Spinal Muscular Atrophy: The High Costs of Innovative Therapies for Rare Diseases

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Research Article

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Abstract

**Background:** Despite numbers of prescriptions filled remaining constant, expenditures for drugs are rising. Among others, this is caused by high prices for orphan drugs and advanced therapy medicinal products (ATMPs). Despite attempts by policymakers to intervene, the increasing use of these therapies poses numerous challenges on the health care system.

**Results:** Using data from the University Hospital Heidelberg, we found that the division of pediatric neurology is experiencing a strong increase in drug costs, caused by two pharmaceuticals for the treatment of spinal muscular atrophy (SMA), Nusinersen and Onasemnogene Abeparvovec. To put this finding in a broader context, we conducted a survey of 41 German SMA treatment centers revealing a general lack of human and infrastructure resources for therapy and follow-up care, which demonstrates insufficient reimbursement of treatment. To improve structural conditions, we propose that disease-independent registries for medication surveillance that comply with the rules of the European Union are needed as well as the development of a fair funding model.

**Conclusion:** Innovative forms of therapy require a critical discussion and concise regulation of treatment application and follow-up reimbursement as well as international industry-independent registry work. Based on the previously described model of “evidence-based dynamic pricing” by the Techniker Krankenkasse, we propose a revised model which offers an internationally scalable solution to meet these challenges.

**Background**

The pharmaceutical market has been experiencing rising expenditure on prescription drugs over the past decades although the number of prescriptions filled has remained constant. This is mainly attributed to high costs and increased availability of patented drugs (mainly oncology-related medication), including orphan drugs (OD) and advanced therapy medicinal products (ATMPs), a group which includes gene therapies, somatic cell therapies and tissue engineered products. As these therapy forms often represent the first causative treatment approach, they are commonly referred to as “innovative therapies”. In 2019, expenses for drugs in the statutory health insurance system in Germany exceeded € 45 billion for the first time, and while OD accounted for only 0.05% of all prescribed daily doses, they caused 10% of the total expenditures with a drug market share expected to further increase. This will have a strong impact on the health care system, as patients with rare diseases will increasingly be entitled to complex forms of therapy that can only be performed in specialized treatment centers. Thus, university hospitals with longstanding experience in treating rare diseases will have to cope with increased indirect personnel and infrastructure costs.

Since the early 1990s, the European Union has set incentives for the development of orphan drugs. Pharmaceutical companies have since begun to target a market that would otherwise be unattractive due to the low number of cases, which has ultimately resulted in high costs for individual preparations. National legislators are therefore trying to find ways to improve regulation of drug prices. In Germany, the conditional marketing authorization stipulated in the 2011 German Pharmaceutical Market Restructuring Act (Arzneimittelmarktneuordnungsgesetz, or AMNOG) is the linchpin of the Federal Joint Committee (G-BA, the German main regulatory institution for legally binding decisions in healthcare) for price negotiations of the statutory health insurance companies and the pharmaceutical industry. However, during the first 12 months after drug approval, prices are freely chosen by the manufacturers, only afterwards negotiations are possible. Nonetheless, years after its introduction, the AMNOG has improved the ratio of negotiated prices and the clinical benefit of evaluated compounds. Recently, the G-BA formulated the requirement of an “application-accompanying data collection”, whose legal basis was established in Germany in the so-called Law for More Safety in the Supply of Medicines. This is intended to help close the existing evidence gap in the approval of ODs and ATMPs, since their efficacy and safety is proven in the context of the centralized approval for the European Economic Area. As a result, clinical trials are performed on small groups of patients with only sparse long-term data on clinical efficacy and safety.

A sharp increase in medication expenditure was observed with the approval of two drugs for the treatment of spinal muscular atrophy (SMA), Nusinersen, which was approved in 2017, followed by Onasemnogene Abeparvovec, a gene therapy for the treatment of SMA. Onasemnogene Abeparvovec received a conditional approval based on the results of a phase 1/2 study with as little as 15 SMA-patients as compared to historical control cases and preliminary non-published data of an international phase 3 study with 55 individuals suffering from SMA. With costs of € 1.945 million per single application, Onasemnogene Abeparvovec is the world’s most expensive drug to date. The high costs associated with such innovative therapies require standards in research and risk assessment that are at least equivalent to those of non-orphan drugs. Regardless of their therapeutic potential, ODs and ATMPs generate major challenges for national healthcare systems, healthcare providers and insurance companies. Many issues regarding their use, associated (organizational and personnel) costs as well as the reimbursement of follow-up care remain to be addressed.

In order to address the challenge of rising drug costs and to help close the evidence gap regarding efficacy and safety of innovative therapies, we have developed a cost model in collaboration with the Techniker Krankenkasse, Germany’s largest health insurance company. This model proposes a structural framework for financing of medication-associated costs and patient registries, as well as follow-up care.

**Results**

From 2010 to 2020, inpatient departments of the Heidelberg University Hospital incurred average annual costs of € 48.7 million (SD = € ± 14.4 million) for drugs. In 2020, the highest cost ever of € 88.1 million was recorded. Table 1 shows the annual expenditure on drugs of the five departments with the highest annual costs for drugs at Heidelberg University Hospital.

The trend of rapidly rising costs for medications can be illustrated by the figures from the Center for Pediatric and Adolescent Medicine. Since 2016, there have been annual increases in expenditures here. Most recently in 2020, there were costs of € 34.05 million and an increase of 135% compared with the previous year (Table 1 and Figure 1 A). Compared to 2010, 12.5 times the amount was spent on medications in 2020, while the number of prescriptions filled remained constant throughout the observation period. The majority of these costs (92%) can be attributed to the field of pediatric neurology (Figure 1 B).
A detailed investigation identified in particular two drugs for the treatment of SMA as the main cost drivers: Nusinersen, responsible for an increase of drug costs from 2017 on and Onasemnogene Abeparvovec with a single dose applied in 2019 and a total of 10 doses applied in 2020. In 2019, 92 doses of Nusinersen were applied at the Centre for Children and Adolescent Medicine Heidelberg with a total expenditure of € 8.44 million. The average drug cost of a single application was € 91,739.13. In the same year, a first patient was treated with Onasemnogene Abeparvovec, the net drug cost amounted to € 1.945 million.(19) The conditional marketing authorization of Onasemnogene Abeparvovec by the EMA was granted in May 2020 which has led to a rapid increase in demand for the drug. During 2020, a total of 10 patients were treated with Onasemnogene Abeparvovec, resulting in total drug spending worth € 19.45 million plus import VAT.

To put these findings in a broader context, we concluded a survey of 41 German SMA treatment centers caring for a total of 1,097 patients. Within the patient cohort, 646 (59 %) were younger than 18 years of age at the time of the survey. Based on our survey, in Germany, 92 patients are expected to qualify for start of treatment with Onasemnogene Abeparvovec during the following 12 months, confronting insurance companies with total drug costs of € 178.94 million plus VAT. Compared to other drug groups, such as TNF-alpha inhibitors (Adalimumab: € 468.1 million) or modern anticoagulants (Apixaban: € 475.3 million)(20), this amount appears to be small, but it must be emphasized that the number of patients treated with Onasemnogene Abeparvovec is much lower and it remains unclear whether recurrent drug administration will be necessary for individual patients. According to the survey, the number of patients with Nusinersen therapy will decrease from 867 during the most recent 12 months to 761 in the coming 12 months (Supplementary Table 1).

All 41 centers state that the application of innovative SMA therapies in standard care creates new challenges, 28 (68.3 %) centers expect challenges of medical and non-medical character. A total of 82.9 % (n = 34) report an additional workload of more than at least 5 hours per week. New tasks will primarily arise in the areas of case management, pre- and post-clinical care, and administration of reimbursement or invoicing. The need for additional human resources (even more so than infrastructure or financial resources) is thus perceived as the biggest challenge in the overall process of applying innovative therapies (Figure 2).

Those responsible for the SMA treatment centers see the need for standardization of processes. While both, the indication process as well as the pharmacy process were reported to be well regulated, a strong need for improvement and more precise standardization of follow-up care was reported by 39 (95.1 %) respondents. At the time of investigation, only 25 (61 %) of the centers reported to have standard operating procedures (SOPs) related to SMA treatment. While reporting an increase of workload, 80.5 % (n = 33) of the respondents do not consider the reimbursement for the healthcare providers of innovative therapies to be appropriate. With regard to follow-up care, 87.8 % (n = 36) stated that compensation was insufficient, and 95.2 % (n = 39) saw that the reason for this is in the existing outpatient reimbursement system. When respondents were given the opportunity to prioritize different areas of optimization, the compensation for aftercare was ranked highest.

All respondents indicated that structured documentation of the outcome of innovative therapies should be carried out in international registries. A majority of 94.4% (n = 39) stated that this should happen independently of the pharmaceutical industry. There was also broad consensus concerning financing of clinical trial registries, where 80.5 % (n = 33) of the respondents were in favor of a fund to be administered in trust by the Federal Joint Committee, into which the pharmaceutical company would have to pay an amount based on the price of the drug after approval. Only a small proportion of those surveyed saw responsibility for structured documentation with the insurance companies (12.2 %, n = 5) or with the health-care providers (7.3 %, n = 3). With few exceptions, (21) international recommendations for the implementation of registry work are missing so far.

Discussion

The present analysis uses the example of Heidelberg University Hospital to demonstrate a considerable annual increase over the last years in drug costs in the field of pediatric and adolescent neurology largely attributable to orphan drugs and ATMPs. As more complex therapies, such as ATMPs will soon reach market maturity, adequate standards of organization and structured pre- and post-treatment pathways for patients and caregivers are needed.

The current reimbursement model exposes treatment centers to a potentially threatening liquidity problem if drug prices keep rising. Costs for medication are pre-funded by the treatment center and can only be claimed from the insurance company weeks to months later. Such interest-free loans to a pharmaceutical company by means of public resources is highly questionable. This is especially critical due to the increasing numbers of patients being treated with innovative therapies with high direct and indirect costs.

To overcome challenges of direct costs, direct billing between the insurance companies and the pharmaceutical industry has the potential to allocate processes not directly related to patient care to the primarily responsible actors, as seen with Zynteglo®, a gene therapy drug for the therapy of Beta-Thalassemia.(22)

The incidence of SMA is estimated at 1:7,500 for Germany. It represents the most common genetic cause of infant and childhood mortality.(23, 24) Most patients suffer from subtype 1 (Werdnig-Hoffmann) and are diagnosed in infancy. Our survey of 41 SMA treatment centers revealed that personnel resources for case management and administration are lacking. These and the associated indirect costs arising through the application of innovative forms of therapy must be refinanced. In 2019, the Techniker Krankenkasse introduced a model of dynamic evidence pricing (DEP),(25) which serves to ensure the sustainable financing of innovative forms of therapy, in particular gene therapies. Most gene therapies are used in a single-stage setting, so that the total therapy costs do not accrue over a longer period of time, meaning that the associated cost-risk lies entirely with the insurance companies. Considering that data availability at the time of approval is low for many ATMPs and their use places high demands on staff and clinicians, we feel a need to address this issue. Under the DEP model, the Federal Joint Committee (G-BA) decides 6 months prior to approval whether a drug will go through the traditional AMNOG process or be assessed using the DEP. The DEP requires mandatory inclusion of patients in industry-independent registries to close the evidence gaps that exist at the time of approval. In this regard, the introduction of so-called “application-accompanying data collection” was recently initiated for the German pharmaceutical market. (13) The G-BA can request the pharmaceutical manufacturer to conduct an extended data collection after (conditional) marketing authorization. In doing so, the G-BA determines the requirements for the type, duration and scope of data collection and evaluations, including the patient-relevant endpoints to be
recorded, the methodology of the data collection, as well as the possibility of the evaluation of said data by the pharmaceutical company. However, numerous legal and economic questions remain unanswered.

Since neither the initial DEP model nor the "application-accompanying data collection" clarifies the funding for registry structures or financing of costly outpatient follow-up, we propose a revised DEP (rDEP) to meet this challenge. Similar to the original DEP, the G-BA decides 6 months before market approval whether a pharmaceutical product will be assessed via the traditional route or with the rDEP method. At this stage, the relevant medical societies are mandated to develop a treatment pathway and criteria for quality assurance based on the clinical trial data available to date. The G-BA also determines which registry, study modality, and monitoring period will be used for subsequent generation of evidence. In order to clearly regulate financing of such registry structures, we propose to initiate a trust fund via means of the pharmaceutical companies managed by the G-BA. The collection of the agreed amount of data to monitor diagnostic and therapeutic processes in combination with valid patient outcomes enables the stratification of treatment success. The legal framework of the European Union has defined clear requirements for such registries. In the rDEP model, cross-disease registries are to be maintained by academic centers and independent of the pharmaceutical industry based on the FAIR principles. Data must be Findable, Accessible, Interoperable and Reusable to ensure the efficiency of the registry structures. Figure 3 provides an overview of the rDEP and depicts the timeline from approval submission to the iterative process of pricing.

A maximum price for the therapeutic product in the first year of use should be based on European average prices for comparable therapies and determined by means of health technology assessment methods (described in detail elsewhere). Thus, the adjustment of the cost of medication based on registry-based data analysis of clinical endpoints leads to a dynamic process of price regulation that takes into account the actual positive (or lack of, or even negative) effect, drug safety, and the availability of alternative treatment options. This will ultimately ensure long-term availability of high-quality drugs for improved patient care with innovative therapies and ensure the cost-effectiveness of the health care system.

Conclusions
The example of SMA is suitable as a blueprint for the rapidly increasing number of ATMPs and innovative orphan drugs expected in the coming years. First experience shows that existing organizational structures are not sufficiently prepared for the associated challenges. However, the health care system with its multiple stakeholders (clinicians, insurance companies, pharmaceutical companies) must prepare for upcoming (cost-)relevant therapies by creating appropriate structures and regulations. The revised dynamic evidence price model presented here serves as a basis for discussion and offers a possible way to address the rising direct and indirect costs of innovative drugs. To put this cost model in simple terms, the higher the documented efficacy of a drug, the higher the cost of that drug may be. In case of low evidence or missing data, the maximum price for the drug can be set lower. This will secure high quality care in the long term, benefiting treatment centers but ultimately the patients as well.

Methods

Data sources
Total quantities and costs for prescriptions and ready-to-use drugs of the University Pharmacy of the Heidelberg University Hospital were analyzed for the time period of 2009 – 2020. Data from the Center for Pediatric and Adolescent Medicine were assigned to individual departments and the main driving forces behind drug costs were identified. A structured questionnaire survey distributed to all German SMA treatment centers was used to investigate the following dimensions: 1) workload before and after the introduction of innovative forms of therapies, 2) standardization of procedures, and 3) availability of registries. Questionnaire items were designed as 5 point Likert scales, implemented into the Limesurvey tool as an anonymous survey and then sent via e-mail to the participating centers of the SMArtCARE registry. A total of 41 questionnaires were completed, covering 1,097 SMA patients (see Supplementary Table 1) corresponding approximately to the SMA prevalence of 1:100,000 expected for Germany. The complete questionnaire can be found in the supplementary material.

Limitations
The National Center for Tumor Diseases (NCT) is located at Heidelberg University Hospital, where patients receive highly specific and individualized oncological therapy. These treatments generate extremely high costs (€ 36.46 million per year corresponding to 37.6% of total expenditure on drugs at the University Hospital Heidelberg). Due to the lack of comparability to other sites, NCT data were excluded from the analysis. The true cost of medicines in Germany is partly subject to individually negotiated discount rates between the health care provider and the health insurance company, which are highly confidential. In our assessment we only consider the direct costs caused by drugs. Costs for the implementation of the therapy, such as personnel costs and costs for the maintenance of the infrastructure, could not be considered due to their complexity. Our cost analysis can therefore only provide an approximation of the true costs, but it nevertheless expresses a clearly discernible trend in the application of innovative therapies.

Abbreviations

AMNOG: Arzneimittelmarktneuordnungsgesetz / German Pharmaceutical Market Restructuring Act, ATMP: Advanced therapy medicinal products, DEP: Dynamic Evidence Price, EMA: European Medicines Agency, DGM: German Society for Muscular Diseases, NCT: National Center for Tumor Diseases, OD: Orphan drugs, SMA: Spinal muscular atrophy, rDEP: Revised Dynamic Evidence Prize, SOP: Standard operating procedure, VAT: Value added tax

Declarations

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

H.B., K.G., D.S., T.H.-T., P.B., U.K., S.N., G.S., T.S., J.B., G.F.H., I.A. do not declare to have any conflict of interest as defined in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the ICMJE. A.Z. declares to have received fees for consulting services related to the subject of the publication from the companies Biogen, AveXis, Roche and PTC. A.Z. declares to have received funds from Biogen to a third-party account for conducting clinical trials related to the subject of the publication. A.Z. declares to have received funds from Biogen into a third-party account for a research project it initiated related to the subject of the publication.

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**Authors’ contributions**

Conceptualization, H.B., A.Z.; methodology, H.B., K.G., D.S., T.H.-T., P.B.; validation, H.B., P.B., K.G., D.S., S.K.; formal analysis, H.B., A.Z.; writing—original draft preparation, H.B.; writing—review and editing, K.G., D.S., T.H.-T., P.B., U.K., S.N., G.S., T.S., J.B., G.F.H., I.A., A.Z.; visualization, H.B.; supervision, A.Z.; all authors have read and agreed to the published version of the manuscript.

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Tables

Table 1: Annual costs for drugs (in € million) and the percentage change compared to the previous year for the five most cost-intensive centers at Heidelberg University Hospital.
| Year | Child and Adolescent Medicine Costs (Mio. €) | % | Internal Medicine Costs (Mio. €) | % | Surgery Costs (Mio. €) | % | Anesthesiology Costs (Mio. €) | % | Neurology Costs (Mio. €) | % |
|------|-------------------------------------------|---|---------------------------------|---|------------------------|---|-------------------------|---|------------------------|---|
| 2010 | 2.72                                      | -6.04 | 19.51                          | -2.91 | 6.77                   | 16.89 | 4.53                   | 3.9 | 2.24                   | -15.37 |
| 2011 | 2.79                                      | 2.6   | 15.25                          | -21.8 | 5.76                   | -14.82 | 4.88                   | 7.6 | 3.02                   | 34.84  |
| 2012 | 3.48                                      | 24.77 | 16.3                           | 6.9   | 5.85                   | 1.55   | 4.57                   | -6.24 | 2.86                   | -5.27  |
| 2013 | 2.97                                      | -14.6 | 18.49                          | 13.39 | 4.6                    | -21.35 | 4.14                   | -9.54 | 3.04                   | 6.25   |
| 2014 | 3.05                                      | 2.69  | 17.82                          | -3.63 | 4.33                   | -5.92  | 4.33                   | 4.66  | 3.28                   | 7.83   |
| 2015 | 3.13                                      | 2.66  | 17.94                          | 0.72  | 4.15                   | -4.12  | 5.11                   | 17.99 | 4.08                   | 24.5   |
| 2016 | 3.64                                      | 16.36 | 20.35                          | 13.41 | 4.23                   | 1.92   | 4.35                   | -14.84 | 3.74                   | -8.32  |
| 2017 | 6.73                                      | 84.94 | 23.61                          | 15.99 | 3.96                   | -6.54  | 3.46                   | -20.54 | 3.48                   | -7.08  |
| 2018 | 11.04                                     | 63.96 | 23.18                          | -1.79 | 4.27                   | 7.9    | 3.42                   | -0.98  | 8.85                   | 154.51 |
| 2019 | 14.46                                     | 31.01 | 23.14                          | -0.17 | 4.52                   | 5.83   | 4.44                   | 29.59  | 7.76                   | -12.35 |
| 2020 | 34.05                                     | 135.45| 28.85                          | 24.66 | 4.17                   | -7.6   | 4.83                   | 8.81  | 9.46                   | 22.07  |

### Figures

**A**

Graph showing drug costs in million € and order quantities in million units from 2009 to 2020.

**B**

Pie chart showing the distribution of drug costs across departments in 2020:
- Pediatric Neurology (92%)
- Pediatric Cardiology (0%)
- Neonatology (1%)
- Pediatric Hematology & Oncology (4%)
- General Pediatrics (3%)

*Figure 1*

Total drug costs at the Center for Child and Adolescent Medicine Heidelberg from 2009 – 2020. A) Drug costs (bars) and order quantities (dots and lines) at the Center for Child and Adolescent Medicine Heidelberg. B) Distribution of drug costs across the departments of the Center for Child and Adolescent in 2020.
Figure 2

Newly emerged tasks and challenges in the application of innovative forms of therapy. Abbreviations: IOT = Innovative Orphan (or ATMP) - Therapeutics, SOP = Standard Operating Procedure.

Figure 3

Revised Dynamic Evidence Price. Abbreviations: AMNOG = German Drug Market Restructuring Act, EMA = European Medicines Agency, G-BA = Joint Federal Committee, PC = pharmaceutical company.
Supplementary Files

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- OJRD20210211SupplementaryMaterial.docx