Multiple sclerosis: New standards required for planning clinical trials

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How can the perspectives of patients with multiple sclerosis (MS) be given more consideration in clinical trials? This question was investigated and corresponding recommendations were developed by a working group of the Drug Commission of the German Medical Association (AkdÄ), the Charité University Hospital Berlin, and the

Institute for Quality and Efficiency in Health Care (IQWiG). The analysis has now been published in the *EPMA Journal*.

More than 200,000 people affected in Germany

Multiple sclerosis is the most common autoimmune disease of the central nervous system, affecting more than 200,000 people in Germany. They suffer from impaired vision and sensation as well as restrictions in coordination and even paralysis. The diagnosis is usually made between the ages of 20 and 40—women are affected more frequently than men. The disease is chronic and inflammatory and so far there is no cure. In 85 to 90 percent of patients, the disease often starts with relapsing neurological deficits, which usually disappear completely or partially after weeks or months. After years or decades, a transition into a chronic progressive course often occurs: The patients' neurological state gradually worsens; in particular, their walking distance decreases.

Since the development of the first immunotherapy (interferon beta-1b) in 1995, numerous substances have been approved for the immunomodulatory treatment of MS, with the aim of reducing the number of relapses. Since then, the therapeutic landscape has expanded considerably. In parallel with the increasing number of available immunotherapies, treatment strategies have shifted from a pure "relapse prevention approach" to individualized medical care.

Working group systematically analyzed 29 pivotal phase III trials

The working group of AkdÄ, Charité and IQWiG systematically analyzed 29 drug approval ("pivotal") phase III trials on disease course-modifying / immunomodulating drugs for the treatment of MS. The analysis showed that the patient perspective and thus symptoms such as

fatigue (i.e. tiredness and increased exhaustibility) or health-related quality of life were generally not taken into account. In contrast, biological indicators and endpoints of imaging procedures with unclear relevance for the severity of the disease were routinely investigated.

Friedemann Paul, Scientific Director of the Experimental and Clinical Research Center (ECRC), a joint establishment of the Charité and Max Delbrück Center for Molecular Medicine (MDC), notes: "If in future we design the studies in such a way that they are more closely orientated to the needs of patients, we will obtain study results that are more likely to enable us to provide patients with more targeted and individualized medical care."

Suggestions for improvement by the working group

All drugs available on the market were tested in mainly one- to two-year drug approval studies. Beyond this period, hardly any methodologically sound data on the benefits or side effects of these drugs are available. Wolf-Dieter Ludwig, Chairman of the AkdÄ explains: "Due to their duration and usually short follow-up, drug approval studies are not suitable for collecting data on the sometimes very serious side effects that only occur after long-term treatment." Due to these shortcomings in the design of clinical trials, the working group developed suggestions for improvement. Sinje Gehr, Project Head of the Charité MS Initiative states: "With our recommendations, we want to make a contribution to improving the care of patients with MS."

Certain symptoms and consequences of the disease are highly relevant for patients. It is therefore also important to collect data on the patient perspective in studies by means of patient-reported outcomes (PROs). Thomas Kaiser, Head of IQWiG's Drug Assessment Department explains: "If no data on symptoms and quality of life are collected in studies, then these studies do not provide a complete picture of the

benefit of a drug." In general, patients are very focused on whether disabilities progress and whether symptoms such as fatigue, depression, cognitive impairment, pain, spasticity, sleep disorders or loss of vision increase. This was also evident in the MS Initiative discussion rounds. He adds: "Many of these symptoms could and should in the future be documented with the help of internationally established and validated patient questionnaires."

Future studies on MS should attribute greater importance to the immediate experience of patients with MS by focusing more on patient-reported outcomes. The individualized focus of medical treatment requires that studies consider not only clinical and radiological findings relevant for approval, but also the patient perspective. This applies in particular to very burdensome symptoms such as fatigue, pain, depression and cognitive impairment. Likewise, in view of the often-required long-term treatment with immunomodulating drugs, study participants should be observed for longer periods in order to gain more insight into significant complications and side effects.

More information: Sinje Gehr et al, Suggestions for improving the design of clinical trials in multiple sclerosis—results of a systematic analysis of completed phase III trials, *EPMA Journal* (2019). DOI: 10.1007/s13167-019-00192-z

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