What the tominersen failure taught Huntington disease drug development

Written by The Life Science Feed Editorial Team · Edited by William Lopes

Huntington disease, a devastating neurodegenerative disorder, has long presented an intractable challenge for drug developers. The genetic basis is clear, but translating that understanding into effective therapies has proven exceptionally difficult. The failure of tominersen, an antisense oligonucleotide designed to reduce mutant huntingtin protein, offered a stark lesson in the complexities of intervening in this progressive condition.

KEY TAKEAWAYS

- The Pivot: The tominersen trial's discontinuation forced a re-evaluation of target engagement strategies and patient selection in Huntington disease.
- The Data: No specific numeric results were provided for tominersen, but its failure underscored the difficulty in demonstrating clinical benefit in this complex disease.
- The Action: Clinicians should remain aware that while genetic targeting holds promise, the path to effective disease-modifying therapies for Huntington disease is still under active investigation and requires careful patient stratification.

Huntington disease (HD) is an inherited neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric symptoms. It is caused by an expansion of CAG trinucleotide repeats in the huntingtin (HTT) gene, leading to the production of an abnormal, toxic huntingtin protein (mHTT). This mutant protein accumulates in neurons, particularly in the striatum and cerebral cortex, leading to neuronal dysfunction and eventual cell death. The disease typically manifests in mid-adulthood, progressing relentlessly over 10 to 25 years, with no approved disease-modifying treatments currently available. Standard care focuses on symptomatic management, including medications for chorea, psychiatric disturbances, and supportive therapies.

The clear genetic etiology of HD made it an attractive target for gene-silencing therapies. The hypothesis was straightforward: reduce the production of the toxic mHTT protein, and the disease progression might slow or halt. Tominersen, an antisense oligonucleotide (ASO), was designed to do precisely this. Administered intrathecally, the ASO aimed to bind to the messenger RNA (mRNA) produced from the HTT gene, leading to its degradation and a reduction in both wild-type and mutant huntingtin protein levels. This approach represented a significant scientific effort, building on years of preclinical research and a strong biological rationale. The trial aimed to assess the safety and efficacy of reducing huntingtin protein in patients with manifest HD.

The promise and the reality of huntingtin reduction

The development of tominersen was rooted in the understanding that mHTT is central to HD pathogenesis. Early studies in animal models and initial human trials had shown that ASOs could indeed reduce huntingtin protein levels in the cerebrospinal fluid (CSF). This reduction was seen as a surrogate marker for target engagement in the brain, fueling optimism that a direct attack on the root cause of the disease could finally alter its devastating course. The field had been waiting for a therapy that moved beyond symptom management, and genetic approaches seemed to offer that potential. For a deeper dive into the challenges faced by gene-silencing programs in HD, consider our previous coverage on Roche's decision to halt its gene-silencing programs.

But the path from target engagement to clinical benefit proved more complex than anticipated. The tominersen program, after progressing through various stages of clinical development, was ultimately discontinued. This decision was not due to a lack of target engagement; the drug did reduce huntingtin protein levels. Instead, the primary reason for discontinuation was a lack of clinical benefit, and in some subgroups, a potential worsening of clinical outcomes. This outcome forced a critical re-evaluation of several assumptions underpinning HD drug development.

Rethinking patient selection and disease stage

One major lesson from the tominersen experience was the importance of patient selection and disease stage for achieving clinical success. The trial enrolled patients with manifest HD, meaning they already exhibited clear symptoms of the disease. By this stage, significant neurodegeneration may have already occurred, potentially limiting the ability of a protein-lowering therapy to reverse or even halt progression. The brain's capacity for recovery or compensation might be severely diminished once symptoms are overt. This raises the question of whether interventions need to occur much earlier, perhaps in the prodromal or even pre-symptomatic stages, before irreversible damage accumulates. The regulatory setbacks and clinical impact on Huntington's disease therapies have often highlighted this challenge.

Another consideration is the specific population within manifest HD. The disease is heterogeneous, with varying rates of progression and symptom profiles. It is possible that a single therapeutic approach, even one targeting the root cause, may not be equally effective across all patients. Subgroup analyses, though often exploratory, become essential in understanding who might benefit most, or conversely, who might be harmed. The open-label design of some earlier phases, while necessary for initial safety and dose-finding, also presented challenges in definitively assessing efficacy signals without the rigor of a fully blinded, placebo-controlled design.

The challenge of measuring clinical benefit

Measuring meaningful clinical benefit in a slowly progressive neurodegenerative disease like HD is inherently difficult. Traditional endpoints, such as changes in motor scores or cognitive assessments, may not capture subtle but important effects of a disease-modifying therapy, especially over shorter trial durations. The Unified Huntington's Disease Rating Scale (UHDRS), while comprehensive, can be influenced by symptomatic treatments and natural fluctuations in disease course. Developing more sensitive and objective biomarkers of disease progression and treatment response remains a critical unmet need. These biomarkers could include neuroimaging markers, electrophysiological measures, or novel fluid biomarkers beyond total huntingtin protein.

The tominersen trial also highlighted the potential for unintended consequences when broadly reducing huntingtin protein. While mutant huntingtin is toxic, wild-type huntingtin (wtHTT) plays essential roles in neuronal function, development, and survival. Reducing both forms of the protein, as ASOs typically do, might have detrimental effects,

particularly if the reduction is too profound or sustained. This raises questions about the optimal level of huntingtin reduction and whether selective targeting of mHTT over wtHTT is necessary. Future strategies may need to explore allele-selective approaches to preserve the beneficial functions of wtHTT.

Looking ahead: new strategies and targets

The lessons from tominersen have not deterred the field but rather refined its approach. Drug development for HD continues, with a renewed focus on several key areas. One area is the exploration of alternative mechanisms to reduce mHTT, including gene editing technologies, mRNA degradation enhancers, and small molecules that selectively lower mHTT. These approaches aim to achieve more precise or allele-selective reduction, potentially mitigating the risks associated with broad huntingtin lowering. The development of new Parkinson's drugs, for example, shows how sustained levels of therapeutic agents can be achieved through different delivery methods.

Another area of intense investigation is the identification of novel therapeutic targets beyond huntingtin protein itself. These include pathways involved in neuroinflammation, mitochondrial dysfunction, oxidative stress, and synaptic plasticity, all of which are implicated in HD pathogenesis. Modulating these pathways could offer complementary or alternative strategies to protect neurons and improve function. The development of therapies for other complex neurological conditions often involves a multi-pronged approach, and HD is unlikely to be an exception. Clinicians looking for a comprehensive overview of neurological conditions and their management might find the Oxford Handbook of Neurology (2nd ed) a useful quick-reference.

The field is also placing greater emphasis on natural history studies and biomarker development. Understanding the earliest changes in HD, even before symptom onset, is essential for identifying the optimal window for intervention. Longitudinal studies that track pre-symptomatic carriers are providing invaluable data on disease progression and the utility of various biomarkers. These efforts will be essential for designing future trials that can more accurately assess the efficacy of disease-modifying therapies. The goal is to identify patients who are most likely to benefit and to measure that benefit with greater precision.

The tominersen experience shows that even with a clear genetic target, developing effective therapies for complex neurodegenerative diseases is a formidable challenge. It highlighted the need for rigorous trial design, careful patient stratification, and a deeper understanding of the disease's natural history and the precise role of both mutant and wild-type proteins. The scientific community continues to learn from these setbacks, adapting strategies and pursuing new avenues with the ultimate goal of bringing meaningful treatments to patients living with Huntington disease. The next generation of trials will undoubtedly incorporate these hard-won lessons, aiming for more targeted and earlier interventions.

> **CLINICAL IMPLICATIONS**
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> The tominersen failure was a sobering reminder that a clear genetic target does not guarantee clinical success. For clinicians, this means tempering expectations around single-target therapies for complex neurodegenerative conditions, even those with a well-defined genetic cause. The disease's insidious progression likely involves multiple, interconnected pathways that may require more than one intervention. The experience also reinforces the importance of early intervention in neurodegeneration. By the time manifest symptoms appear in Huntington disease, irreversible damage may have already occurred. Future trials will likely shift towards pre-symptomatic or prodromal populations, which presents its own ethical and practical

challenges for patient identification and long-term follow-up.
Industry must now focus on more selective approaches, perhaps targeting only the mutant huntingtin allele, or exploring combination therapies that address multiple pathogenic mechanisms. The field needs better biomarkers of disease progression and treatment response, as current clinical scales may not be sensitive enough to detect subtle benefits or harms in slowly progressing conditions. The road to effective disease modification for Huntington disease remains long, but these lessons are invaluable.

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