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Commentary

Raising Awareness of Therapeutic Misconception and Optimism Around Clinical Trials in Huntington's Disease

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Abstract. The Huntington's disease (HD) community is moving into an exciting time with Huntingtin lowering strategies entering human clinical trials. These upcoming targeted therapeutic approaches for this devastating disease with unmet medical needs, are believed to be a last resort for many patients and their families. Recently, patients with HD were shown to be at high risk for therapeutic misconception, mistaking research for actual treatment. It is important that investigators are aware of their patient's, as well as their own, vulnerability to therapeutic misconception. To limit therapeutic misconception, information should be provided on the rationale for clinical trials and the differences between clinical research and clinical care should be carefully discussed.

Keywords: Huntington's disease, therapeutic misconception clinical trial

We are moving into an exciting time, with huntingtin lowering strategies entering human clinical trials to evaluate these new treatment options for one of the most serious neurodegenerative diseases, Huntington's disease (HD). This excitement is shared by patients, caregivers, clinicians and researchers. All sense the uniqueness and potential of more targeted strategies as opposed to compounds previously tested in HD and expectations are high.

In this issue of the Journal, Kristina Cotter and her colleagues draw attention to the concept of therapeutic misconception, which they show to be significantly more present in HD patients than in HD mutation carriers and caregivers [1]. Therapeutic misconception has been studied quite extensively in a few other neurologic conditions, but thus far not so much in HD. The current study is very timely, since many HD centers are currently recruiting or in the informed consent process of the phase 3 double-blind, randomized clinical trial (RCT) investigating bi-monthly intrathecal administration of HTT_{Rx} (now named RG6042). HTT_{Rx}/RG6042 is an antisense oligonucleotide (ASO) shown to reduce concentrations of mutant huntingtin by inhibiting *HTT* messenger RNA in a phase 1/2 dose-finding safety study [2]. Additional targeted -huntingtin lowering-therapeutic approaches are in late stage pre-clinical or early stage clinical development, and some may involve even more invasive procedures, such as, for example, intraparenchymal injections.

In their survey-based study Cotter, et al. confirmed that the HD population has a very high willingness to participate in (gene) therapy trials, especially when the route of administration is minimally invasive. Moreover, they showed that patients with HD are at high risk for therapeutic misconception, mistaking research for actual treatment [1]. In other words:

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they are unable to make the distinction between their role as a research participant contributing to increasing generalizable knowledge and their role as patient receiving personalized medical care [3].

One of the limitations of the current study, put forward in the discussion, is that there may have been a selection bias for individuals with a positive attitude towards HD-related research. Not only did 2/3 of the respondents to this survey participate in previous HD (clinical) studies, each respondent decided to participate in this survey-based HD study, which in itself may have caused a source of bias. Even so, this study confirms what the HD field already suspected, considering recent experiences with HD patient optimism towards participation in the phase 3 antisense oligonucleotide trial; GENERATION HD1. The extremely fast recruitment, which is also reinforced by the competitive recruitment strategy, has overwhelmed everyone. This is of course easily explained by the long-lasting hope that an effective therapy might finally be within our reach for this devastating disease. Clinicians may also have experienced that patients who were not invited, not included or had a screening failure for this particular clinical trial became so upset, that they had to be comforted by the treating physician or investigator who needed to explain over and over again that it is 'just' a scientific trial to test the compound for its safety and efficacy and that it does not constitute the only chance of receiving a proven treatment. This indicates with certainty the latent presence of therapeutic misconception.

It would be a misconception to think that these positive attitudes towards participation in and outcomes of clinical trials only occur in HD patients, gene carriers, and caregivers: they are probably equally present among HD specialists. A very illustrative paper in Neuromuscular Disorders emphasized the risks of therapeutic misconception, driven by both patients and clinicians to consider $n = 1$ trials with compounds that were at that time in preclinical development for Duchenne muscular dystrophy [4]. The upcoming targeted therapeutic approaches using ASOs for these rare and devastating diseases with unmet medical needs, are believed to be a last resort for many patients and their families. This is highly understandable. However, it is the responsibility of the investigator, who may be the treating physician as well, to assess whether patients suffer from therapeutic misconception (e.g. unrealistic expectations from trial participation). This touches on another interesting potential conflict: being both the treating physician of a patient and (principal) investigator in the trial for which the patient may be recruited. Although one may suspect that this will increase therapeutic misconception for the patients and physician, this was not confirmed in a study performed in 90 advanced stage Parkinson's disease patients involved in sham surgery clinical trials [5]. However, this result does not exclude the possibility that both treating physicians and investigators were equally excited about the potential clinical benefit to individual participants. It is important that investigators themselves are aware of their own vulnerability to therapeutic misconception. Involving a research ethicist in the informed consent process may help [3].

So how should we manage or prevent therapeutic misconception? First, by raising awareness of this phenomenon, but also by providing education to the community. The HD community is well informed; scientific and lay press publications on promising orphan drugs are read by many. While it is clear to most scientists that these communications are often overselling their results in cell or animal models, as well as phase 1 studies, and that further research is required to affirm efficacy in humans, this may not be the case for patients and their families. Therefore, potential participants need to be provided with more information, stressing what can and cannot be expected from a certain strategy. For example, the loss of neurons is irreversible and therapeutic strategies currently in (pre)-clinical development cannot restore function that has already been lost. Furthermore, it would be better to use words like 'study compound' instead of drug, therapy or treatment when talking about the experimental drug compound. Second, education on the rationale behind clinical trials and the specific differences between clinical trial research and clinical care should be discussed, prior to going through the informed consent forms. This ideally would follow the scientific reframing method, which was proven to reduce therapeutic misconception in a randomized trial design [6].

In addition, based on experiences in (HD) research in the past, it may be wise to reflect on the possibility of disappointing outcomes, while still at the start of the trial. In general, we tend to explain reasons for early trial termination, for example one or more serious adverse events. However, one does not always explain the possibility that the development of the test compound will stop if the primary endpoint is not met, and that the implications are that the supply of the study compound will stop, possibly after many study visits and being on active compound for months

or even years in an open label phase. This is especially the case when participants experience a positive effect on their symptoms (although not significantly different from placebo effect); they may not want to terminate and insist on keeping the remaining tablets, as we recently experienced with participants in the open label phase of the pridopidine trial. Another example is the negative randomized clinical trial investigating intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease [7]. An intriguing BBC documentary (The Parkinson's Drug Trial: A Miracle Cure?) shows exactly what happens to both participants and researchers when they are informed that the primary outcome has not been met. Discussing all these different scenarios may feel time consuming, but helps everyone to have more realistic expectations and prevent participants from unnecessary (extra) disappointments.

Therefore the recommendations brought forward by Cotter et al. are very timely and important for all the investigators involved in starting and upcoming trials with targeted, huntingtin lowering compounds.

CONFLICTS OF INTEREST

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