Treatment options for neuroinflammation: Focus on Huntington's disease

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Abstract

Huntington's disease (HD) is rare but fatal inherited neurodegenerative disorder that clinically manifests as chorea, psychiatric disturbances, and progressive functional impairment. The most affected part is cerebral cortex and striatum leads to dysfunction in neurons and eventual cell death ensue. The current treatment options aim to decrease symptoms and slow down the progression of HD. Treatments such as tetrabenazine and deutetrabenazine target motor symptoms by reducing involuntary movements. Additionally, antipsychotic and antidepressant medications are utilised to treat HD's mental and cognitive symptoms. Research has led to the exploration of potential gene-based treatments and RNA interference (RNAi) techniques. Ongoing research into CRISPR-associated protein 9 (CRISPR-Cas9) and other techniques related to gene editing offer hope to eventually find a cure for this crippling illness.

Keywords: Huntington's disease, tetrabenazine, deutetrabenazine, gene editing techniques

1. Introduction

Huntington's disease (HD) is a type of progressive neurodegenerative disorder which involves uncontrollable movements, emotional problems and loss in thinking ability. As HD is inherited autosomally-dominant (1), it adheres to Gregor Mendel's theories of inheritance. An individual with pathogenic variation, known as a heterozygote, has a 50% chance of passing on the disease-causing allele to their progeny. The huntingtin (HTT) gene on chromosome 4 has an autosomal dominantly inherited CAG trinucleotide repeat expansion that causes HD. As a result, a mutant huntingtin (mHTT) protein with an unusually lengthy polyglutamine repeat is produced. Reduced penetrance is shown between 36 and 39 CAG repeats, but those with more than 39 repeats are guaranteed to have the disease (2). The anticipation will occur, when the gene is passing through the paternal line. For example, a kid born to a father with an intermediate CAG repeat length may have an increased pathogenic repeat length. This is because the male sperm exhibits bigger repetition sizes and more repeat variability compared to somatic tissues (3).

HD is of two types: (i) Adult onset HD, and (ii) Juvenile HD. Adult onset, the most prevalent kind, HD typically strikes people in their thirties or forties. Involuntary jerks, impatience, poor coordination, depression, and difficulties understanding and making decisions are some of the first signs and symptoms. At the final stage, the person's thinking and reasoning skills deteriorate. The life expectancy thereafter is for 15 to 20 years.

Juvenile HD manifests as emotional, mental, and mobility issues. Other symptoms include slurred speech, clumsiness, drooling, seizures and frequent falls. Compared to adult-onset HD, this form progresses more swiftly, and the patient typically lives for 10 to 15 years after the signs and symptoms first manifest (4).

2. Management and therapeutic approaches

Optimising quality of life and anticipating the patient's evolving demands as the illness worsens are the therapeutic goals. Pharmacological and non-pharmacological therapies are typically used in conjunction for achieving this.

2.1. Motor symptoms therapy (Chorea)

Tetrabenazine is the only medication that licensed by FDA for the treatment of chorea (5) in a dose between 50 and 75 mg daily. This synaptic vesicular amine transport inhibitor produces a long-term anti-choreic action. It modulates dopamine by selectively inhibiting VMAT2. The side effects include are sleeplessness, depression, restlessness and anxiety. With the addition of deuterium molecules, deutetrabenazine is a modified form of tetrabenazine. This leads to reduced metabolic variability and a longer half-life (6). The FIRST-HD study found that deutetrabenzine significantly reduces chorea when compared to a placebo. Additionally, the research states that deutetrabenazine may have fewer side effects (7).

2.2. Treatment for psychiatric symptoms

Non-pharmacological treatments for depression, anxiety, OCD and irritability include cognitive behavioural therapy and psychodynamic therapy. Although these methods may not be as effective when cognitive impairment is present. Pharmacological treatments include the serotonergic and noradrenergic actions of mirtazepine and venlafaxine, and selective serotonin uptake inhibitors like citalopram, paroxetine, fluoxetine & sertraline (8). Neuroleptics may be helpful in the treatment of psychosis and aggressiveness. Apathy has been treated with a variety of drugs, such as bupropion, methylphenidate, atomoxetine, modafinil, amantadine, and bromocriptine; however, no RCTs have been conducted (9).

2.3. Antisense oligonucleotides (ASOs) based therapies

Single-stranded oligonucleotide analogues known as ASOs can act through a variety of methods, including as RNA degradation, translation stalling, and splice manipulation, which eventually change the expression of proteins. The ASOs are located throughout the CNS and don't need require of viral as well as lipid carrier for simple and effective treatment (10). They attach to either pre-mRNA or mRNA. An ASO may be allele-specific, meaning it only targets mHTT and non-allele-specific, meaning it targets both mHTT and wild type HTT (wtHTT). WVE-120101, WVE-120102, and Tominersen, an allele-non-specific ASO, are the three ASOs presently undergoing clinical trials. Tominersen attaches itself to mHTT & wild type HTT mRNA. ASOs effectively reduce the Huntingtin gene when infused into non-primate cerebrospinal fluid. Since they do not reduce wtHTT, their allele-specificity may help prevent long-term adverse consequences. All HD patients can't be treated by WVE-120101 and WVE-120102 since they target SNPs, but when used together, they may be able to treat 80% of HD patients in Europe (11). The most promising ASO series: A1, A2, and A3. We found 40 and 10 fold increase in potency for A2 and A3, respectively, compared to A1.

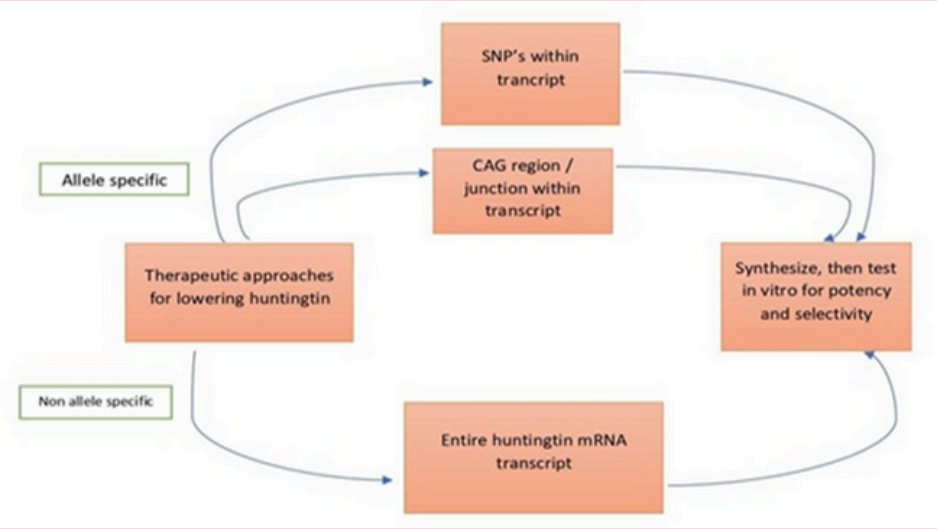

Figure 1. Targets for oligonucleotide therapy

2.4. FAN1 gene therapy

FAN1 was discovered to be widely expressed in both peripheral tissues and the central nervous system after being first discovered as KIAA1018 in a human brain cDNA collection (12). FAN1 haplotypes independently alter HD; uncommon genetic variations accelerate the start of HD by reducing the FAN1 protein's nuclease activity or DNA binding (13). One important modifier gene was the FAN1 gene, which codes for a nuclease that cleaves DNA during the process of repairing crosslinks between DNA strands. One possible protective factor for HD has been shown to be FAN1 (14).

2.5. Antibody therapy

A particular kind of monoclonal antibody called ANX005 blocks the C1q, which is the initial molecule in the innate immune system's complement cascade and serves mainly as the host's first line of defence against infections (15).

2.6. CRISPR-Cas9 mediated therapy

There are two main parts of the CRISPR-Cas9 DNA-editing system i.e., single guide RNA (sgRNA) and a Cas9 nuclease which attaches with the Cas9 (16) and uses RNA-DNA base complementarity to guide it to a specific genomic location. When Cas9 binds to DNA, it causes a double-strand break (DSB) that triggers non-homologous end joining (NHEJ), a faulty DNA repair pathway that makes it easier to introduce random base insertions and deletions (17). These indels can result in a frameshift mutation, which can then cause nonsense-mediated mRNA decay to disrupt gene expression. Cell replacement therapy and CRISPR-Cas9 mediated gene editing could be used to treat HD in two ways: (1) using CRISPR to disrupt the endogenous mHTT gene to reduce its neurodegenerative effect, then integrating a functional striatal graft to replace lost cells, and (2) combining the benefits of both approaches to potentially treat HD more successfully (18). The study observed that the two plasmids of CRISPR-Cas9 i.e. CRISPR-gRNA1 (UTR targeted) and CRISPR-gRNA2 (exon1-intron) resulted in 79% and 58% reduction in mHTT production.

2.7. RNA interference therapy

Short interfering RNA (siRNA), short hairpin RNA (shRNA), bi-functional shRNA, and microRNA (miRNA) are all used in the gene-silencing technique known as RNA interference (19). When combined with brain progenitor stem cell therapy, RNAi therapy can lessen symptoms in animal models of HD. To improve motor function and lessen neuropathology, siRNA, shRNA, and miRNA therapies have been applied to animal models of HD. An artificial miRNA found in the adeno-associated viral vector AMT-130 generates a compound that lowers huntingtin (20). In several rodent models for HD, viral-based expression of shRNA targeting mutant htt mRNA in brain reduced transcript and protein levels by ~50–70% which improving behavioural and neuropathological phenotypes.

3. Conclusion

The development of contemporary technologies and the availability of numerous potential agents/molecules have made efficient treatments possible that will significantly enhance the outcomes for HD patients. These advancements are necessary to address the challenges posed by movement disorders, depression, anxiety, and psychosis, all of which have a significant negative impact on patients' overall well-being. Drugs that disrupt the effects of the mHTT protein and target its synthesis are the most promising.

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