boosters every 10 years.[13] Routine annual influenza vaccination is recommended for all persons six months and older who do not have contraindications, and a vaccine appropriate for age and health status should be used.[14] Among adults, the projected vaccination rate for 2021–2022 in the U.S. is 58.5 percent.[15] This is 3.7 percentage points higher than the 54.8 percent who reported being vaccinated during 2020–2021.

Tdap vaccination every 10 years is recommended for adults. Despite routine vaccination of children, pertussis is the least well-controlled of bacterial vaccine-preventable diseases in the U.S. Because immunity wanes four to 12 years after vaccination,

Exhibit 2: Adolescent Vaccination Rates[6]



adolescents and adults are susceptible.[16] For adults over 50, shingles (herpes zoster) and pneumonia vaccines are also recommended.[13] Other vaccines may be recommended based on individual comorbidities and other risk factors.

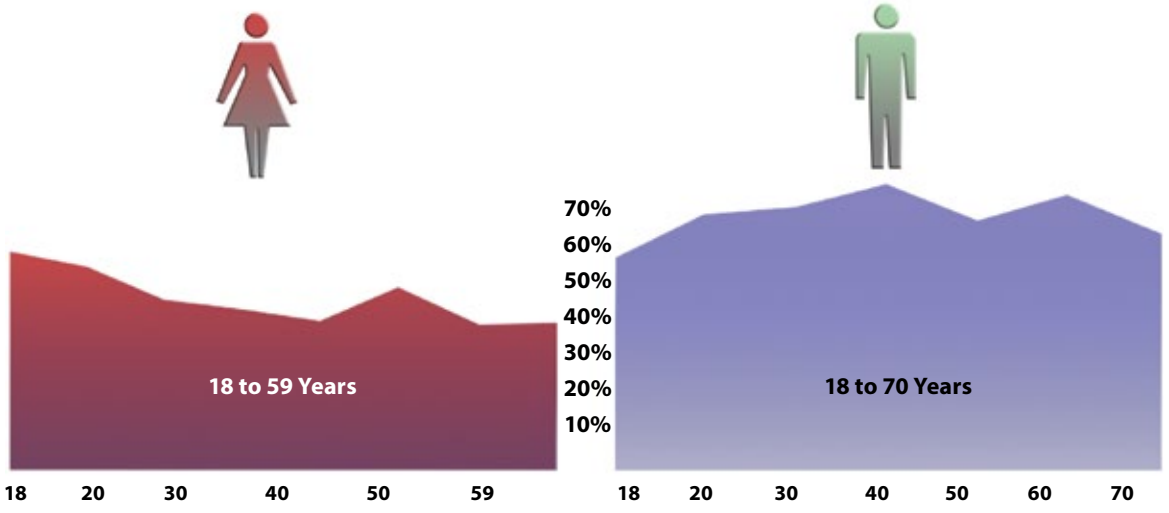
Herpes zoster, also known as shingles, is caused by the reactivation of the varicella-zoster virus (VZV), the same virus that causes varicella (chickenpox). Once the illness resolves, the virus remains latent in the dorsal root ganglia and can reactive later in a person's life. Acute herpes zoster causes significant pain and interference with health-related quality of life. Over one million cases occur every year among those 50 years of age and older. One-third of adults will have zoster if not vaccinated.[17] Among those who live to 85, there is a 50 percent lifetime risk for zoster. Risk factors include being immunocompromised, female gender, Caucasian race, and family history of zoster. Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, and the related pain can last for weeks or months, and occasionally, for years. A person's risk of having PHN after herpes zoster increases with age. Older adults are also more likely to have longer lasting, more severe pain and to require hospitalization. Approximately 10 to 13 percent of people 60 years and older with herpes zoster will develop PHN.[18] Other complications of herpes zoster include ophthalmic involvement with acute or chronic ocular sequelae, including vision loss, bacterial superinfection, cranial and peripheral nerve palsies, and visceral involvement, such as meningoencephalitis, pneumonitis, hepatitis, and acute retinal necrosis.

Zoster vaccine recombinant (Shingrix®, RVZ) is recommended for the prevention of herpes zoster and related complications for immunocompetent adults aged 50 years and older.[19] RZV is also recommended for immunocompetent adults who previously received the earlier version of the vaccine (Zostavax®) and those with a history of herpes zoster.

The two-dose regimen is 97 percent effective in preventing zoster in the 50- to 69-year-old group and 91 percent in the 70 years and over population.[19] For preventing PHN, it is 91 percent effective in the younger age group and 89 percent in those over 70 years. Protection remains high (more than 85%) in people 70 years and over four years following vaccination.

Pneumococcus species cause 400,000 cases of pneumonia, meningitis, otitis media, and sinusitis annually. Pneumococcal infection leads to 445,000 hospital admissions and 22,000 deaths annually in the U.S. The recommendations for those who should receive pneumococcal vaccination depends on risk and varies by age and underlying medical conditions.[5,13,20] There is a 13-valent pneumococcal conjugate vaccine (PSV-13) and a 23-valent

Exhibit 3: Genital HPV Prevalence is Higher in Males than in Females and Does Not Decrease with Age[9,10]



pneumococcal polysaccharide vaccine (PPSV-23). All adults 65 years or older should receive a dose of PPSV23, and those with selected risk factors should also receive a dose of PSV-13.

Because of many factors, rates for most vaccinations for adults and adolescents have significant room for improvement. One of the biggest contributors to the lack of vaccinations is the fact that clinicians do not strongly and clearly recommend vaccination. A strong, consistent presumptive recommendation, rather than a participatory approach, should be used. The clinicians should state: "Today, you are due for two vaccines, HPV and pneumococcal, and someone will be right in to administer those vaccines" rather than asking, "Do you want to get the HPV and pneumococcal vaccines today?" In addition to a lack of a strong, clear recommendation, other things clinicians or practices do can provoke doubt in patients. These include following invalid contraindications to immunization (low-grade fevers, mild illness), providing reading material rather than directly discussing individual vaccines, equivocating on recommendations or answers, and inconsistent recommendations from the clinical team.[21]

Providers, health systems, and payers can work together to maintain and improve routine vaccinations and identify those patients who need to catch-up on missed vaccines. Every time a patient encounters the healthcare system represents an opportunity to discuss, encourage, and offer vaccinations.

Conclusion

Vaccines prevent numerous serious diseases, eliminate suffering for many patients and, in one case, even prevent cancer. Vaccines for adolescents and adults do not receive the same focus as pediatric vaccines but are still essential and considered cost effective. Payers and clinicians need to work together to improve adolescent and adult vaccination rates.

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Navigating Recent Advances in the Management of HIV: Optimal Treatment Strategies for Improved Clinical and Economic Outcomes

Anne Monroe, MD, MSPH

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

Summary

Ending the HIV epidemic in the United States (U.S.) is possible with therapies to prevent infection in those with ongoing risks and newer effective once-daily regimens which can achieve high rates of viral suppression. More needs to be done to diagnose infections as early as possible and get those infected into continuing care.

Key Points

- Three one tablet per day complete regimens are recommended for initial therapy.
- A new category of therapy for heavily treatment-experienced patients with a great deal of drug resistance was approved in 2020.
- A combination of two long-acting injections has been approved.

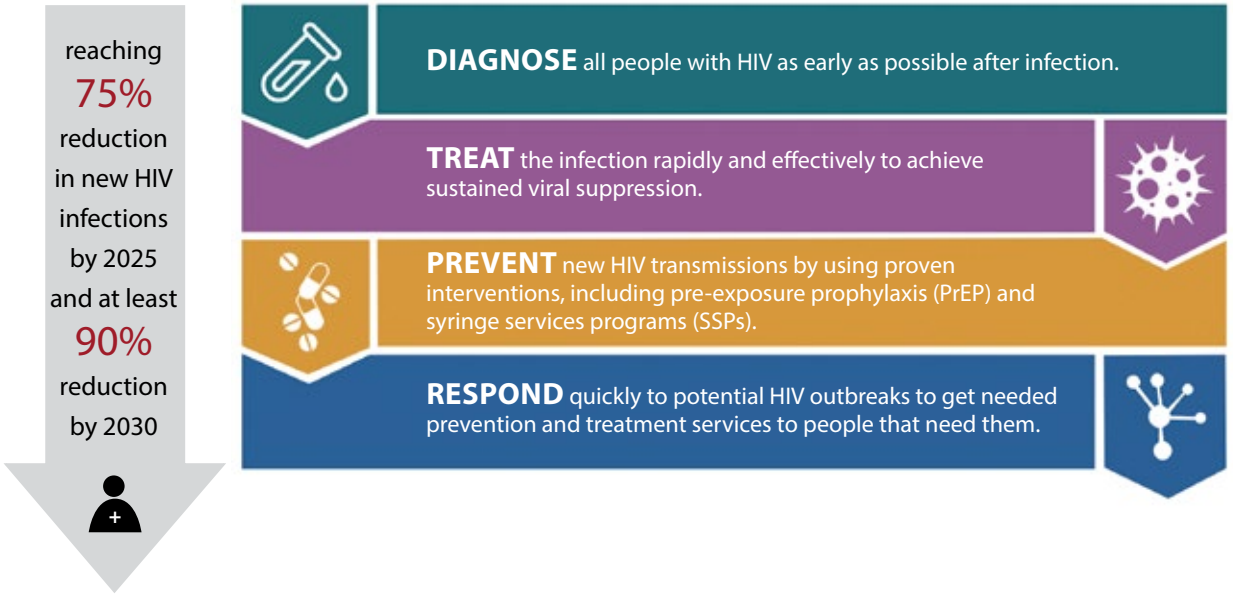
AT THE END OF 2018, AN ESTIMATED 1.2 million people aged 13 and older had human immunodeficiency virus (HIV) infection in the U.S., including an estimated 161,800 (14%) people whose infections had not been diagnosed.[1] In 2018, 37,968 people received a new HIV diagnosis in the U.S. and dependent areas. On a positive front, new infections in the U.S. have been decreasing since 2008.

Inequities still exist in HIV infections. The highest rates of infection are among Black/African American and Hispanic/Latino males who have sex with other males (MSM).[1] The third-highest rates are among white MSM. Better targeting of these groups for prevention is needed.

Ending the HIV Epidemic Initiative is a program from the U.S. Department of Health and Human Services (DHHS) that aims to reduce new infections by 75 percent by 2025 and 90 percent by 2030. The strategies within this initiative are shown in Exhibit 1.[2] Ending the HIV epidemic is possible now because of several advances in therapy. Pre-exposure prophylaxis (PrEP) and treatment as prevention (TASP) are the main strategies. PrEP is the use of a single tablet of antiretroviral therapy (ART) taken daily by people at risk for HIV to prevent getting HIV from sex or injection drug use. Two combination products are currently approved for PrEP (Truvada® and Descovy®). TASP is starting ART as soon as a person is diagnosed and using ART to achieve undetectable levels of virus which makes the virus untransmittable.

Overall, there is still no cure for HIV, but people living with HIV (PLWH) without significant comorbidities and who start and maintain treatment can live a near normal lifespan. The benefits of ART include viral suppression, improved immunity, and reduced immune activation. There are still risks of complications of HIV infection for some patients. An older age at infection is associated with more rapid progression to acquired immunodeficiency syndrome (AIDS) without ART. PLWH have a disproportionate risk of non-AIDS related comorbidities over their life course including cancer, cardiovascular disease, and chronic kidney disease. People with late diagnosis or treatment are less likely to have complete immune cell recovery and are more

Exhibit 1: Ending the HIV Epidemic Initiative[2]



likely to have the non-AIDS related comorbidities. Mortality from opportunistic infections is much less common than in the past; these may be observed in people with late diagnosis or non-adherence to care.

The estimated lifetime cost for persons who become HIV infected at age 35 is $326,500.[3] The medical cost saved by avoiding one HIV infection is estimated at $229,800. The cost saved would reach $338,400 if all HIV-infected individuals presented early and remained in care. ART is the most significant contributor to HIV costs (60%), and these costs have been increasing.[3,4] Costs increased about 35 percent from 2012 to 2018.[4]

The DHHS provides regularly updated treatment guidelines for HIV, and the most up-to-date guidelines should be consulted because these can rapidly change. ART should be initiated immediately (or as soon as possible) after HIV diagnosis. Therapy started within seven days of HIV diagnosis (rapid ART) results in an increased likelihood of ART start, retention in care, viral suppression, and shorter time to viral suppression. There is also a decreased likelihood of loss to follow-up and death. The recommended initial regimens for most people with HIV are shown in Exhibit 2.[5] Combination regimens are required to prevent development of viral resistance. Some newer regimens only require two agents instead of the typical three, but they are only appropriate for certain patients.

There are numerous considerations in selecting both initial and any subsequent HIV treatment regimens. Some of these include the presence of chronic kidney disease, osteoporosis, psychiatric illness, cardiovascular disease risk, hyperlipidemia, hepatis B or C, tuberculosis, potential for pregnancy, concomitant medications, risk of viral resistance, and prior ART.

Notable adverse events of ART include weight gain, increased cardiovascular disease risk, renal toxicity, bone toxicity, and neuropsychiatric symptoms. Strategies to minimize risk of long-term adverse events are to reduce the number of antiretrovirals needed and to develop novel medications with fewer toxicities. The newer regimens which only have two agents in a single tablet [dolutegravir/lamivudine (Dovato®) and dolutegravir/rilpivirine (Juluca®)] limit exposure to antiretrovirals.

ART is part of cardiovascular disease (CVD) prevention in people living with HIV (PLWH) because of possible increased risk from the disease itself, and some antiretrovirals can modestly increase CVD risk. CVD risk is higher for those who have poorly controlled or late control of HIV. The protease inhibitors (except atazanavir) increased risk by increasing weight gain and inducing metabolic syndrome. Abacavir is associated with increased

Exhibit 2: Recommended Initial Regimens for Most People with HIV[5]

- Bictegravir/emtricitabine/ tenofovir alafenamide (Biktarvy®)*
- Abacavir/dolutegravir/lamivudine (Triumeq®)**
- Dolutegravir (Tivicay®) + tenofovir alafenamide or tenofovir disoproxil fumarate + lamivudine or emtricitabine*
- Dolutegravir/lamivudine (Dovato®)†

* also recommended for rapid ART
** if HLA-B*5701 negative
† HIV RNA < 500,000 K copies, no hepatitis B (HBV) coinfection, must have genotype and HBV test results completed prior to prescribing.

risk of myocardial infarction (MI) in observational studies. The population-level impact of ART toxicities on CVD risk is low and may be attenuated by the use of antiplatelet agents and statins among high-risk individuals. Guidelines for managing CVD risk in PLWH are available from the American Heart Association.[6] More emphasis on smoking cessation to reduce risk in PLWH is needed.

A new option for heavily treatment-experienced (HTE) patients is fostemsavir (Rukobia®). HTE patients account for a very small proportion (about 1%) of PLWH. Fostemsavir is the first FDA-approved attachment inhibitor and is indicated for combination therapy in HTE adults with known multi-drug resistance who are failing current ART due to potential resistance, intolerance, or safety considerations. Binding of this agent to GP120, a viral envelope glycoprotein necessary for viral attachment, prevents viral entry into CD4 lymphocytes, effectively stopping viral replication. Fostemsavir was evaluated for both safety and efficacy in a randomized, double-blinded, placebo-controlled clinical trial (BRIGHTE) with 371 HTE HIV-1 subjects. This study had two cohorts – a randomized cohort, in which patients with one or two fully active antiretrovirals remaining received oral fostemsavir (600 mg twice a day) or placebo in combination with their failing regimen for eight days, followed by fostemsavir plus optimized background therapy, or the non-randomized cohort, in which patients with no remaining antiretroviral options received oral fostemsavir (600 mg twice a day) plus optimized background therapy from the start. In the randomized cohort, rates of virological suppression (HIV-1 RNA < 40 copies/mL) increased from 53 percent at week 24 to 60 percent at week 96.[7] Response rates in the non-randomized cohort were 37 percent at week 24 and week 96. Mean CD4 counts increased from baseline at week 96.

Another innovation in HIV care is a long-acting injectable combination. A newly approved (January 2021) two medication regimen of long-acting injectable cabotegravir and long-acting injectable rilpivirine (Cabenuva®) is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Prior to initiating the injectables, oral lead-in dosing with the separate components should be used for one month to assess the tolerability to each component. Injectable therapy is initiated on the last day of oral dosing with monthly intramuscular injections (each medication requires a separate intramuscular injection). Higher doses (cabotegravir 600 mg and rilpivirine 900 mg) are used for the first injection with subsequent injections of 400 mg and 600 mg. Trials have examined use of this combination as switch therapy and for treatment naïve patients. Monthly injections were noninferior to standard oral therapy for maintaining HIV-1 suppression.[8] In treatment- naïve patients, viral suppression at week 48 was found in 93.6 percent who received long-acting therapy and in 93.3 percent who received oral therapy.[9] Injection site reactions are the most common adverse event.

The HIV care continuum is a public health model that outlines the steps that PLWH go through from diagnosis to achieving and maintaining viral suppression. The steps are diagnosis of HIV infection, linkage to HIV medical care, actual receipt of HIV medical care, retention in medical care, and achievement and maintenance of viral suppression. In 2019, 87 percent of those infected with HIV in the U.S. were estimated to be diagnosed, and 81 percent were linked to care within a month of diagnosis.[10] Unfortunately, only 66 percent received care, 50

percent were retained in care, and 57 percent achieved sustained viral suppression. Overall, these numbers all improved from 2016 but, in order to stop the HIV epidemic, they still need to be improved.

The best way to improve linkage to care is an immediate referral to HIV care. Patient navigators or case managers can be used to facilitate linkage and ongoing care. There should be proactive engagement and reengagement of patients who miss clinic appointments and/or are lost to follow-up.[11] Intensive outreach is needed to reach those not engaged in care within one month of a new HIV diagnosis.

Managed care can consider implementing some proven strategies to improve linkage to care and retention in care. Case management, patient navigators, eliminating cost barriers for ART, adherence support programs, and pharmacist-provided medication therapy management (MTM) are all options. Some targets of MTM programs for PLWH include minimizing drug-drug interactions, managing medication adverse events, addressing periconception concerns, optimizing management of comorbid conditions (medical, mental health, and substance use), optimizing an ART regimen, and reducing polypharmacy in elderly PLWH. In one three-year study of a Medi-Cal population, patients who received MTM services consistently had higher medication adherence rates, were more likely to remain on a single type of ART regimen throughout the year, had fewer excess fills, and used fewer contraindicated regimens than those who did not receive service.[12] There were no significant differences in mean total cost per patient per group, and the additional MTM services payment added less than 3 percent to the total cost.

Conclusion

Easy to use one tablet a day ART regimens are available and produce high rates of viral suppression with minimal adverse events. Improvements in ART regimens continue to occur with the first long-acting injectables having recently come to market. Although effective ART regimens are available, there are still deficiencies in the diagnosis and care of those infected with HIV. Managed care can help improve outcomes in PLWH by targeting linkage to care, retention in care, and medication management/adherence.

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New Frontiers in the Treatment and Management of Extensive-Stage Small-Cell Lung Cancer: A Closer Look at the Role of New and Emerging Immunotherapy

Joshua Bauml, MD

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

Summary

Small-cell lung cancer is a devastating disease with poor survival despite effective treatments. First-line treatment for the majority of patients has recently changed to include the use of checkpoint immunotherapy. Hopefully, with this addition, five-year survival will increase.

Key Points

- Atezolizumab and durvalumab are now standard additions to chemotherapy for first-line treatment of extensive-stage small-cell lung cancer.
- These agents improve overall survival.

SMALL-CELL LUNG CANCER (SCLC) accounts for 15 percent of all lung cancer cases and is universally associated with smoking. Staging of this disease is dichotomous and divided into limited and extensive. Limited disease can be incorporated in a single radiation field, and extensive is anything beyond that. The majority of patients are diagnosed in the extensive disease stage. SCLC is a rapidly growing disease and is quite responsive to chemotherapy. Relapses are common in limited-stage disease and inevitable in extensive stage disease. SCLC is one of the few potential emergencies in solid tumor oncology.

For limited-stage SCLC, chemotherapy is of paramount importance with cisplatin and etoposide the standard combination. The addition of concurrent radiation improves survival by about 5 percent. After treatment prophylactic cranial irradiation is considered because SCLC commonly metastasizes to the brain. This provides an absolute survival improvement of about 5 percent.

For many years, first-line treatment of extensive-stage SCLC has been platinum with etoposide, with a preference for carboplatin because of equivalent efficacy compared to cisplatin and more tolerable toxicity profile. Consolidative chest radiation after chemotherapy improves survival at two years by 10 percent. Overall, five-year survival for SCLC remains dismal (Exhibit 1).[1]

Exhibit 1: Five Year Survival Rates for SCLC[1]

SEER Stage	Five-year Relative Survival Rate
Localized	27%
Regional	16%
Distant	3%
All SEER stages combined	7%

SEER = Surveillance, Epidemiology, and End Results
These numbers are based on people diagnosed with SCLC between 2010 and 2016.

To attempt to improve survival in SCLC, immunotherapy has been investigated both as second-line monotherapy and as first-line therapy in addition to chemotherapy. SCLC has been found

Exhibit 2: Preferred Combinations for Primary Therapy for Extensive Stage SCLC[6]

- Carboplatin/etoposide/atezolizumab 1,200 mg x 4 cycles followed by maintenance atezolizumab 1,200 mg every 21 days
- Carboplatin/etoposide/atezolizumab 1,200 mg x 4 cycles followed by maintenance atezolizumab 1,680 mg every 28 days
- Carboplatin/etoposide/durvalumab 1,500 mg x 4 cycles followed by maintenance durvalumab 1,500 mg every 28 days
- Cisplatin/etoposide/durvalumab 1,500 mg x 4 cycles followed by maintenance durvalumab 1,500 mg every 28 days

Exhibit 3: First Line Immunotherapy Combined with Standard Chemotherapy Trial Comparison[4,5,7,8]

	PD-L1 Inhibitor		PD-1 Inhibitor	
	Atezolizumab (IMPOWER 133)	Durvalumab (CASPIAN)	Pembrolizumab (KEYNOTE 604)	EA5161 (Nivolumab)*
Median OS versus Chemotherapy alone	12.3 versus 10.3 months	13 versus 10.3 months	10.8 versus 9.7 months**	11.3 versus 9.3 months**
Median PFS	5.2 months	5.1 months	4.5 months	5.5 months
ORR	60.20%	68%	70.60%	52%
Median DOR	4.2 months	5.1 months	4.2 months	5.6 months

*Only published so far as abstract
**Not statistically significant

to have an extremely high mutation rate of protein-changing mutations per million base pairs which is typically a marker of immunotherapy efficacy.[2,3]

The standard first-line treatment of SCLC changed with the publication of trials with atezolizumab and durvalumab in addition to platinum/etoposide chemotherapy followed by immunotherapy maintenance demonstrating improved overall survival (OS) compared to platinum/etoposide alone. Both are programmed death ligand one (PD-L1) inhibitor checkpoint immunotherapies. In the atezolizumab trial, the median OS was 12.3 months in the atezolizumab/carboplatin/etoposide/atezolizumab maintenance group and 10.3 months in the carboplatin/etoposide group (p = 0.007).[4] Similarly, the one-year OS rate was 51.7 percent versus 38.2 percent, favoring the atezolizumab group (p = 0.007). The rate of Grade 3 or 4 adverse events was similar in both groups (56%). Durvalumab plus platinum (carboplatin or cisplatin)/etoposide followed by durvalumab maintenance was also associated with a significant improvement in OS (p=0.0047) compared to platinum/etoposide.[5] Median overall survival was 13.0 months in the durvalumab/platinum/etoposide group versus 10.3 months in the platinum/etoposide group, with 34 percent versus 25 percent of patients alive at 18 months. Any-cause adverse events of Grade 3 or 4 occurred in 62 percent of both treatment groups and adverse events leading to death occurred in 5 percent of the triple therapy group and in 6 percent of the chemotherapy group. Both agents have been FDA-approved for first-line SCLC treatment in combination with chemotherapy and are now part of the preferred regimens in the National Comprehensive Cancer Network guidelines for extensive-stage SCLC (Exhibit 2).[6] Atezolizumab or durvalumab are continued as maintenance therapy after chemotherapy ends until disease progression occurs.

Exhibit 3 compares the first-line immunotherapy trials with PD-L1 and programmed death one (PD-1) inhibitors.[4,5,7,8] When comparing the trials, the clinical outcomes for the various agents are more similar than different. Unlike other cancers, the trials with the two PD-L1 inhibitors are positive and the ones with PD-1 inhibitors are negative in terms of survival benefit. In other cancers where checkpoint inhibitor therapy has been studied,

both PD-L1 and PD-1 inhibitors are both effective if immunotherapy is effective. It is unclear if the findings of the PD-1 trials reflect unmeasured biases for both chemotherapy and immunotherapy or an inappropriate selection of patients based on available biomarkers. Improved biomarkers may be able to help researchers understand why there is a difference and whether there is a subset of patients who would benefit from PD-1 inhibitors. This is an area of ongoing research, but thus far neither pembrolizumab nor nivolumab have an FDA-approved indication for treating SCLC.

Conclusion

The treatment paradigm for first-line treatment of extensive-stage SCLC has changed recently with the publication of trials showing improved survival with the addition of checkpoint immunotherapy to standard chemotherapy. At this time, only agents targeting PD-L1 have shown statistical survival benefits in SCLC and achieved FDA approval for this indication, but a better selection of patients for PD-1 therapy with biomarkers may find that select subgroups do benefit.

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Improving Outcomes in Alzheimer's Disease and Dementia: Emerging Treatment Advances and Recommendations

R. Scott Turner, PhD, MD

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Summary

Alzheimer's disease (AD) is a devastating disease which is a growing concern as the United States (U.S.) population ages. Although improvements in diagnosis have been made, finding an effective treatment has been a challenging task. Targeting this disease for treatment in the very earliest stage is becoming the object of numerous studies and the place in therapy for the newest agent.

Key Points

- The number of people in the U.S. with AD continues to grow.
- Biomarkers for AD are available to help improve diagnosis.
- Aducanumab is a newly approved but controversial agent for treating AD.

ALZHEIMER'S DISEASE, A NEUROCOGNITIVE disorder, is the most common cause of dementia and accounts for 60 to 80 percent of dementias in older people.[1] An estimated 6.2 million Americans aged 65 and older are living with AD in 2021.[1] The percentage of people with AD increases dramatically with age, with 5.3 percent of people aged 65 to 74, 13.8 percent aged 75 to 84 and 34.6 percent aged 85 or older being affected. The aging of the baby boom generation is significantly increasing the number of people in the U.S. with AD. Costs for caring for the AD population are predicted to continue to exponentially increase through 2050 (Exhibit 1).[2,3]

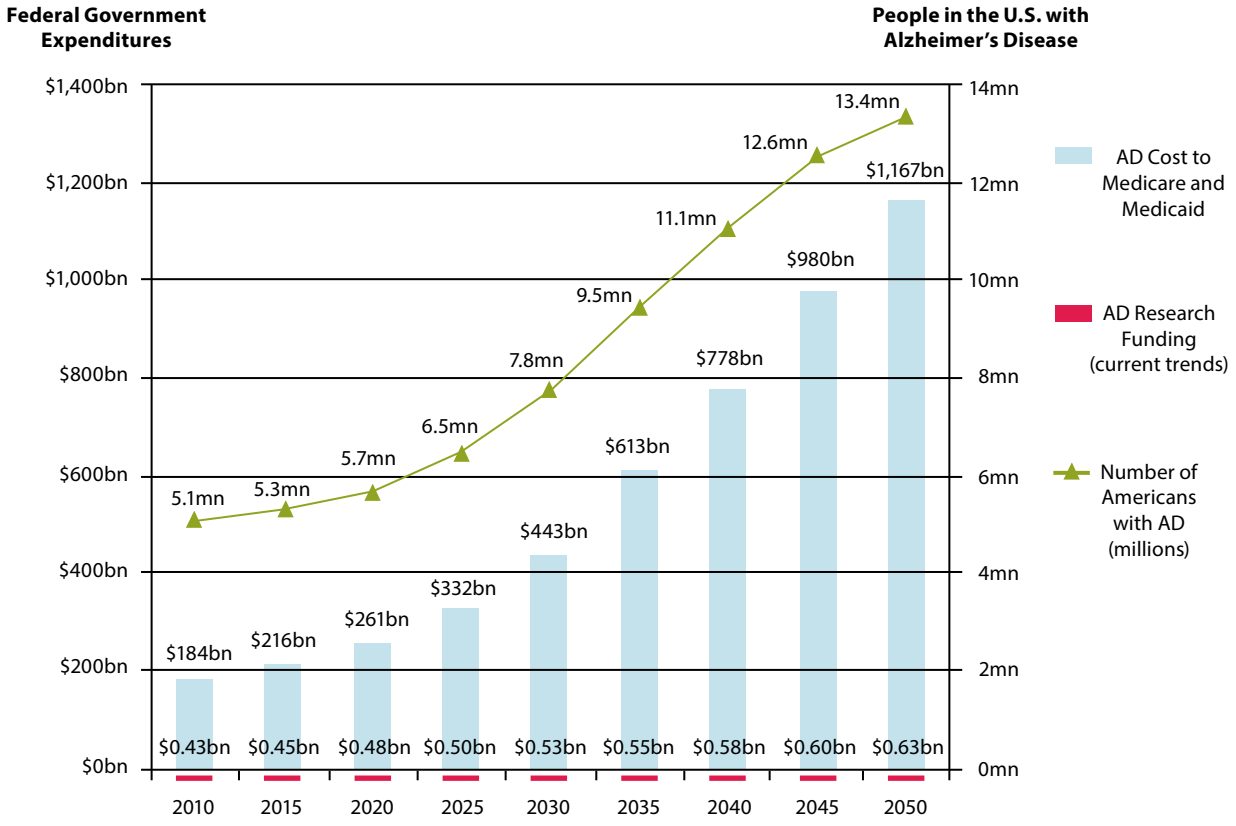
As shown in Exhibit 2, everyone experiences some cognitive decline with aging. However, it is important to note that AD is not a normal part of aging, and older age alone is not sufficient to cause Alzheimer's dementia.[1] Those with dementia go through several stages, including a preclinical stage, mild cognitive impairment (MCI), and mild through severe dementia.[4]

The diagnostic criteria for dementia include: cognitive difficulties that interfere with the ability to function at work or at usual activities; there is a decline from a previous level of functioning; there is no delirium or a psychiatric disorder which can account for the decline; and at least two cognitive domains are affected (memory, reasoning and judgment, visuospatial, language, personality, behavior, comportment). The differential diagnosis for AD includes many other causes of dementia such as Parkinson's disease and Lewy body dementia. The criteria for probable AD include dementia with an insidious onset and worsening of cognition over time not due to another dementia diagnosis.[5] Probable AD with evidence of AD pathophysiology includes demonstration of beta-amyloid deposition through cerebrospinal fluid (CSF) or amyloid positron emission tomography (PET) or neuronal injury shown on CSF tau, fluorodeoxyglucose (FDG)-PET, or structural MRI. These biomarkers have made the diagnosis of AD much easier than in the past.

The risk factors for MCI and AD are numerous. Besides aging, family history and genetics, race (African-American, Hispanic), Down's syndrome, diabetes, midlife obesity, metabolic syndrome, traumatic brain injury with loss of consciousness, smoking, stroke, low education level, low occupational level, and female gender are all risk factors.

The apolipoprotein e4 gene (APOE-e4) variant is the most commonly known genetic risk factor,

Exhibit 1: Rising Case and Costs of AD[2,3]

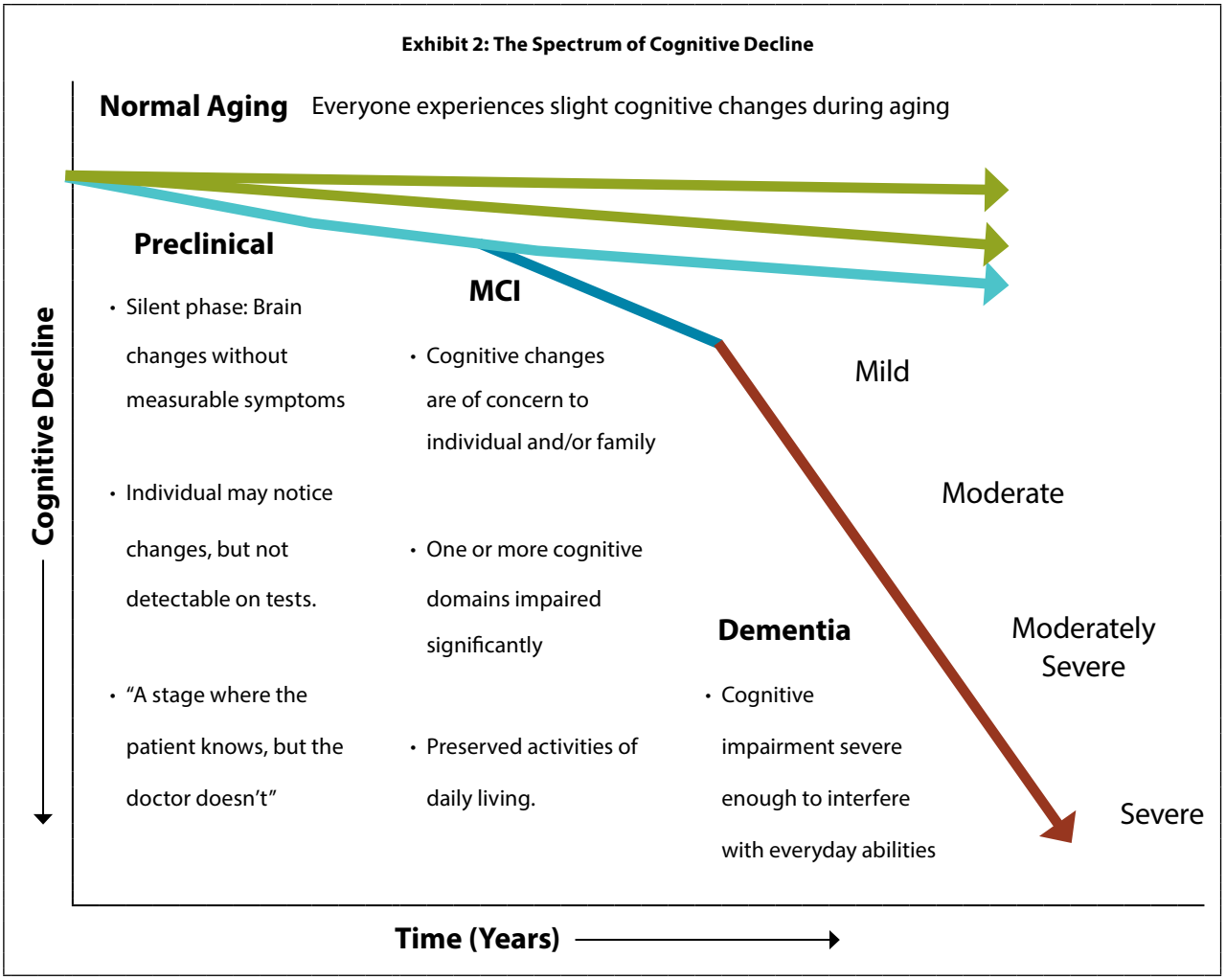


but other genetic variants including APOE-e3 have been discovered. Having APOE-e4 leads to earlier accumulation of amyloid in the brain by about 15 years.[6] Those who inherit one copy of the APOE-e4 have about three times the risk of developing AD compared with those with two copies of the APOE-e3, while those who inherit two copies of the APOE-e4 have an eight- to 12-fold risk.[1] About 25 percent of the U.S. population carries at least one copy of APOE-e4 and 2 percent carry two copies.

The main target of dementia research is now preventing development of overt dementia in those with MCI. Targeting modifiable risk factors may help preserve brain health with aging (Exhibit 3).[7] Following all of these recommendations for preserving brain health will put off the development of AD by five to 10 years.

The two pathologic hallmarks of AD are extracellular beta-amyloid deposits (in senile plaques) and intracellular neurofibrillary tangles (paired helical filaments).[8] Amyloid plaques are composed of beta-amyloid peptides (Abeta40, Abeta42, etc.). There are an estimated 50 million people in the U.S. with significant amyloid deposits in their brain. Approximately 50 percent of those over 80 years of age, who are cognitively normal, will have a positive amyloid scan.[6] The neurofibrillary tangles are composed of tau and phosphorylated tau (p-tau). The beta-amyloid deposition and neurofibrillary tangles lead to loss of synapses and neurons, which results in gross atrophy of the affected areas of the brain, typically starting at the medial temporal lobe. The mechanism by which beta-amyloid peptide and neurofibrillary tangles cause such damage is not completely understood. Exhibit 4 illustrates the path of changes in the brain that lead to AD and when biomarkers become positive. In addition to being used for diagnosis, the biomarkers are being used to identify subjects for preclinical and MCI intervention studies. Additional biomarkers are under investigation, including a blood screening test.

Until 2021, the FDA-approved treatments for AD were aimed at improving cognition and function in the mild to moderate stages of AD, but they did



not target the underlying pathology of the disease. These include donepezil, rivastigmine, galantamine, and memantine. Treatments for MCI and AD are now exploring three major pathophysiologic targets – the cleavage of amyloid precursor protein into plaque-prone amyloid by inhibition of beta- or gamma-secretases, interference of plaque formation using inhibitors of beta-amyloid aggregation and enhancing the clearance of beta-amyloid using immunotherapy. Trials of secretase inhibitors found that these agents were very good at eliminating beta-amyloid, but they actually worsened memory. Because these initial agents were nonspecific, the search is still on for secretase inhibitors which are specific to amyloid precursor protein breakdown.

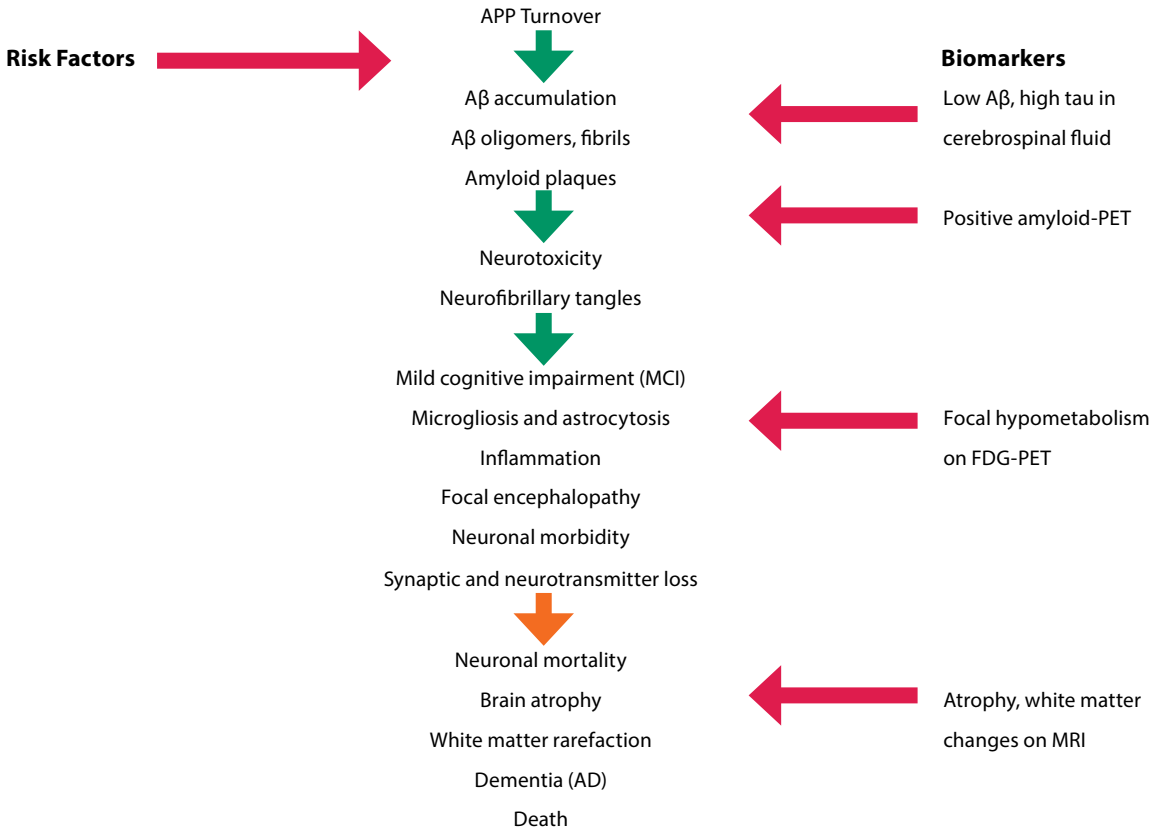
Aducanumab (Aduhelm™) recently became the first novel therapy approved for AD since 2003. More significantly, it is the first treatment directed at the underlying pathophysiology of AD. It is a beta-amyloid directed antibody indicated to treat AD. It received a controversial accelerated approval by the FDA in June 2021. The accelerated approval was based on the surrogate endpoint of reduction of beta-amyloid plaques. The accelerated approval pathway requires the company to verify clinical benefit in a post-approval trial.

The late-stage development program for aducanumab consisted of two Phase III clinical trials (EMERGE and ENGAGE). Results from these trials have not yet been published. In EMERGE, high-dose aducanumab modestly reduced clinical decline as measured by primary and secondary endpoints (Exhibit 5).[9] In ENGAGE, aducanumab did not reduce clinical decline (Exhibit 6).[9] In March 2019, the manufacturer issued a press release in which they announced that they were halting both trials for futility. The rationale for the termination of the trials was that the prespecified outcome required that both trials had to demonstrate benefits. A subsequent press release stated that in a post-hoc analysis of ENGAGE, data from a subset of patients exposed to high-dose aducanumab supported the

Exhibit 3: to Preserve Brain Health with Aging[7]

- Regular exercise and physical activity.
- Maintain ideal body weight – throughout life.
- Mediterranean diet (fruits, vegetables, nuts, beans, olive oil, fish).
- Greater quantity and quality of education.
- Limit alcohol consumption (1 to 2 drinks/day).
- Mental activities, social connections and activities.
- Avoid traumatic brain injury (seat belts, helmets, fall prevention…).
- Adequate sleep.
- No smoking.
- Minimize stress.
- Avoid air pollution.
- Use glasses and hearing aids as needed.
- Treat hypertension, diabetes, cholesterol, sleep apnea, and depression/anxiety.
- If memory problems develop, rule out thyroid disorder, vitamin B12 deficiency, and perhaps syphilis and HIV.

Exhibit 4: The Process of Alzheimer's Disease Development



APP = amyloid precurser protein; Aβ beta-amyloid; PET = positron emission tomography; FDG = fluorodeoxyglucose

Exhibit 5: Primary and Secondary Endpoints from Final Data Set at Week 78 in EMERGE Trial[9]

	Placebo Decline (n = 548)	Difference versus Placebo (%) *p*-value	
		Low Dose (n = 543)	High Dose (n = 547)
CDR-SB	1.74	**-0.26** (-15%) 0.0901	**0.39** (-22%) 0.0120
MMSE	-3.3	**0.1** (3%) 0.7578	**0.6 (-18%)** 0.0493
ADAS-Cog 13	5.162	**-0.701** (-14%) 0.1962	**-1.400** (-27%) 0.0097
ADCS-ADL-MCI	-4.3	**0.7** (-16%) 0.1515	**1.7** (-40%) 0.0006

CD-SB = Clinical Dementia Rating scale Sum of Boxes; MMSE = mini mental status exam;
ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale;
ADCS-ADL-MCI = Alzheimer's disease cooperative study activities of daily living mild cognitive impairment

Exhibit 6: Primary and Secondary Endpoints from Final Data Set at Week 78 in ENGAGE Trial[9]

	Placebo Decline (n = 545)	Difference versus Placebo (%) *p*-value	
		Low Dose (n = 547)	High Dose (n = 555)
CDR-SB	1.56	**-0.18** (-12%) 0.2250	**0.03** (2%) 0.8330
MMSE	-3.5	**0.2** (-6%) 0.4795	**-0.1** (3%) 0.8106
ADAS-Cog 13	5.14	**-0.583** (-11%) 0.2536	**-0.588** (-11%) 0.2578
ADCS-ADL-MCI	-3.8	**0.7** (-18%) 0.1225	**0.7** (-18%) 0.1506

CD-SB = Clinical Dementia Rating scale Sum of Boxes; MMSE = mini mental status exam;
ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale;
ADCS-ADL-MCI = Alzheimer's disease cooperative study activities of daily living mild cognitive impairment

positive findings of EMERGE and thus the agent was submitted to the FDA for approval. The FDA defended its approval of this agent by stating "in all studies in which it was evaluated, aducanumab consistently and very convincingly reduced the level of amyloid plaques in the brain in a dose- and time-dependent fashion. It is expected that the reduction in amyloid plaque will result in a reduction in clinical decline."[10] Others have published criticisms of the trial design and data presented from the studies.[11]

Aducanumab should only be considered for use in people who have a firmly established diagnosis of AD in its very mildest symptomatic stages. This may include people with MCI or mild dementia. Aducanumab is administered intravenously via a 45- to 60-minute infusion every four weeks. Infusion can be done at hospitals or infusion therapy centers.

The most common adverse events of aducanumab are related to inflammation in the brain which cause amyloid-related imaging abnormalities (ARIA) including ARIA-E (edema/effusion) and ARIA-H (hemorrhage). ARIA-E occurred in 35 percent (asymptomatic in 74%) and ARIA-H in 14 percent of patients. Symptoms of ARIA include headache, dizziness, nausea, confusion, and vision changes, but

it is asymptomatic the majority of the time. People with APOE-e4 appear to be particularly susceptible to developing ARIA.

The current list price of aducanumab is $56,000 annually. A report from the Institute for Clinical and Economic Review (ICER) suggested that in order for this agent to be cost-effective, its price would need to be significantly lower. When calculating the price based on assumed "optimistic" treatment benefits—relying only on the results of the positive study – the price would need to be between $11,100 and $23,100 annually for it to be considered cost-effective.[12] Based on an assumption of "conservative" treatment benefits, the cost-effective range was reduced to between $1,200 and $4,200.[12] The Centers for Medicare and Medicaid Services (CMS) announced in July 2021 they were starting a National Coverage Determination (NCD) analysis of aducanumab. Analysts have had concerns about the impact of this agent on the CMS budget, given that Medicare covers the majority of AD patients.

Conclusion

The development of biomarkers for AD which help improve diagnosis and identification of subjects for studies has been one of the major developments in AD management. A new antibody treatment which reduces beta-amyloid in the brain has been FDA-approved. Uptake of this agent, efficacy over time, and third-party payer coverage are still to be determined.

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