Securing reimbursement for patient centered haemophilia care: major collaborative efforts are needed

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Challenges for patient-centered health care provision

Policy makers and payers are increasingly mandating what physicians can prescribe and thus the need for proven evidence of the benefits and cost-effectiveness of new drugs has become imperative. A range of access hurdles are already in use. At their heart is the goal of improving effectiveness and value in healthcare as a way of balancing limited resources. Treatments for rare diseases, including hemophilia, must compete with treatments for other more common conditions in terms of their benefits and risks.

Clotting factor concentrates are amongst the most expensive specialty drugs. With years of research finally bearing fruit, a selection of new clotting factor concentrates are now entering the therapeutic market.[1] As more treatment options become available and their costs continue to rise, there is increasing scrutiny of the value they bring and demand for proof of their benefits. In this context, the present communication focuses on options that should be considered in a climate of increasing demands for high levels of evidence.

Decision making for rare diseases including hemophilia has to follow the same paradigms as for common diseases, including evidence-based medicine (EBM), health technology assessment (HTA) and comparative effectiveness research (CER).[2-4] EBM works with, integrates and evaluates the existing evidence considering both benefits and harms. It has as its goal the facilitation of making health care decisions by providing information about the improvement of outcomes and quality of care.[1] As defined by EBM, recent regulations in several countries stipulate that randomized controlled trials (RCTs) generate the highest level of evidence possible.[3] Outcome endpoints are required to focus on: morbidity, decrease in disease mortality, adverse events and the quality of life.

HTAs evaluate published literature according to evidence-based criteria to present a high quality scientific synthesis of available evidence regarding clinical benefits, harms, economic consequences, and ethical or social issues. HTAs are increasingly leveraged as a basic requirement for healthcare decision making. Ideally a HTA is expected to give an evaluation of the long-term benefits and risks of a given medical intervention in relation to its costs.[4]

CER compares treatments, generates information about patients, caregivers, diagnostic and therapeutic methods during daily routine, and helps consumers, caregivers and policy makers to come to reasonable decisions concerning the best medical care for the individual patient.[5,6] CER has to consider not only the benefits and risks, but also the costs.[1,4] RCTs, which provide care in an experimental setting, are no longer considered to be the only source of information. Observational studies reflecting day-to-day practice are increasingly recognized to be important.[5,7] New methods for rating clinical evidence allow for the appraisal of high quality nonrandomized comparative effectiveness trials. The current tool, 'The Grading of Recommendations Assessment, Development and Evaluation' (GRADE), used for rating the evidence levels of studies, ranks observational studies as low (2+) and randomized trials as high (4+), similar to previous rating nomenclatures. However, additional factors, i.e. strong association based on consistent evidence from 2 or more observational studies (+1) and very strong evidence of association based on direct evidence with no major threats to validity (+2), can increase the evidence grade from low (2+) to moderate (3+) and high (4+). Both Investigators and Regulators (or Regulatory Authorities) had taken into account that it is not always feasible to conduct randomized trials and that other factors should also be taken into consideration.[8,9] In this context, the 'Good Research for Comparative Effectiveness' (GRACE) initiative was established to provide criteria to judge the quality of nonrandomized comparative effectiveness trials.[10] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force has further elaborated a detailed report on how to design and conduct prospective observational studies for the assessment of comparative effectiveness.[11]

Unique challenges of hemophilia to meet payer's expectations

Lack of requested evidence

In hemophilia, variations in medical practice reflect the manifold therapeutic uncertainties and the lack of evidence for optimal standardized treatment strategies. A Swedish HTA on hemophilia states that prophylactic factor substitution is considered effective in patients with

hemophilia, but data concerning many important relevant and related issues are still insufficient.[12] Current questions concern dosing issues, the duration of prophylaxis, and prophylaxis in adult patients with hemophilia with and without co-morbidities.

Barriers to randomized trials

There are several barriers that threaten the conduct of randomized trials in hemophilia. First, the number of patients required: many of the questions to be solved would require large patient numbers in order to get a statistically meaningful answer. In addition, research questions concerning dosing and prophylactic treatment would require decades of follow-up to assess hemophilic arthropathy and its consequences. Studies to address these questions would require observation periods of many years thus making randomized trials not feasible because of the problems of patient drop out, lack of adherence, and of course costs.[13]

Endpoints in hemophilia

Information on 'hard' patient-relevant clinical endpoints has to be provided to prove the evidence of therapeutic benefit. These endpoints are morbidity, mortality and quality of life. Mortality was high before the introduction of factor concentrate replacement treatment, and still is in resource constrained countries.[14,15]

Repeated joint bleeds cause morphological changes and eventually lead to crippling arthropathy. Multifactorial influences lead to individual variations in a small patient population regarding bleeding type, the development of arthropathy, and the development of inhibitory antibodies. In this situation, the measurement of health-related quality of life (HRQoL) is a reasonable indicator of the long-term outcome and effectiveness of the therapeutic intervention chosen. HRQoL measurement may be most important from the payer's perspective. It can also be converted into utility values to enable the assessment of quality-adjusted life years (QALYs) gained, and to calculate cost-effectiveness. Both hemophilia disease-specific instruments and generic instruments are available and should be implemented as a standard procedure. Consensus should be reached on the choice of instruments to allow for a more effective combination of data from different sources.

A key role for real-world evidence to prove requested effectiveness of hemophilia care

Within the context of CER, the informative value and significance of observational studies and real-world data in comparison to randomized trials is the subject of ongoing debate.[5,16] The evaluation of routine data in health service databases has thus far been challenging due to the limitations of available datasets, particularly in terms of reported outcomes measures.

Real-world evidence in hemophilia

Expectations for future hemophilia treatment success are high due to a variety of treatment options in development. Yet, authorities fear rising costs and request evidence for rational treatment decisions.

In the United States, The Patient Protection and Affordable Care ACT (ACA) signed into law on March 23, 2010, enables comprehensive health insurance reforms that will increase access to health insurance and make health care coverage more affordable. For people with hemophilia, the benefits of the new law include the elimination of lifetime insurance caps, the ability to obtain health insurance regardless of pre-existing health conditions, and the expansion of Medicaid coverage. The ACA also includes provisions to improve the quality and comprehensiveness of health care coverage, thus creating a demand for evidenced-based decision making.

Real-world evidence (RWE) holds the key to gathering the necessary information about all aspects of care, including clinical and patient-relevant outcomes, therapy profiles in real-life practice, as well as patient preferences. To satisfy the demand for higher levels of performance for reimbursement and market access in hemophilia, the ability to generate and access RWE will be essential.

Several initiatives have already emerged in the past. The European Paediatric Network for Haemophilia Management (PEDNET) is a collaboration of pediatricians from European countries, established to promote clinical research and management of children with hemophilia by providing the necessary infrastructure.[17] This initiative has generated important information, and demonstrates that high quality prospective observational studies can be conducted by the collaboration of many treatment centers through joint efforts. Important results associated with this kind of real-world data collection have the potential for lowering the rate of adverse events, thereby improving outcomes and achieving considerable savings in the future. Further initiatives worthy of mention are the European Haemophilia Safety Surveillance system (EUHASS),[18] The International Factor IX Treatment Network Survey,[19] and the ISTH-SSC international FIX inhibitor registry.[20]

Future needs

To achieve the generation of RWE with a high quality standard requires amongst other factors:

- To formulate research questions, to define the relevant patient subpopulations, and to determine the patient numbers necessary for a clear statement in the forefront of the intended study.
- To combine data from different sources in the future. This will require connecting currently fragmented information through the use of technologies/methods which allow the linkage and integration of multiple patient-level datasets across the entire treatment journey.
- To intensify national and international collaboration on current topics of interest. Eventually data interoperability at a national and international level may be achieved by leveraging alliances and technical platforms for data-sharing.

Randomized trials will remain the cornerstone for demonstrating the efficacy of medical technologies. The key challenge for reimbursement and market access in hemophilia as a rare disease will be to develop RWE approaches through national and international collaboration, thereby reducing the uncertainty for patients, physicians, payers, and other decision makers.

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