Intracerebral Hemorrhage
New Challenges and Steps Forward

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KEYWORDS

• Intracerebral hemorrhage • Acute brain injury • Anticoagulation

KEY POINTS

- Intracerebral hemorrhage (ICH) takes a toll on patients and society. Advances in the treatment of ICH have not kept pace with those of stroke and acute myocardial infarction.
- The cause of ICH and complications afterward are related to blood pressure control, making this the central strategy for prevention and treatment.
- Limited surgery for some ICH may be beneficial. Studies are ongoing.
- Anticoagulation associated ICH is best treated by early correction of coagulopathy.

INTRODUCTION

Intracerebral hemorrhage (ICH) is a devastating disease that all too frequently leaves patients dead or severely disabled. Attempts over the last decade to improve the outcome of these patients have met with only marginal success. As the population ages and the use of anticoagulation for the treatment of atrial fibrillation increases, the incidence of ICH is expected to rise.[1] This will have a major impact on health resources because the number of patients who remain permanently debilitated after ICH is high.

Any hemorrhage that primarily affects the substance of the brain or the ventricular spaces (compared with the subarachnoid spaces) is considered ICH. There is considerable overlap between ICH and subarachnoid hemorrhage in regard to the causes of the ictus and many patients have bleeding in more than one compartment. Most intraventricular hemorrhage (IVH) is a consequence of ICH where the hemorrhage ruptures into the ventricular space. There seems to be an independent entity of isolated IVH that differs from ICH but likely constitutes a small proportion of patients with IVH.[2] In addition, there are a considerable number of patients who have ICH as a consequence of secondary hemorrhage subsequent to ischemic stroke.

This article deals specifically with nontraumatic isolated ICH with or without IVH. The frequency, causes, treatments, and outcomes of patients with ICH are discussed. In addition, some of the more recent scientific inquiries into the causes of ICH are explored.

EPIDEMIOLOGY, PROGNOSIS, AND IMPACT

The annual incidence rate for ICH is approximately 28 hemorrhages per 100,000 people.[3] It is the second most common form of stroke accounting for 10% to 15% of new strokes per year.[1] Thirty-day mortality is estimated to be 30% to 50%, although these numbers are likely skewed by the reluctance

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Neurosurg Clin N Am 24 (2013) 349–359
http://dx.doi.org/10.1016/j.nec.2013.03.002
1042-3680/13/$ – see front matter © 2013 Elsevier Inc. All rights reserved.

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of physicians and family to aggressively manage patients with ICH.[4] This self-fulfilling prophecy has limited the evaluation of the actual mortality of the disease.[5] There is concern that therapeutic nihilism may lead to abnormally high mortality projections, which lead physicians and families to limit care in patients with the potential for recovery. It has been observed that hospitals with a higher proportion of patients with "do not resuscitate" orders have higher mortality for ICH.[4,6]

The most common risk factors for ICH are chronic hypertension and evidence of previous microhemorrhages on magnetic resonance imaging (MRI).[7] The most rapidly increasing population of patients with ICH is patients on oral anticoagulation therapy (OAT), discussed later.

The incidence and prevalence of ICH varies among different ethnic and racial groups largely because of racial variation in the incidence and management of hypertension.[8] Across the board, chronic hypertension is responsible for approximately 50% of ICH. The classic vessel damage associated with chronic hypertension–associated hemorrhages occurs in small penetrating arteries that come off of larger parent vessels, such as the lenticulostriate arteries emanating from the middle cerebral artery and perforators that arise from the basilar artery. These small arteries feed deep central areas of the brain.

The next most common cause of ICH is cerebral amyloid angiopathy, which accounts for about 20% of cases.[1] The angiopathy typically occurs in older patients and is unrelated to systemic amyloidosis.[9,10] Although there has traditionally been a view that lobar hemorrhages are more likely to be associated with amyloid angiopathy, it is more accurate to say that amyloid angiopathy hemorrhages are more likely to be lobar than deep.[10]

ICHs often have small subclinical hemorrhages that can now be visualized by MRI sequences that exploit the susceptibility artifact that is generated by hemosiderin deposits in the brain. These small hemorrhages, termed "microhemorrhages," also have been associated with stroke and vascular dementia suggesting that they are a general marker of microvascular disease of the brain (**Fig. 1**).[11–16] How chronic hypertension and anticoagulation contribute to microhemorrhages is not clear.

Prediction of outcome after ICH is essential for informed discussions with patient families. It is clear that the size of the hemorrhage, location, and age of the patient are strong predictors of mortality.[1] The ICH score uses these risk factors to quantify the chance of survival.[17] Points are assigned for age greater than 80, Glasgow Coma Score, hemorrhage volume greater than 30 mL

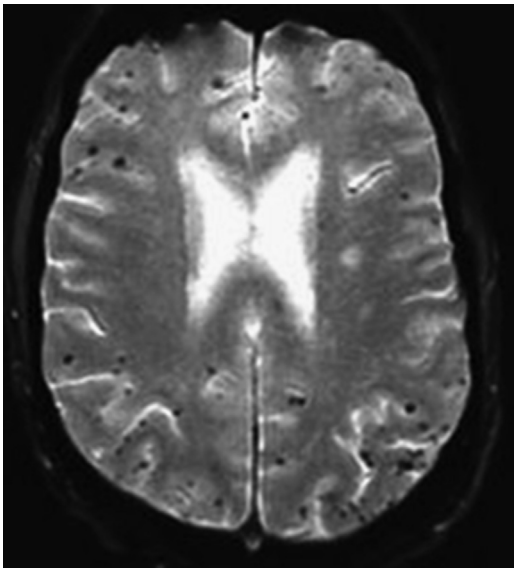

Fig. 1. Magnetic resonance imaging of multiple cerebral microbleeds detected on spin echo gradient imaging. These microbleeds most likely represent amyloid angiopathy but may also be a marker for small vessel disease. (*Data from* Walker DA, Broderick DF, Kotsenas AL, et al. Routine use of gradient-echo MRI to screen for cerebral amyloid angiopathy in elderly patients. Am J Roentgenol 2004;182:1547–50.)

by computed tomography (CT) scan, infratentorial location, and intraventricular extension of blood. The grading scale predicts mortality from a score of 0 at 0% mortality to a score of 5 with a mortality of 100%.[17] A similar score was developed to predict independent functional survival, which also includes an assessment of prehospital cognitive status.[18] Both scores have been validated and seem to be useful in clinical practice. Neither scale took into account the effect of therapeutic nihilism that may have resulted in the reporting of increased mortality.

The impact of ICH on society is great. Stroke of all kinds is particularly costly because of the prolonged disability of patients who survive. It is estimated that ICH costs $125,000 per ICH per year resulting in $6 billion cost per year in the United States.[19] In a similar assessment, the lifetime cost of ICH in Spain was found to be €46,193 (euros) per patient suggesting that the costs in the United States may be higher than other developed countries.[20]

INTENSIVE CARE UNIT MANAGEMENT

Most patients with ICH are critically ill on admission, so appropriate critical care management seems likely to make an important contribution to

outcome. Important issues that arise in patients with ICH include poor control of their airway protective reflexes, hypoventilation, and increased intracranial pressure (reviewed in[21]). In a few patients with severe damage to critical areas of the brain, specific cardiac and pulmonary complications, such as takasubo cardiomyopathy and neurogenic pulmonary edema, may occur.[22,23] These entities are more common in patients with subarachnoid hemorrhage and traumatic brain injury. In addition, pressure on the hypothalamic-pituitary axis can lead to several electrolyte abnormalities, such as diabetes insipidus and cerebral salt wasting.

Specific understanding of systemic complications that occur in ICH may lead to improved outcomes. A retrospective review of outcome data from the Project IMPACT database of intensive care units showed that admission to a dedicated intensive care unit with neurologic specialization was an independent predictor of decreased mortality.[24] In addition, a before-and-after study of management of patients with ICH showed that the addition of physicians trained in neurointensive care decreased mortality.[25]

The mainstay of ICH management for the last 30 years has been the control of systolic blood pressure to prevent hematoma expansion.[7] Until recently, this was done without convincing evidence that control of blood pressure made a difference. There is concern that untreated systolic blood pressure leads to hemorrhage expansion. However, concerns were also raised that aggressive control of blood pressure could lead to ischemia in the perihematomal area. Previous evidence by positron emission tomography scanning of patients with ICH showed that moderately decreasing blood pressure does not significantly decrease perihematomal perfusion.[26] In fact, positron emission tomography scans evaluating cerebral metabolism suggest that any decreased blood flow to the perihematomal area is caused by matched perfusion-metabolism demand, which precludes the worry about ischemia.[27]

Recently, two studies have supported the suspicion that blood pressure control is valuable. The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial randomized 404 patients to aggressive blood pressure control (systolic blood pressure <140 mm Hg) or standard therapy (systolic blood pressure <180 mm Hg).[28] CT scan comparing a baseline CT imaging with 24- and 72-hour scans showed significantly less hemorrhage and cerebral edema in the aggressive blood pressure management group. The study was not powered to evaluate clinical outcome but a larger study to address this is planned.

A second, large randomized trial called the Antihypertensive Treatment of Acute Cerebral Hemorrhage is also planned to specifically assess acute blood pressure control and clinical outcome. The phase 1 dose-escalation arm of the study randomized 60 patients to different dosing regimens of antihypertensives. Patients with lower blood pressure were less likely to have hematoma expansion, perihematomal edema, and poor 3-month outcome.[29] It is hoped that the results of the larger trial will address the question of the benefit of acute blood pressure management.

TREATMENT BASED ON PATHOPHYSIOLOGY

The brain injury that occurs after a spontaneous ICH evolves over time but the initial injury is likely caused by mechanical disruption of brain tissue and the subsequent mass effect of the blood compressing vital brain structures. Hematoma size is a powerful predictor of mortality and hematoma expansion correlates with increase mortality.[30] Hematoma growth occurs in approximately 38% of patients with most occurring within the first hour and the remaining over the subsequent 20 hours.[31] Hematoma expansion may be predicted by the patient's presenting blood pressure but has been difficult to quantify. Patients with contrast extravasation inside of the hematoma area seen on contrasted CT of the brain (called the spot sign) have been clearly documented to predict hematoma expansion (**Fig. 2**).[32]

Secondary injury after ICH is still not well understood. Neurotransmitters (mostly glutamate),[33] inflammatory cytokines,[34] matrix metalloproteinases,[35] heme,[36] iron,[37,38] and thrombin[39] injure the brain at different times in the evolution of the hematoma. It is likely that there is temporal evolution of susceptibility of the brain to injury. The development of toxic mediators may take a similar course making the identification of a particular offending agent at a particular time difficult.[40]

Secondary injury after ICH may be related to the development of perihematomal edema. Perihematomal edema is a zone of viable tissue around the core of the hemorrhage that is vulnerable to the secondary insults similar to the ischemic penumbra in ischemic stroke. Perihematomal edema is believed to develop in three phases.[41] Within the first few hours after the hemorrhage, the hematoma develops and retracts as the red cell mass and coagulation factors organize into a compact mass leaving serum molecules from the hematoma into the surrounding tissue. These proteins seem to be toxic to neurons. During the ensuing 2 to 3 days, these toxic elements lead to

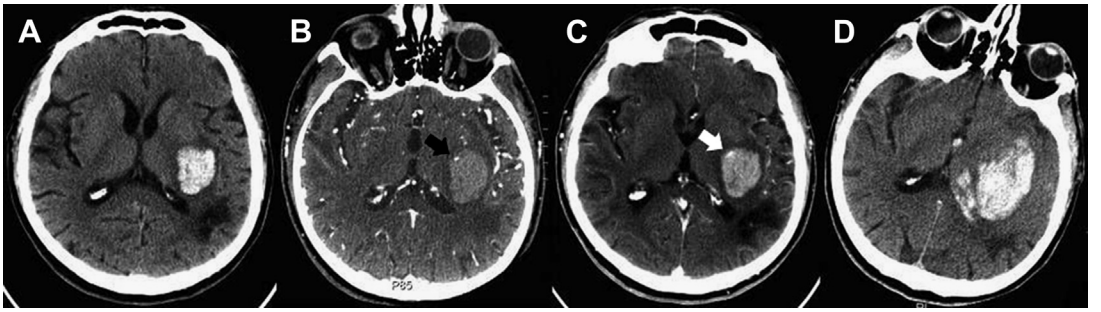

Fig. 2. (*A*) Computed topographic imaging of a left putaminal hemorrhage. (*B*, *C*) CT angiography demonstrating contrast extravasation (spot sign) black arrow in image B and white arrow in image C. (*D*) Subsequent hematoma expansion detected on CT. (*From* Wada R, Aviv RI, Fox AJ, et al. CT angiography "spot sign" predicts hematoma expansion in acute intracerebral hemorrhage. Stroke 2007;38(4):1257–62; with permission.)

endothelial activation and extravasation of inflammatory mediators. In the final step, as the clot dissolves, red blood cells are lysed and hemoglobin breakdown products mediate toxicity.

Thrombin, a trypsin-like serum protease that plays a pivotal role in the coagulation cascade, is present in high concentrations in the brain after an ICH and may be neurotoxic.[39,42] Studies done in animals show that injection of thrombin inhibitors in the hematoma site results in less edema formation suggesting that thrombin plays a direct role in production of perihematomal edema.[43,44]

From these data, there seems to be competition between hematoma expansion prevention (in part by thrombin) and thrombin-mediated neuronal damage. One report found that patients with higher relative volumes of perihematomal edema have better prognosis.[45] This study could reflect a more intact coagulation system with correspondent clot retraction and less hematoma expansion highlighting the possible balance of expanding clot and neuronal toxicity.

Possibly the most detrimental preventable complication of ICH is hematoma expansion after the original hemorrhage. Recent studies show that hematoma expansion is common and independently affects mortality.[46] There has not been much research into the specific cellular or molecular changes that lead to rehemorrhage but clinical evidence suggests that systolic hypertension contributes. Several studies have tested procoagulants in patients on anticoagulation but only one randomized study investigated procoagulants in patients not on anticoagulation therapy.[47,48] The FAST trial analyzed the effect of administering recombinant activated factor VIIa acutely in patients with spontaneous ICH who were not receiving anticoagulation.[49] A lower incidence of hematoma expansion was observed in the treatment group without significant change in the overall prognosis. The disappointing results could be a reflection of increased thrombin concentrations inside of the hematoma or the increased rate of secondary thrombotic complications.

Several trials have investigated preventing secondary brain injury by affecting molecular and cellular mechanisms. To date, no clinical studies have shown significant benefit. A neuroprotective free radical scavenger NXY-059 was tested in patients with ICH to evaluate safety and tolerability. The purpose of the study was to test the feasibility of administering medications to symptomatic patients before CT evaluation.[50,51] Although the study was not powered for efficacy, there was no trend toward improvement in the study group.

The most promising current medical therapy being investigated is an iron-chelating drug called deferoximine. The development of reactive oxidant species formation during iron metabolism has been well established; however, the development of these agents was thought to be too early in the course of the disease to be good targets for treatment.[52,53] Ferric iron, stored in hemoglobin, is converted to ferrous iron, a reactive oxidant species, when red blood cells are lysed. Lysis may be delayed for several hours or days making the approach of chelating iron before its conversion a hopeful treatment target.

Animal studies have been promising and a safety and tolerability study was significantly promising to support a phase 3 trial.[52,54] It is possible that if chelating iron is not feasible, other ways of interacting with the late radicalization of iron may still represent meaningful treatment targets.

SURGERY FOR ICH

It has long been recognized that surgery for cerebellar hemorrhages with significant mass effect on the brainstem can be life saving.[55] There is still

controversy about whether there is a role for external ventricular drainage alone in patients with hydrocephalus from impingement of the fourth ventricle without decompressive craniectomy, or whether both therapies should be initiated together.

Surgery for supratentorial ICH has been attempted for years without evidence of improvement in patient outcome. Previous small, randomized studies with one exception showed no benefit compared with aggressive medical therapy. Interestingly, the one study that did show benefit in the surgery arm used a minimally invasive technique to decompress hemorrhages that came close to the surface.[56]

An attempt to definitively address the possible benefit of surgery for ICH was undertaken with the Surgical Trial in Intracerebral Hemorrhage (STICH) trial.[57] The design of this multinational trial was to randomize patients based on the theory of equipoise randomizing patients when the admitting surgeon was unsure if surgery would be beneficial. This left two groups (patients the surgeon believed would definitely benefit from surgery and patients in whom the surgeon at the local facility believed would not benefit from surgery) out of the study. There were thus large differences in how severe and what types of hemorrhages were included between centers.

The study randomized 1000 patients. Six-month mortality, modified Rankin Scale scores, and Barthal Index scores were no different between the surgery and medical management groups. Subgroup analysis did show that hemorrhages that were closer to the surface had better outcomes with surgery (similar to the previous study by Auer and coworkers[56]).

The failure of open surgery to improve outcomes in deep hemorrhages and the suggestion that less invasive surgery may be beneficial has led to three ongoing trials. The STICH trial investigators have devised a follow-up study to investigate open surgery for peripheral hemorrhages. In addition, a single center trial using a minimally invasive approach with external ventricular devices placed into the clot with lytic agents shows promising results.[58] This new approach using external ventricular catheters to administer recombinant tissue plasminogen activator into the clot with removal of lysed blood is being tested in The Minimally Invasive Surgery Plus T-PA for Intracerebral Hemorrhage Evacuation trial.[59] This trial exploits the CT scan volumetric evaluation of the hemorrhage to determine the approach of the external ventricular catheters and the administration of the lytic medicine. The result of these studies is expected in 1 to 3 years.

ICH ASSOCIATED WITH ORAL ANTICOAGULATION

ICH in patients on OAT (OAT-ICH) is an increasing problem, mostly because of the aging population and the increased use of anticoagulants for patients at high risk for thrombosis.[60] It is speculated that approximately 5.6 million patients in the United States will have atrial fibrillation by 2050 and many of them will likely be taking oral anticoagulants.[61] Moreover, ICHs are eight times more frequent in patients on oral anticoagulants,[62] with an annual estimated incidence of 0.25% to 1.1%.[63]

The mechanism through which anticoagulation promotes ICH has not been completely elucidated, but animal data using a mouse model demonstrated that hematoma size was directly related to the intensity of anticoagulation.[64,65] Although anticoagulation may not increase the risk of ICH, it is hypothesized that a greater bleeding tendency increases the size of spontaneous ICHs that otherwise might be asymptomatic.

Not surprisingly, anticoagulated patients have a higher risk of hematoma expansion. This has been observed in up to 56% of patients[66] occurring as far as 7 days postictus (despite correction of the underlying coagulopathy).[67,68]

Patients on oral anticoagulation also have increased incidence of volume expansion into the ventricular system.[69,70] Some studies have observed an association of higher mortality with the presence of IVH, especially in patients in which all the ventricles were involved.[70] In general, patients with OAT-ICH have an overall worse prognosis than patients with spontaneous ICH[67,71,72] with mortality rates almost doubling those reported in noncoagulopathic patients.[71,73]

Risk factors for OAT-ICH are advanced age; hypertension; history of cerebrovascular disease; the intensity of anticoagulation (mainly if international normalized ratio [INR] >4)[74,75]; and the concomitant use of aspirin.[76] Recently, the presence of microhemorrhages on brain MRI gradient echo weighted scans,[77] leukoaraiosis,[78] and genetic factors (CYP2C9, VKORC1, and apolipoprotein E genotype variants)[79–84] are believed to contribute to an increased risk of OAT-ICH. Although most OAT-ICH occurs in patients with INR less than 3,[60] higher INR values (>3.5) are directly correlated with OAT-ICH occurrence[85–87] and the size of the hematoma on arrival to the hospital.[88]

A radiographic finding observed in roughly 60% of patients with OAT-ICH is a distinct fluid level in the hematoma. This is believed to occur because of the inability of the blood to coagulate creating a level of serum over red blood cells as the patient is laying flat for the scan.[89,90] At the same time, the

Table 1
Suggestions for reversal of anticoagulants commonly used in clinical practice

Agent	Coagulation Monitoring	Reversal Strategies	Comments[a]
Heparinoids			
Heparin	Activated partial thromboplastin time or anti-Xa heparin assay (in patients in whom activated partial thromboplastin time is unreliable)	Protamine sulfate	Typical dosing: 1 mg of protamine/100 IU of heparin infused during the previous 6 h maximum dose of 50 mg. Smaller doses may be appropriate for infusions that are stopped >2 h (heparin half-life approximately 90 min)
Low-molecular-weight heparins	Anti-Xa heparin assay	Protamine sulfate	No consensus on appropriate dosing. Protamine is less effective to reverse the effects of low-molecular-weight heparin than heparin sulfate.
Vitamin K antagonists			
Warfarin	Prothrombin time INR	PCC, fresh frozen plasma, vitamin K, recombinant activated factor VII	For reversal of therapeutic INR: 10 mg intravenous vitamin K plus 50 IU/kg PCC For patients with INR >4: 10 mg of vitamin K plus 10–20 mcg/kg although higher doses of PCC plus the addition of recombinant activated factor VII or fresh frozen plasma to replete factor VII depletion (not necessary if a four-factor PCC is used)
Direct thrombin inhibitors			
Dabigatran	Possibly echarin clotting time, thrombin time, thromboelastography	Hemodialysis, possible reversal with PCC	PCC can be tried but there are no data to support efficacy or specific dosing. Currently, only hemodyalysis has been shown to reverse the effect.
Factor Xa inhibitors			
Rivaroxaban	Possibly thromboelastography	Possibly PCC	Some existing data support PCC use (usually 50 IU/kg)

Abbreviations: INR, international normalized ratio; PCC, prothrombin complex concentrates.
[a] The described doses have not been validated. The comments are suggestions based on common practice at the authors' institution and are not the only possible therapies.

hematoma shape is usually not significantly different than what is observed in spontaneous ICH. Similarly, the standard ABC/2 volumetric measuring method offers reasonable approximation of hematoma volume in OAT-ICH.[91] Interestingly, OAT-ICH has a predilection for the cerebellum. The reason for this is unclear.[72,92,93]

OAT-ICH is a neurologic emergency, because patients with elevated INR are at high risk of hematoma expansion during the first 24 to 48 hours. Even small hematomas can transform into neurologic catastrophes in a matter of minutes. Currently, there are no randomized trials assessing clinical outcomes of different anticoagulation reversal strategies in patients with OAT-ICH. Most of the evidence and guidelines derive from several small studies or case series, most of which are retrospective analyses.

There is no absolute consensus on how to reverse the effects of anticoagulation. For warfarin there are well-studied choices, but for heparinoids and direct thrombin inhibitors there are fewer options. **Table 1** summarizes suggested reversal strategies for the most used anticoagulants.

There is a theoretical concern that reversing anticoagulation could lead to thrombus generation especially in patients with mechanical heart valves and procoagulant states, which was refuted by recent studies.[94–96] Finally, the four pillars of OAT-ICH treatment are (1) prompt reversal of anticoagulation; (2) hypertension control; (3) surgery (if indicated); and (4) specialized neurologic intensive care. It is important to collect a meticulous history about the kind of anticoagulant the patient is receiving, last dose, renal and liver function, and the indication for anticoagulation and occurrence of previous bleedings.

IVH COMPLICATING ICH

IVH occurs in 50% of patients with spontaneous ICH. Mortality is five times higher than in patients with isolated ICH.[97] IVH complicates the management of patients in several ways. In addition to forming a low-pressure outlet for hematoma expansion, blood in the cerebrospinal fluid spaces often leads to hydrocephalus that can cause further brain damage from increased intracranial pressure.

Traditional management of IVH is cerebrospinal fluid diversion by placing an external ventricular drain. Further treatment of the IVH component is still investigational. One study of patients with predominant IVH with small volume of ICH is currently underway. The Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage trial seeks to evaluate whether administration of small doses of intraventricular recombinant tissue plasminogen activator can decrease IVH size and improve outcome.[98] Preliminary results show decreased intraventricular clot in the intervention group without obviously increased rates of infection and rebleeding. The final results of the study are expected in the next few years.

SUMMARY

For many years, the management of ICH was left to convention and predictions based on the pathophysiology of the hemorrhage. Unlike such diseases as subarachnoid hemorrhage and traumatic brain injury that have been subjects for serious clinical trials for many years, ICH has only in the last 10 to 15 years begun the period of systematic research to evaluate therapies. Although no great breakthroughs have yet been made, there is a great deal of optimism that effective therapies for the management and treatment of ICH will be developed in the near future. Because of the significant impact of this disease financially and the human toll on patients and caregivers, improvements in therapy are welcomed.

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