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COMMENTARY

Expensive drugs for rare disorders: to treat or not to treat? The case of enzyme replacement therapy for mucopolysaccharidosis VI

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ABSTRACT

Background: Mucopolysaccharidosis VI (MPS VI) is a very rare, chronically debilitating lysosomal storage disorder that develops in people with an enzyme deficiency. Clinical characteristics and progression rates vary widely between patients. The recent introduction of enzyme replacement therapy (ERT) has improved considerably the lives of patients with MPS VI, at an annual cost of treatment between €150 000 and €450 000 per patient.

Scope: This Commentary article addresses the controversial topic of granting reimbursement for expensive treatment options for orphan diseases, such as MPS VI. The discussion reflects clinical, economic and ethical aspects and incorporates insights from the relevant literature (based on a Medline search to September 2008) on MPS VI, efficacy of ERT, orphan drugs, and the economics and ethics of health-care prioritisation.

Findings: Although ERT for MPS VI received marketing authorisation in the European Union in January 2006, patients' access to this therapy varies geographically due to differences between national reimbursement schemes for orphan drugs. Some inclusion and exclusion criteria for treatment of MPS VI patients with ERT appear arbitrary and may contribute to the exclusion from treatment of patients who could benefit in the long term. Reimbursement schemes which rely on proof of short-term treatment effectiveness may discriminate against slowly progressive patients, as health gain can often not be confirmed over a short period of time in these patients. Conventional cost-effectiveness analysis remains silent on crucial issues related to budgetary impact, i.e. opportunity cost from a system perspective, and fair access to treatment.

Conclusions: To prevent patients from being deprived of effective treatment, it is suggested that inclusion and exclusion criteria for treatment should be primarily based on a careful individual assessment of expected long-term clinical benefits. Once treatment has been agreed to as the correct option on clinical grounds, it is further argued that the conventional cost-effectiveness criterion currently in widespread use does not offer a sufficient basis for rejecting reimbursement of expensive treatments for exceptionally rare disorders, providing that decisions on reimbursement are intended to reflect public preferences.

Introduction

The group of lysosomal storage disorders (LSDs) encompasses more than 40 rare and very rare metabolic diseases including mucopolysaccharidosis VI (MPS VI) with an incidence estimate ranging from 1 : 248 000 to 1 : 1 300 000[1–5]. Swiedler and colleagues estimated that there are about 1100 MPS VI patients in the developed world[6]. Based on the definition of the European Commission, MPS VI is an example of a rare or 'orphan' disease because it is a life-threatening or chronically debilitating disease which has such a low prevalence (<5 : 10 000) that special combined efforts are needed to address it[7]. The lack of commercial incentives to research and develop specific therapies for orphan diseases is particularly due to the need for pharmaceutical entrepreneurs to recoup the high fixed development costs of a new therapeutic principle. Therefore, an increasing number of countries have enacted a legislation specifically designed to encourage investment in orphan drug development. Patients' organisations have played an active role in this realisation[8]. In the European Union (EU) the 'Orphan Medicinal Products Regulation', which became valid in 1999, introduces incentives to develop and market medicinal therapies for orphan diseases.

In parallel, however, policy-makers responsible for drug reimbursement have become increasingly concerned about the high cost per patient of many orphan treatments. Increasingly, they have turned to cost-effectiveness assessments, applying a benchmark of the maximum acceptable incremental cost per quality-adjusted life year (QALY) gained, as an important criterion for assessing 'value for money'[9,10].

Recently, an enzyme replacement therapy (ERT) for the treatment of MPS VI has become available and management guidelines have been published[11]. The aim of this manuscript is to describe the current situation of reimbursement of ERT for MPS VI and other LSDs and to draw attention to the inconsistency between marketing authorisation regulation and some local reimbursement schemes. A literature search was performed on the Medline database from inception until September 2008 including the MeSH terms: 'mucopolysaccharidosis VI', 'efficacy', 'orphan drug production/economics' and 'orphan drug production/ethics'. Only English language publications and studies in humans were included. Bibliographies of retrieved papers were also screened for additional references.

Lysosomal storage disorders

LSDs result from an inherited deficiency of a particular protein that is involved in lysosomal biogenesis. The genetic enzyme defect results in the accumulation of partly degraded substrates within lysosomes. The LSDs are divided into broad subgroups: the mucopolysaccharidoses (MPS), lipidoses, glycogenoses, and oligosaccharidoses, based on the nature of the stored substrate.

Disorders belonging to the MPS group are characterised by a deficiency in one of the enzymes that are involved in the breakdown of certain complex carbohydrates called glycosaminoglycans (GAGs). This leads to accumulation of partially degraded GAGs in the cells of a wide range of tissues.

MPS VI, also referred to as Maroteaux–Lamy syndrome, develops in people with a deficiency of *N*-acetylgalactosamine 4-sulfatase (arylsulfatase B [ASB]). Like most LSDs, MPS VI is a progressive and clinically heterogeneous disorder involving multiple organs, with a broad continuum of clinical severity and age of presentation. Most patients with the rapidly progressive phenotype die before they reach adulthood. Patients with the more slowly progressive phenotype may live into their 40s or 50s. Typical features of MPS VI are short stature, coarse facial features, skeletal and joint deformities and upper airway obstruction.

Diagnosis and treatment of LSDs

Most patients with LSDs are detected after the onset of clinical signs. In the case of MPS VI this is usually before 2 years of age for patients at the severe end of the clinical spectrum[12,13]. Patients with the more slowly progressive phenotype can evade detection for many years until the disease pathology is advanced. Proper diagnosis of MPS VI requires evaluation of the ASB enzyme activity in an accredited laboratory. An ASB enzyme activity of <10% the lower limit of normal confirms the presence of MPS VI in patients with clinical findings of the disease[11].

In the past, treatment of LSDs was limited to palliative care, which was focused on alleviating individual disease manifestations. The perspective of many patients improved considerably with the introduction of new technologies such as hemapoietic stem cell transplantation (HSCT) and ERT. HSCT involves transplantation of hemapoietic stem cells that produce the missing enzyme from a healthy, matched donor. ERT supplies the missing enzyme through repeated intravenous infusions. HSCT has had a variable impact on the natural course of different LSDs. Whereas it has proven to be a viable treatment option for MPS I (Hurler syndrome), no or only limited treatment effect could be proven for other types of LSDs

such as MPS III[14]. Major drawbacks of HSCT are its associated risks of morbidity and mortality and the difficulty of finding a matched donor[15]. Due to the risk associated with HSCT, ERT is generally regarded as the safer treatment option[11].

ERT has been developed for a number of LSDs. ERT for MPS VI with the recombinant human ASB enzyme (rhASB) (galsulfase [Naglazyme®, BioMarin Pharmaceutical Inc., Novato, CA, USA]) has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of MPS VI and is available in the United States, Europe and Australia[11]. Hitherto, three clinical trials, including a total of 56 patients, have evaluated the efficacy and safety of rhASB ERT[16–18]. Treatment with rhASB reduces lysosomal storage, as shown by a dose-dependent decrease in urinary GAG levels, and improved endurance, mobility and joint function[16–18]. Long-term follow-up data from patients included in these clinical trials showed that rhASB ERT up to 5 years is associated with sustained improvements in endurance. Infusions of rhASB were well-tolerated during all clinical trials and their open-label extensions[19].

In order to further characterise the natural progression of MPS VI and to maximise the evidence on clinical response to and safety of long-term rhASB treatment, an MPS VI Clinical Surveillance Program (ClinicalTrials.gov Identifier NCT00214773) is ongoing[20]. This phase IV study started in July 2005. At the moment, more than 100 patients are registered in this programme, representing more than half of all patients on rhASB treatment.

Currently, there are no objective markers other than GAG that clearly reflect MPS VI disease severity or therapeutic responsiveness in humans. In a recently published study in four Italian patients undergoing ERT, the proinflammatory cytokine TNF-α was identified as a potential biomarker for MPS VI responsive to therapy[21]. However, the potential of TNF-α as a biomarker for MPS VI needs to be confirmed in larger studies.

Recently, a consensus panel of international experts in medicine, genetics and biochemistry drafted management guidelines for MPS VI[11]. The expert panel recommended ERT, when available, as first-line therapy. Management of disease manifestations using adaptive or supportive devices, physical and occupational therapy, symptom-specific medications, and surgery also remain an important part of integrated care of patients with MPS VI.

In a chronic progressive disease, any slowing of the rate of progression may be regarded as a treatment benefit; even a continuous progression at a slower rate reflects an improvement to the patient's condition[22]. The clinical heterogeneity of LSDs and the limited information on their natural course make it impossible to identify a single clinical endpoint. The variability in treatment responses between patients and the need for composite endpoints is illustrated in Table 1, showing the effects of rhASB treatment on joint mobility and hepatosplenomegaly in nine Italian MPS VI patients[23]. Although all patients appear to benefit from treatment to some extent, the type and magnitude of benefit varied considerably between patients. This variability between patients compromises in particular the evaluation of the impact of treatment in patients with slowly progressive disease, as in these patients treatment benefits may only become apparent after several years. Depending on the phenotype, some damage cannot be reversed by ERT; this stresses the need for early detection and treatment to prevent the development of irreversible functional defects[24,25].

Orphan drug designation and marketing authorisation

Without extra incentives, the pharmaceutical industry is reluctant to develop medicinal products for orphan diseases due to the high costs related to research, development, and marketing and the low patient numbers to recoup these costs from. To prevent patients with orphan diseases from being deprived of the benefits of medical progress simply because of the rarity of their disease, several public authorities have enacted specific legislation. This legislation aims at stimulating the development and marketing of medicinal products for rare diseases by providing incentives for research and clinical development, reduced fees for approval applications, and guarantees of market exclusivity to sponsors.

In the EU, orphan drug legislation consists of two primary pieces, which are directly applicable in all member states. The first one, Regulation (EC) No 141/2000, provided objective criteria for designation of medical products as 'orphan', described procedures for requesting community marketing authorisations for orphan medicinal products through the centralised procedure and access to incentives, and demanded the establishment of a Committee for Orphan Medicinal Products (COMP) within the EMEA[26]. The second regulation, Commission Regulation (EC) No 847/2000, established the provisions for implementation of the criteria for designation, and provided definitions for 'similar medicinal product' and 'clinical superiority'[27].

The objective criteria for designation of medicinal products as 'orphan' in the EU are based on the

prevalence of the condition, with a prevalence of ≤5 : 10 000 being regarded as the appropriate threshold for life-threatening or chronically debilitating conditions. Exceptions to this threshold are made for medicinal products intended for life-threatening, seriously debilitating or serious and chronic conditions with a prevalence >5 : 10 000 if, without special incentives, it is unlikely that the marketing would generate sufficient return to compensate the investment. Another European criterion for designation is the absence of any other satisfactory methods of diagnosis, prevention or treatment of the condition. If an alternative already exists, the medicinal product should be of significant benefit to those affected by the condition.

In the EU, orphan medicinal products are eligible for reduction of several fees relating to the marketing authorisation procedure, including protocol assistance (scientific advice), application for marketing authorisation, inspections, renewals, etc. They are also granted a 10-year market exclusivity in the EU, which prevents the Community or a member state from subsequently issuing a marketing authorisation of a similar medicinal product (e.g., the same active substance).

Since the introduction of the orphan drug legislation, the development and marketing of treatments for rare diseases in the EU have increased considerably. From April 2000 to April 2005, 268 medicinal products received European orphan drug status with the main therapeutic categories being oncology (36%), metabolic (11%), immunology (11%), and cardiovascular or respiratory (10%)[28]. To date, 44 orphan drugs have been granted European marketing authorisation, including galsulfase for the treatment of MPS VI patients[29]. The logical next step forward is making these drugs accessible and affordable to those patients who can be expected to show medical benefit.

Clinical guidelines for management of MPS VI with ERT

In England, the National Commissioning Group (NCG), formerly known as the National Specialist Commissioning Advisory Group (NSCAG) was established to decide on the commissioning of extremely rare conditions or very unusual treatments on a national basis[30]. The NCG supports specialised centres for orphan diseases and can provide primary care organisations with contingency funding to support expensive treatments. All licensed therapies have to be prescribed by nationally designated centres according to agreed clinical protocols which set out the criteria under which a patient will start and terminate treatment.

The NCG provides national service standards for care of people with LSDs and individual management guidelines for infantile and late onset Pompe disease, Gaucher disease (adult and paediatric), Anderson–Fabry disease, MPS I, MPS II and MPS VI[31].

The clinical protocol for the management of MPS VI with rhASB ERT was published by NCG in 2006[32]. The protocol provides inclusion criteria for treatment based on the presence of symptoms. MPS VI patients with signs of upper airway obstruction, symptomatic or asymptomatic airway disease, myocardial dysfunction, impaired endurance, or symptoms and signs of raised intracranial pressure are considered eligible for treatment with rhASB. The protocol gives detailed instructions on how any of these symptoms should be evaluated. Patients with severe MPS VI who are too young to carry out any of the prescribed assessments should also receive rhASB as they have the rapidly progressive form of the disease. Proper follow-up of patients treated with rhASB implies evaluation in an out-patient setting every 3 months. According to the protocol, ERT should be discontinued whenever the patients develops a life-threatening complication unlikely to benefit from further ERT, if the patient fails to comply with the recommended dose regimen or follow-up clinic visits or investigations, or if there is evidence of disease progression despite regular therapy. Disease progression was defined as a 10% reduction in predicted forced vital capacity (FVC), ejection fraction or 6-minute walk test (6MWT) distance in the absence of a disease-specific complication amenable to surgery. Treatment of an individual patient outside the clinical protocol has to be considered by an Expert Advisory Group. However, there are no clear criteria that guide the decisions of this committee.

Table 1. *Change in clinical findings in nine Italian patients with MPS VI since the start of rhASB treatment*[23]

Clinical finding	Patient								
	1	2	3	4	5	6	7	8	9
Reduced joint mobility	↑	↑	—		—		↑	↑	↑
Hepatosplenomegaly	↑	↑	↓	—	↑	↓	↑	↑	—

↑: improvement; ↓: worsening; —: stability since start treatment

In Germany and Italy, there are no formal guidelines for management of MPS VI with ERT. In principle, every physician can prescribe the drug for a patient who is affected by MPS VI, regardless of age and severity. In Germany, this situation changed with enactment of the latest health-care reform, effective from the end of 2008: in order to qualify for reimbursement, prescriptions of certain pharmaceutical products exceeding an annual cost of €20 000 now have to be confirmed by a 'second opinion', which has to be obtained from a specialised physician registered with the statutory sick funds[33].

Reimbursement of orphan drugs

Whereas in the EU orphan drug designation and marketing authorisation are centralised processes, therapeutic value assessment, pricing and reimbursement for these products remain the responsibility of the member states. Health service funding of orphan drugs varies across the EU, leading to geographical inequalities in the patients' access to treatment with approved drugs. Policy-makers throughout different regions have turned to health-technology assessments (HTAs) to support pricing and reimbursement and hence prioritisation decisions. Typically, HTAs comprise systematic reviews of the available evidence of clinical effectiveness and increasingly are complemented by formal economic evaluations[34]. The application of this approach to expensive drugs for rare disorders poses a range of specific challenges.

Not surprisingly, given the low prevalence rates of orphan conditions, some of the clinical datasets accepted for approval have been very small. Therefore, documentation of clinical effectiveness has been more limited compared to that supporting a typical non-orphan new product. In a recent paper, Joppi *et al.* state that unquestionably, less stringent criteria are acceptable for orphan drugs than for drugs for more common diseases, particularly in view of the very small numbers of patients. However, studies are needed to establish the clinical benefit of the new therapies[35]. Clearly manufacturers of orphan drugs face a moral obligation to provide as much high-quality clinical evidence of efficacy as possible, in particular on which patients can benefit most from the treatment. As mentioned above, in the case of rhASB treatment, an observational phase VI study is ongoing to collect additional data regarding clinical response and safety of the treatment[20]. There can be little if any doubt, however, that a smaller clinical database will inescapably be associated with higher decision uncertainty on clinical judgements as well as on judgements about cost effectiveness.

An even more critical difference between many orphan and non-orphan medicines has been the frequently observed impossibility of orphan products meeting widely-used criteria for cost effectiveness. Basically, the underlying logic of cost effectiveness relies on the consequentialistic assumption that the objective of the health-care system should be to maximise the total health output, i.e. the distribution-independent sum of QALYs produced, in the whole community given an existing resource (or budget) constraint[36,37]. Given very high prices and cost-effectiveness estimates for orphan drugs, it is clear that applying the logic of cost effectiveness to decide on health-care resource allocation will conflict with the individual interests of patients with very rare diseases[38,39]. The cost of 1-year treatment with rhASB, for example, is around €150 000–450 000, dependent on the patient's weight (Table 2).

Although cost-effectiveness analysis (CEA) represents a valuable tool to increase the transparency of reimbursement decision-making from an economic point-of-view, there are strong reasons to believe that the quasi-utilitarian way of thinking – in which maximising aggregate health output is the (assumed) ultimate goal – is not shared by the general community. For example, in conventional CEA, outcome is measured in terms of (unweighted) QALYs gained. The initial health state of a patient matters indirectly only, because the incremental health improvement depends on the quality of life before and after an intervention. There is evidence that the general public prefers to give strong priority to those with the worst initial health state, i.e. to give priority to treatment of patients with life-threatening or severe illnesses, even if this approach leads to a less 'cost-effective' allocation of resources[40–43]. The powerful imperative to rescue

Table 2. *Yearly cost of rhASB treatment*

Factors determining cost of rhASB treatment	
Recommended dose*	1 mg rhASB/1 kg bodyweight/week
Mean weight/patient	25 kg[18]
Mean No. vials/week/patient	Five with each vial containing 5 mg rhASB
Cost/vial	€1400† (£982)
Mean cost/patient/year	€350 000

*According to Summary of Product Characteristics available at http://www.emea.europa.eu/humandocs/PDFs/EPAR/naglazyme/H-640-PI-en.pdf
†Obtained from the *British National Formulary* 2008 available at http://www.bnf.org/bnf/

identifiable individuals from avoidable death that people feel – also called the 'rule of rescue' – may be interpreted as a related but special case, with the dimensions of severity of the initial health state and urgency of an intervention added to the *separate* issue of affecting an identifiable person instead of an entire category of anonymous individuals[42]. The criterion of visibility may however be interpreted as unjust and not morally defensible[42].

These empirical observations correspond to a rights-based ethical view – as opposed to the quasi-utilitarian cost-effectiveness view – which puts the non-abandonment[44] of 'those who are unfortunate enough to have a high-cost illness' at the centre[45]. The EU's legislation appeals to the rights-based view, demanding that all patients should have the same quality of treatment[26].

Apart from normative considerations, from an economic perspective a more appropriate question might be what society is willing to pay in these rare cases[46], where total budget impact is low but cost per patient substantial (Figure 1). Importantly, CEAs reporting incremental cost-effectiveness ratios (ICERs) do not provide information about the size of the numerator (costs) and the denominator (effects) of the ratio, hence failing to capture budgetary impact and therefore the opportunity cost of adopting a programme from a health-care system perspective[47,48]. (It could, however, be argued that ICERs reflect the opportunity cost in terms of QALYs to be gained elsewhere in the system; this argument rests on the flawed assumption that people value all QALYs equally, and that the primary objective of a national health scheme is indeed QALY maximisation. See discussion below.) To illustrate this, taking the example of Australia, the cost per year is in a range between A$200 000 (for a young child) to A$400 000 per patient. Of course, these funds might be spent elsewhere in the health system for possibly a greater aggregate gain in health outcomes. At the same time, however, the total burden for the system is comparably small, with perhaps 12 MPS VI patients in Australia at less than A$5 million annually. This figure is dwarfed when compared to annual drug spending by the Australian Pharmaceutical Benefits Scheme (PBS), which was running at around A$6 billion in 2005. Under the Australian 'Life Saving Drugs Program', treatment with galsulfase has been reimbursed since September 2008[49]. Likewise, a European study estimated the total budgetary impact of orphan drugs at 0.7–1% of total pharmaceutical spending in member states[50].

A key reason for often unfavourable ICERs associated with orphan treatments, however, is the need to recoup high fixed (volume-independent) research and development expenditures[51] from a small number of patients treated. For this reason, strict application of the logic of cost effectiveness inevitably would imply systematic discrimination of those with rare disorders – in effect, these patients would inevitably be deprived from any chance to receive effective treatment.

Therefore the fundamental issue, as we see it, is neither 'should we value rarity?'[52], nor 'should we consider some kind of 'symbolic value' and provide care that is cost ineffective according to a quasi-utilitarian theoretic framework'[53]; rather it is – as John Rawls and Amartya Sen remarked when they rejected utilitarian distribution-indifference – to take the distinction between persons adequately serious: 'if a person remains miserable or painfully ill, her deprivation is not obliterated or remedied or overpowered simply by making someone else happier or healthier'[54].

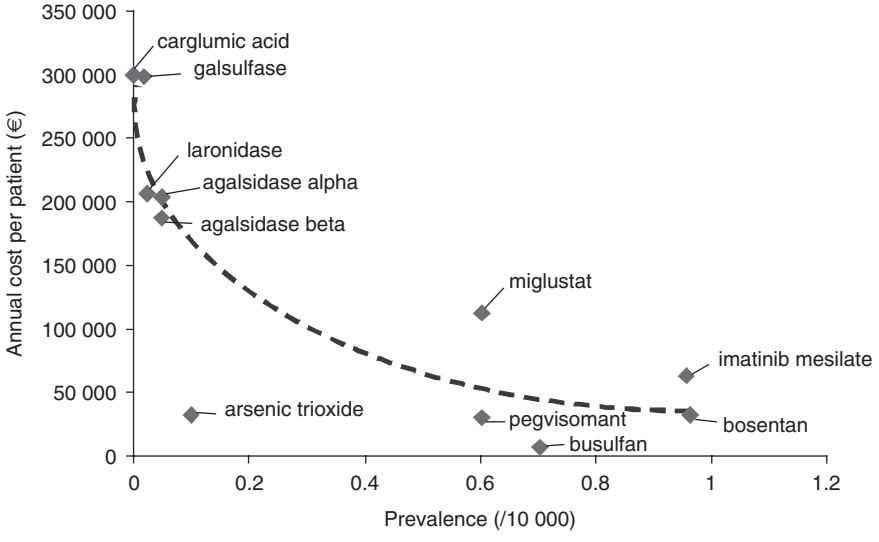

Figure 1. *Orphan drugs in Europe: relationship between prevalence and annual cost per patient (Adapted from Alcimed, 2005[50], with permission)*

In a departure from the descriptively flawed[43] 'a QALY is a QALY is a QALY' premise, this raises important issues of vertical equity, i.e. the unequal, yet equitable treatment of unequals[54,55]. As a starting point, distributional concerns might be taken more seriously, for instance by applying the simple idea of weighting health gains differently for different recipients of the gains[56], which might lead to some kind of weighted QALY maximisation algorithm[57]. As Gavin Mooney[56] pointed out, it is crucial to realise that vertical equity is about *all* differences on the vertical dimension, i.e. not necessarily limited to some kind of a Rawlsian maximin position or to positive discriminatory according to severity or urgency of a health problem. Following Sen's notion of 'rights as goals'[58] would take things one step further, with the underlying ideas of justice focusing on positive freedoms and autonomy, resulting in a priority for measures designed to provide people – or, for that matter, patients – with 'basic capabilities to function'[59].

We do recognise that an obvious issue – yet to be resolved convincingly – associated with these (in our view appealing) ideas is the risk of sacrificing efficiency and exposing health systems to problems of moral hazard, in the present context notably including profit maximising behaviour of drug manufacturers. Nevertheless, we suggest a more important role for considerations of equal access to quality care, as compared to judgments about cost effectiveness[60]. Until formal economic evaluation models will have been developed that adequately incorporate these principles (in our view, further development of such methods should be given high priority: concepts such as 'relative social willingness-to-pay'[46] and 'cost-value analysis'[61] provide examples for valuable starting points), we argue that decisions on reimbursement of orphan drugs should be guided primarily by evidence of treatment benefit, rather than be determined by an artificial cost-effectiveness (ICER) benchmark, which is insensitive to contextual factors, such as severity or urgency of a state problem[61,62] and, notably, programme dimension or opportunity cost from a system's perspective[47,48].

Reconsidering reimbursement schemes

Reimbursement conditions for orphan drugs based on short-term effectiveness of treatment are subject to several issues. Inclusion and exclusion criteria for treatment, such as those applied in England, appear arbitrary and may well be regarded as discriminating for some patients. Using the presence of certain symptoms as a criterion to decide on treatment regimen and reimbursement is only straightforward if these symptoms effectively predict disease outcome. For progressive diseases such as MPS VI, there is no evidence that patients with severe or early presenting symptoms benefit more from treatment than patients with less severe or late presenting symptoms. On the contrary, it seems desirable to start treating these patients at an early stage, before irreversible damage has occurred; although there is a need to generate more robust clinical data to support this strategy.

Another issue is the difficulty in assessing effectiveness of therapy in patients with clinically heterogeneous progressive diseases in the short term. One of the NCG criteria for discontinuing ERT treatment in patients with MPS VI is disease progression, measured by a 10% reduction in predicted FVC, ejection fraction or 6MWT[32]. As already emphasised in the protocol, the threshold of 10% is arbitrary and subject to review as there are currently no scientific grounds for this recommendation. The validity of the measures that are used to evaluate effectiveness of treatment can also be questioned. Due to the clinical heterogeneity of the disease, some patients might feel better with treatment despite worsening of one of the recognised measures for effectiveness. In addition, it is difficult to define health gain from therapy for progressive diseases as it is unclear what would happen in the absence of treatment. As every patient with an LSD has a unique phenotype and progression rate, they all require a unique treatment approach. For patients with slowly progressive MPS VI, the impact of therapy may only become apparent after several years. The evaluation of treatment benefit in these patients should therefore be focussed on the long term. There is anecdotal evidence of some unpublished cases where clinicians discontinued treatment, under threat of financial consequences, because short-term efficacy could not be proven.

Conclusions

Under some reimbursement systems for orphan drugs there seems to be a serious mismatch between the currently applied conceptually simple logic of cost effectiveness on the one hand and the (overall) low budgetary impact and well-documented public preferences to give priority to patients in more serious initial health states on the other hand. These preferences are already reflected in policies, that were implemented to encourage development and marketing of orphan drugs.

Measures that are currently being used to evaluate treatment effectiveness of ERT for MPS VI and other LSDs are hardly adequate to select those patients who benefit from treatment in the long term. Reimbursement rules that apply short-term treatment

effectiveness may well discriminate against slowly progressive patients. In order to eliminate current inequalities that exist between patients in access to treatment with orphan drugs, alternative funding models should be developed for these drugs. In the opinion of the authors, if and when possible, treatment decisions should take into account expected long-term clinical benefit of therapy rather than short-term effectiveness.

Patient organisations may play an important role in putting these issues on the table of policy-makers. This does not alleviate the moral obligation of orphan drug manufacturers to provide as much clinical evidence as possible on long-term treatment and to keep the price of the treatment as low as possible.

It has been argued that the success of orphan drug legislation, designed to provide incentives for research into rare disorders and to counter its low profitability, should prompt monitoring of its putatively unintended effects on drug prices[63]. Whilst agreeing with this proposition, we believe that widely-used benchmarks for cost effectiveness are of limited use in informing pricing and reimbursement of orphan drugs, primarily (a) for normative reasons (we have taken a sceptical stance towards quasi-utilitarian reasoning, which may well be considered controversial[52,63]), (b) empirically, because they do not reflect prevalent social value judgements regarding severity of health problems and urgency of interventions, and (c) because ICERs fail to capture the dimension of health-care programmes, i.e. the opportunity cost of their adoption from the perspective of the whole system. In our view, there remains a need for intensified research into health-economic evaluation models beyond CEA. These should address the above-mentioned aspects including price volume trade-offs, hereby better addressing the realities of new drug development and the information needs of policy-makers[64,65].

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