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ABSTRACT & COMMENTARY

Antisense Oligonucleotide Treatment of Huntington's Disease: A Novel Potential Treatment

By Claire Henchcliffe, MD, PhD

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Dr. Henchcliffe reports she is a consultant for Amneal Pharmaceuticals, Prevail Therapeutics, and US WorldMeds, and receives grant/research support from Biogen.

SYNOPSIS: In this Phase I/IIa clinical trial, investigators administered antisense huntingtin oligonucleotides intrathecally to patients with early Huntington's disease (HD), and demonstrated safety, tolerability, and dose-dependent reduction in CSF mutant huntingtin. This approach now is being tested for clinical efficacy in HD in a Phase III clinical trial.

SOURCE: Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, et al. Targeting huntingtin expression in patients with Huntington's disease. *N Engl J Med* 2019;380:2307-2316.

In this Phase I/IIa clinical trial in individuals with early Huntington's disease (HD), antisense huntingtin (HTT) oligonucleotides (termed HTTRx, also known as RG6042) were used to specifically target mutant HTT mRNA (mHTT) in the study participants. These patients, recruited between 2015 and 2017, were randomized to receive intrathecal administration of HTTRx (n = 34) or placebo (n = 12). The study drug was administered four times, once every four weeks in ascending doses: placebo (n = 12); 10 mg (n = 3); 30 mg (n = 6); 60 mg (n = 6); 90 mg (n = 9); or 120 mg (n = 10), followed by a four-month observation period. The mean age in the treated group was 46 ± 10 years vs. 49 ± 10 years in the placebo group, with 14/34 (41%) women in the treated group vs. 4/12 (33%) in the placebo group. CAG repeat numbers were similar between the groups, and disease-burden, independence, and motor scores were well matched. The primary endpoint of safety was successfully achieved, with no deaths, no serious adverse events related to HTTRx, and no dose-limiting adverse events. Milder adverse events occurred in almost all of participants (98%),

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Neurology
[ALERT]

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most commonly postprocedural pain and headache after intrathecal HTTRx and after lumbar punctures for cerebrospinal fluid (CSF) collection. Just one study participant had an increased leukocyte count at eight weeks' post-procedure (60 mg HTT group) but without any clinical symptoms. HTTRx concentration in CSF was measurable in all but two patients who received the 30 mg and higher doses (although not the 10 mg dose), with trough levels at a plateau from the 60 mg and higher doses. Most importantly for this study, there were dose-dependent reductions in mHTT levels in CSF at 28 days' post-dose (from -20% in the 10 mg group to -42% in the 90 mg group and -38% in the 120 mg group). In contrast, those in the placebo group experienced an increase by 10% from baseline over the course of the study. Unexpected findings included increased ventricular volume in the two highest dose groups revealed by MRI, and elevated CSF neurofilament light protein concentration in some of these individuals. However, no clinical sequelae were linked to these biomarker abnormalities. Clinical measures addressing cognitive, psychiatric, neurological, and functional aspects of HD did not differ significantly between HTTRx and placebo arms, but in a post hoc analysis relationships emerged between the degree of CSF mHTT reduction by HTTRx and components of the composite Unified Huntington's Disease Rating Scale (cUHDRS).

■ COMMENTARY

HD is a severe neurodegenerative disease arising from a triplet repeat CAG expansion in the huntingtin HTT gene. HD is inherited in an autosomal dominant pattern, and the mutation gives rise to a protein with expanded polyglutamine repeats that abnormally aggregates, resulting in degeneration affecting the caudate and multiple other brain regions. Individuals with HD suffer from progressive chorea, cognitive decline, and dementia, and multiple psychiatric symptoms including depression and psychosis. Treatment is symptomatic and despite robust efforts in the research community; as yet, there is no intervention that will prevent HD in mutation carriers or halt or slow progression once it is clinically manifest.

Tabrizi et al undertook this study using antisense oligonucleotides based on the rationale that suppressing mHTT expression will improve HD symptoms, as demonstrated in transgenic mouse models of HD. Therefore, this first-in-human Phase I/IIa clinical trial is encouraging in at least two respects. First, it demonstrated dose-dependent reduction in mHTT in CSF following HTTRx, presumed to reflect a corresponding reduction in the brain. Second, no serious adverse events were encountered, and there were no dose-limiting effects. There were some unexpected findings in exploratory biomarker outcomes. Whether the apparent reduction in brain volume (based on increased ventricular volume) demonstrated on MRI in the higher dose groups is caused by a reduction in inflammation, as the authors suggest, remains to be answered. And why neurofilament light, a marker of neurodegeneration, was increased in some of these individuals was unclear. The main question remaining though, is whether this intervention will show clinical efficacy and improve the lives of those with HD. A Phase III randomized, double-blind, placebo-controlled clinical trial is now underway to evaluate efficacy with a target 660 patients in 101 international sites, including the United States, providing some hope for the HD community. ■

ABSTRACT & COMMENTARY

Calcitonin Gene-Related Peptide Targeting Therapies for Migraine

By Matthew S. Robbins, MD, FAAN, FAHS

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Dr. Robbins reports no financial relationships relevant to this field of study.

SYNOPSIS: Two randomized clinical trials showed that calcitonin gene-related peptide targeting therapies are effective and safe for primary headache disorders.

SOURCES: Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med* 2019;381:132-141.

Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med* 2019;381:142-149.

In the first study, Goadsby et al conducted a multicenter, randomized, controlled trial (RCT) of galcanezumab, a monoclonal antibody targeting calcitonin gene-related peptide (CGRP), for the prevention of episodic cluster headache (CH). Patients 18 to 65 years of age had to have pre-existing CH with bouts lasting for at least six weeks. They were treated with either galcanezumab 300 mg subcutaneously or placebo. Patients were unable to use contemporaneous prophylaxis but could use common acute attack therapies, such as triptans and oxygen. After a screening period and a prospective baseline period lasting 10-15 days, the eight-week treatment period began, featuring galcanezumab administration at treatment period onset and at month one.

Trial enrollment was curtailed because of too few subjects in an active CH period. Ultimately, 57 subjects were treated with placebo and 49 subjects with galcanezumab, without major baseline differences between the two groups. For the primary endpoint, subjects treated with galcanezumab had an 8.7 ± 1.4 reduction in weekly cluster headache attack frequency across weeks 1 through 3, vs. 5.2 ± 1.3 in the placebo group (95% confidence interval, 0.2 to 6.7; $P = 0.04$). The 50% attack frequency reduction rate at week 3 was 71% for galcanezumab vs. 53% for placebo ($P = 0.046$). Efficacy rates in the second month converged across the groups. No serious adverse events were reported, with injection site reactions most commonly reported. Drug discontinuations were rare.

In the second study, Lipton et al conducted a large, multicenter RCT of a single dose of rimegepant, an oral CGRP receptor antagonist, for the acute treatment of migraine. The study included more than 1,000 total subjects 18 years of age and older with two to eight migraine attacks monthly, excluding patients who would satisfy criteria for chronic migraine.

There were no differences in baseline characteristics between the subjects receiving rimegepant 75 mg (n = 537) and placebo (n = 535). For the first primary endpoint, patients receiving rimegepant featured higher rates of two-hour pain freedom than those receiving placebo (19.6% vs. 12.0%; $P < 0.001$). For the second primary endpoint, patients receiving rimegepant featured higher rates of two-hour most bothersome symptom freedom (mostly photophobia) than those receiving placebo (37.6% vs. 25.2%; $P < 0.001$). Serious adverse events were rare and included one patient with back pain in the rimegepant group, one patient with chest pain in the placebo group, and one patient with a urinary tract infection (UTI) in the placebo group. Adverse events overall were uncommon, most commonly nausea and UTI.

■ COMMENTARY

In a single issue of the *New England Journal of Medicine*, two landmark articles documenting safe and effective treatments for primary headache disorders were published. Both treatments target CGRP, either via monoclonal antibody to the ligand itself (galcanezumab) or small molecule receptor antagonist (rimegepant). It is clear that CGRP is pivotally involved in headache pathophysiology in both the peripheral and central nervous system. The site of action of galcanezumab is presumably peripheral, based on limited ability to cross the blood brain barrier, although rimegepant may act both peripherally and centrally.

This study led galcanezumab to become the first-ever FDA-approved preventive treatment for CH, although in a separate study it did not demonstrate efficacy for chronic CH, and fremanezumab, another monoclonal antibody to the CGRP ligand, did not demonstrate efficacy in trials for episodic and chronic CH. This distinguishes CH from migraine, where CGRP-based therapies have shown consistent efficacy across drugs and migraine spectrum severity (episodic and chronic). Previous guidelines show a major gap in preventive treatment for CH, which has a 1/1,000 lifetime prevalence. Whether galcanezumab can supplant verapamil, the most commonly used CH treatment felt to be the most effective, is not yet clear; certainly, cost and access will be major factors. Its potentially short treatment latency may place it at an advantage, reducing the need for simultaneous short-term preventive treatment such as oral steroids or greater occipital nerve injection.

Rimegepant, and potentially other gepants, will prove to be an additional treatment option for patients to treat acute migraine attacks, although efficacy rates seem to be similar to triptans and other acute treatments. Still, tolerability, seeming lack of contraindications (particularly cardiovascular), and lack of evidence for an association with medication overuse may place gepants at a distinct advantage over triptans. Gepants also may be more tolerable than lasmiditan, another triptan alternative, a 5HT1F receptor agonist that likely will receive FDA approval soon. Long-term safety, strategies for repeat dosing, cost, and access will be major factors influencing its clinical practice niche, as may be safety with simultaneous CGRP targeting monoclonal antibodies. ■

ABSTRACT & COMMENTARY

Targeting Fyn Kinase in Alzheimer's Disease: Another Failed Clinical Trial

By Makoto Ishii, MD, PhD

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Dr. Ishii reports no financial relationships relevant to this field of study.

SYNOPSIS: In this multicenter Phase IIa clinical trial in mild Alzheimer's disease dementia, the tyrosine kinase Fyn inhibitor AZD0540 had no significant effects after 52 weeks of treatment.

SOURCE: van Dyck CH, Nygaard HB, Chen K, et al. Effect of AZD0530 on cerebral metabolic decline in Alzheimer disease: A randomized clinical trial. *JAMA Neurol* published online July 22, 2019.

In Alzheimer's disease (AD), the abnormal accumulation of amyloid-beta peptides is believed to be the major pathogenic event leading to synaptic dysfunction, pathological tau accumulation, cognitive impairment, and neurodegeneration. Recent intervention trials in AD have focused on developing therapies to limit the production of amyloid-beta by inhibiting secretase enzymes or by promoting clearance of amyloid-beta through immunotherapy with antibodies against amyloid-beta. Despite several promising drug candidates, all clinical trials specifically targeting amyloid-beta have failed. An alternative approach would be to target downstream effects of amyloid-beta pathology. Although several candidates are being investigated, one promising target is the tyrosine kinase Fyn. Amyloid-beta binds to prion protein on the cell surface of neurons to activate intracellular Fyn kinase, which subsequently mediates synaptotoxicity and tau pathology. In a transgenic mouse model of amyloid-beta pathology, inhibition of Fyn kinase by AZD0530 (saracatinib) results in sustained rescue of memory function. A previous Phase Ib clinical study of AZD0530 demonstrated the safety, tolerability, and central nervous system availability of orally administered AZD0530.

In this multicenter, Phase IIa, placebo-controlled, randomized clinical trial, participants age 55 to 85 years with mild AD and evidence of amyloid pathology by ^{18}F-florbetapir positron emission tomography (PET) scan were enrolled to evaluate the safety, tolerability, and the effects of AZD0530 after 52 weeks of treatment. The primary outcome measure was ^{18}F-fluorodeoxyglucose (FDG) PET measurement of the reduction in relative regional cerebral metabolic rate for glucose (CMRgI). Standard clinical assessments including Alzheimer's Disease Assessment Scale-Cognitive Subscale, Mini-Mental Status Examination (MMSE), Clinical Dementia Rating-Sum of Boxes (CDR-SB), Neuropsychiatric Inventory, and magnetic resonance image (MRI) scans for volumetric analysis were also collected. A subset of participants had cerebrospinal fluid (CSF) collected at baseline and 52 weeks to assess the effects of AZD0530 on CSF tau levels and to measure CSF AZD0530 levels.

A total of 293 participants were screened, and 159 were randomized with 79 to the AZD0530 group and 80 to the placebo. Although the study drug was relatively well tolerated, there were significant number of adverse events, which most frequently were gastrointestinal in nature (48.1% in AZD0530 and 28.7% in placebo). A total of 128 (80.5%) subjects completed the study with early discontinuations owing primarily to these adverse events (26.5% in AZD0530 and 13.8% in placebo group). AZD0530 treatment had no significant effect on ^{18}F-FDG PET-measured reduction in relative CMRgl at 52 weeks. Additionally, there were no differences in all clinical assessments measured. There was a trend toward slowing the decline in hippocampal volume and entorhinal thickness in the treatment group, but these and the other predetermined volumetric measures by MRI did not reach statistical significance. Although the number of participants who had CSF collected was small (34 participants at both baseline and 52 weeks), there were no significant treatment differences for rates of changes in either CSF total tau or phosphorylated tau.

■ COMMENTARY

The overall results from this trial were disappointing, as there were no statistically significant effects of AZD0530 treatment on any of the primary or secondary outcome measures. However, there are important limitations that may have contributed to study failure. First, there was a larger number of participants that discontinued the trial than expected, leading to a significant reduction in the statistical power of the study and the inability to detect all but large effect sizes. Second, in the limited number (13) of study participants receiving active treatment who had a week-52 lumbar puncture, the CSF AZD0530 level was slightly below the predetermined efficacy threshold. The dose of AZD0530 could be increased in

future trials to ensure maximum efficacy, but this may be difficult due to the high number of participants with adverse effects from the drug at the present dose.

The results from this trial highlight the challenges in developing an AD therapy based on inhibition of Fyn kinase. Since Fyn kinase has important physiological functions outside of the central nervous system, off target effects due to inhibition of Fyn kinase may be difficult to avoid. Additionally, none of the Fyn kinase inhibitors are completely selective and will inhibit other members of the Src family of non-receptor tyrosine kinases, which will further increase the likelihood of off target effects. Importantly, inhibiting Fyn kinase may be too late even in mild AD dementia, where there is already significant neurodegeneration. Although Fyn kinase is downstream of amyloid-beta, it is still an early event in the pathogenesis of AD and may need to be targeted at earlier stages of AD such as mild cognitive impairment, where the effects of Fyn kinase may still be reversible. Alternatively, the downstream effects of Fyn kinase activation could be targeted.

Despite the disappointing results from this trial and the challenges in developing Fyn kinase inhibitors as a disease modifying therapy for AD, there were significant advances made in this trial. Notably, the study investigators provided strong evidence for the use of ^{18}F-FDG PET measurement of CMRgI as an outcome measure that was well correlated with traditional clinical measures but with greater precision. Therefore, the use of CMRgl should be considered in future AD intervention trials. Finally, with the increasing number of drug trial failures directly targeting amyloid-beta, especially once dementia develops, this study highlights a need to continue to investigate additional downstream targets of amyloid-beta pathology to develop an effective disease modifying therapy for symptomatic AD. ■

ABSTRACT & COMMENTARY

Risk of Neuropathy With Fluoroquinolones

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: As a class, fluoroquinolones are some of the most commonly used antibiotics worldwide. Their use carries a significant risk of neurotoxicty, for both the peripheral and central nervous system.

SOURCE: Morales D, Pacurariu A, Slattery J, et al. Association between peripheral neuropathy and exposure to oral fluoroquinolone or amoxicillin-clavulanate therapy. *JAMA Neurol* 2019;76:827-833.

Fluoroquinolones, commonly used to treat respiratory, gastrointestinal, and urinary tract infections, include, among others, ciprofloxacin (Cipro), levofloxacin (Levaquin), and moxifloxacin (Avelox). Side effects include gastritis, hepatotoxicity, QT interval prolongation, and, among its most common adverse effects, altered mental status and neuropathy, including mononeuropathy, multiple mononeuropathy, and polyneuropathy. What are the risk estimates for polyneuropathy with fluoroquinolone exposure, and what factors are associated with this risk?

Using The Health Improvement Network (THIN) database, covering approximately 6% of the United Kingdom population from more than 500 general medical practices, a nested case-control study design was used to evaluate the risk of incident peripheral neuropathy. The investigators included adults who were in the THIN database between Jan. 1, 1999, and Dec. 31, 2015, who were 18 years of age or older, and who were issued at least one prescription of oral amoxicillin-clavulanate (controls) or oral fluoroquinolone antibiotic therapy were included. They chose amoxicillin-clavulanate so that controls were sampled from a more representative population prescribed antibiotics. Patients with a prior history of neuropathy or diabetes were excluded. At least one year of observation prior to cohort entry was required of all participants. Cohort exit was defined as outcome occurrence, death, deregistration from the practice, end of study period, or date of last data collection from the general practice. Cumulative antibiotic exposure was measured as the total number of days of oral fluoroquinolone or oral amoxicillin-clavulanate exposure within each risk window. Cumulative days of exposure was calculated by dividing the prescription quantity information by the standard administration schedules for each antibiotic. Adults with incident peripheral neuropathy were matched with up to four controls using incidence density sampling, selected from a cohort prescribed oral fluoroquinolone or amoxicillin-clavulanate antibiotics. Statistical analysis included conditional logistic regression, sensitivity analyses, and multiple imputation, with a two-sided $P < 0.05$ considered statistically significant.

Among 1,338,900 adults issued one or more prescriptions of fluoroquinolone (34.3%) or amoxicillin-clavulanate (65.7%) (mean age, 52.8 years; 57% female) without a diagnosis of peripheral neuropathy at cohort entry, a total of 11,224 incident peripheral neuropathy cases were identified and matched to 42,316 controls. Those with diabetes were then identified and excluded, leaving 5,357 incident peripheral neuropathy cases (mean age, 65.6 years; 2,809 women) matched to 17,285 controls (mean age, 64.4 years; 9,485 women). Median duration of exposure was 10 days for fluoroquinolone and seven days for amoxicillin-clavulanate, with risk of neuropathy calculated as increased by 3% for each additional day of current fluoroquinolone exposure, the risk persisting for up to 180 days following exposure. No significant increased risk was observed with exposure to oral amoxicillin-clavulanate. Absolute risk with oral fluoroquinolone exposure was 2.4 per 10,000 patients per year of use, with number needed to harm for a 10-day course being 152,083 patients, greatest among men and those older than 60 years of age.

■ COMMENTARY

In use for more than 30 years, and presently among the most widely prescribed antibiotics worldwide, representing 10% of prescriptions per 1,000 population in 2015 in the United States alone, fluoroquinolones have been associated with significant side effects in susceptible individuals. Historically, these have included peripheral neuropathy, photosensitivity, prolonged QT interval, hypoglycemia, and tendon rupture, but more recently the U.S. Food and Drug Administration has extended these warnings to include a risk of aortic dissection, thus recommending avoidance of these drugs in patients with peripheral vascular disease, uncontrolled hypertension, vascilitides, and connective tissue disorders, such as Ehlers-Danlos syndrome. In addition to tendon rupture, there is an increased risk of tendonitis, myalgia, muscle weakness, arthralgia and joint swelling, and neuropsychiatric issues occur as well, encompassing psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion and impairment of vision, hearing, smell, and taste. Transplant recipients, those with renal dysfunction, older patients, and those receiving concomitant corticosteroids are at higher risk. Lastly, a fibromyalgia-like syndrome, termed fluoroquinolone-associated disability syndrome (FADS), has been associated with these antibiotics, but the risk of fibromyalgia with fluoroquinolone is similar to that with amoxicillin and azithromycin, and thus the antibiotic is not likely causative.[1,2] ■

REFERENCES

1. Richards GA, Brink AJ, Feldman C. Rational use of the fluoroquinolones. *S Afr Med J* 2019;109:378-381.
2. Ganjizadeh-Azvareh S, Sodhi M, Spangehl T, et al. Oral fluoroquinolones and risk of fibromyalgia. *Br J Clin Pharmacol* 2019;85:236-239.

Neurology [ALERT®]

Stroke Alert

By Matthew E. Fink, MD

Racial and Ethnic Disparities in Thrombectomy in the United States

SOURCE: Rinaldo L, Rabinstein AA, Cloft H, et al. Racial and ethnic disparities in the utilization of thrombectomy for acute stroke. Analysis of data from 2016 to 2018. *Stroke* 2019; 50:00-00. DOI: 10.1161/STROKEAHA.118.024651. [Epub ahead of print].

Mechanical thrombectomy for the treatment of acute ischemic stroke secondary to large vessel occlusion has been accepted and widely deployed in hospitals throughout the United States. However, disparities of treatment across various ethnic and racial groups has not been examined carefully to ensure uniform application of this treatment. The investigators reviewed admissions for acute ischemic stroke to endovascular centers occurring between January 2016 and September 2018 from a national database. They determined the number of patients who were treated with intravenous thrombolysis as well as mechanical thrombectomy at each institution, and recorded patient demographics, including age, sex, race, ethnicity, and insurance status. Demographic variables independently associated with utilization of mechanical thrombectomy were identified using a multivariate linear regression analysis.

There were 206,853 admissions to 173 endovascular centers during the time interval that was explored. Overall utilization of mechanical thrombectomy was 8.4% of acute ischemic stroke patients. The utilization of endovascular mechanical thrombectomy for black and Hispanic patients was lower than among white and non-Hispanic patients (7.0% vs. 9.8%). Black and Hispanic patients also were less likely to receive intravenous thrombolysis (16.2% vs. 20.5%), or to be admitted to the endovascular center after transfer (20% vs. 30%). In a multivariate linear regression analysis, it was determined that presence of female sex, uninsured status or

insurance with Medicaid, and having black or Hispanic race/ethnicity were independently associated with a lower utilization of mechanical thrombectomy. Stroke centers need to address these disparities and focus on the underlying causes that explain them. ■

After Ischemic Stroke Related to Atrial Fibrillation, Direct Oral Anticoagulants Are Superior to Vitamin K Antagonists

SOURCE: Seiffge DJ, Paciaroni M, Wilson D, et al; CROMIS-2, RAF, RAF-DOAC, SAMURAI, NOACISP LONGTERM Erlangen and Verona registry collaborators. Direct oral anticoagulants versus vitamin K antagonists after recent ischemic stroke in patients with atrial fibrillation. *Ann Neurol* 2019;85:823-834.

Oral anticoagulation is effective in prevention of ischemic stroke and systemic embolism in patients with atrial fibrillation. For many years, vitamin K antagonists were the only oral agents available, but there are now several direct oral anticoagulants, including the thrombin inhibitor, dabigatran, and factor Xa inhibitors, apixaban and rivaroxaban. The direct oral anticoagulants have been shown to be at least as effective as warfarin, with a reduced risk of intracerebral hemorrhage. However, the clinical trials that investigated these medications allowed long delays following acute ischemic stroke, before the medications were started. The authors of this trial investigated the benefits and risks of early anticoagulation following acute ischemic stroke, and compared the effects of direct oral anticoagulants vs. vitamin K antagonists.

The investigators performed a meta-analysis by analyzing individual patient data from seven prospective cohort studies. Patients were included if they had atrial fibrillation and a recent cerebral infarct less than three months before starting oral anticoagulation, with a minimum follow-up of three months. They analyzed the association between the type of anticoagulation, direct oral anticoagulant vs. vitamin K antagonist, with the primary composite endpoint of recurrent ischemic stroke, intracerebral hemorrhage, or mortality, using a Cox proportional hazards regression model.

The investigators included 4,912 patients, with a median age of 78 years, 47.5% women, and median NIH stroke scale score of 5, with 45.9% of patients receiving vitamin K antagonist and 54.1% of patients receiving direct oral anticoagulants. The median time from the ischemic event to starting medication was five days for all medications. In follow-up, there were 262 acute ischemic strokes, for a rate of 4.4% per year; 71 intracranial hemorrhages, for a rate of 1.2% per year; and 439 deaths, or 7.4% per year during a follow-up of 5,970 patient-years. Compared to vitamin K antagonists, direct oral anticoagulation treatment was associated with a reduced risk for the composite endpoint (hazard ratio [HR], 0.82; $P < 0.05$) and a reduced intracerebral hemorrhage rate (HR, 0.42; $P < 0.01$). There was no difference between the two drug categories related to the risk of recurrent ischemic stroke or mortality. Overall, treatment with direct oral anticoagulants resulted in a reduced risk of poor clinical outcomes, primarily due to reduced risk of intracerebral hemorrhage. ■

Faster Time to Endovascular Reperfusion Therapy Results in Better Outcomes

SOURCE: Jahan R, Saver JL, Schwamm LH, et al. Association between time to treatment with endovascular reperfusion therapy and outcomes in patients with acute ischemic stroke treated in clinical practice. *JAMA Neurol* 2019;322:252-263.

Endovascular reperfusion therapy has been demonstrated to be of benefit for the treatment of large vessel occlusion in patients with acute ischemic stroke. This effect is time dependent and most of the randomized clinical trials enrolled patients who were no more than eight hours from onset of symptoms to puncture time. These investigators reviewed a real-life cohort of patients who had data recorded in the Get With The Guidelines–Stroke nationwide registry to determine if time to treatment had an effect on clinical outcomes. The database was explored for 6,756 patients with anterior circulation large vessel occlusion during the period January 2015 until December 2016. All patients had onset-to-puncture time of eight hours or less. Main outcomes were substantial reperfusion as determined by the thrombolysis in cerebral infarction (TICI) score of 2b-3, ambulatory status, global disability as determined by the modified Rankin scale, destination at discharge, symptomatic intracranial hemorrhage rate, and in-hospital mortality/hospice discharge. Mean age was 69.5 years, 51% of patients were women, and the median pretreatment score on the NIH stroke scale was 17. In addition, 85.9% of patients achieved substantial reperfusion. Adverse events were symptomatic intracerebral hemorrhage in 6.7% of patients and in-hospital mortality or hospice discharge in 19.6% of patients. At time of hospital discharge, 36.9% of patients were ambulating independently and 23% had functional independence as determined by a modified Rankin score of 0-2.

Overall, in the 30-270 minute time frame after onset of symptoms, faster onset-to-puncture time, in 15-minute increments, was associated with a higher likelihood of achieving independent function and discharge to home. In addition, faster onset to puncture also was associated with a lower in-hospital mortality or hospice discharge and a lower risk of symptomatic intracerebral hemorrhage. ■

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CME QUESTIONS

1. **A recent clinical trial tested an experimental approach using antisense oligonucleotides that target mutant huntingtin protein (mHTT) to treat Huntington's disease (HD). Which of the following is correct?**
   a. Antisense oligonucleotides were surgically targeted to the caudate to test effects of the drug on chorea.
   b. Clinical symptoms of HD improved in the highest dose group only.
   c. The intervention led to measurable levels of antisense oligonucleotide in the brain.
   d. The intervention led to decreased mHTT in the CSF.
2. **Which statement regarding galcanezumab is correct?**
   a. Galcanezumab has been shown to be effective in the treatment of chronic cluster headaches.
   b. Galcanezumab had no benefit in reducing the frequency of cluster attacks.
   c. Galcanezumab is FDA-approved for prevention of episodic cluster headaches.
   d. Galcanezumab is effective in treating all headache types.
3. **For the recent clinical trial investigating the inhibition of Fyn kinase by AZD0530 in AD, which of the following could be a possible explanation as to why the study failed?**
   a. A higher than expected number of participants who discontinued the study drug because of adverse effects resulting in significantly reduced statistical power
   b. The inclusion of a significant number of study participants with non-amyloid dementia
   c. The inability of the study drug AZD0530 to reach the central nervous system to any measurable degree
   d. The inability of the study drug AZD0530 to inhibit Fyn kinase
4. **There are no racial or ethnic disparities in the treatment of acute ischemic stroke in the United States.**
   a. True
   b. False
5. **Every 15 minutes of delay in endovascular thrombectomy for acute ischemic stroke results in a worse clinical outcome.**
   a. True
   b. False
6. **Direct oral anticoagulants have no advantages over oral vitamin K antagonists (warfarin).**
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

[IN FUTURE ISSUES]

Neuro-oncology