POLICY PERSPECTIVES

An Evaluation Framework for Funding Drugs for Rare Diseases

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A B S T R A C T

Objectives: For rare diseases it may be difficult to generate data from randomized trials to support funding of a drug. Enzyme replacement therapies for diseases of inherited metabolic enzyme deficiency provide an example of this dilemma. The Ontario Public Drug Programs convened the Drugs for Rare Diseases Working Group to develop a policy for assessing these drugs. Methods: The Drugs for Rare Diseases Working Group developed terms of reference expecting that the ideal policy product would be transparent and consistent and address unique aspects of the treatment of a specific rare condition while being adaptable to other dissimilar conditions. The perspective was that of a public payer addressing requests for funding generated for a specific drug, and included respect for the principles of “accountability for reasonableness” of Daniels and Sabin. Results: A seven-step framework was developed and tested by using the case study of idursulfase for mucopolysaccharidosis II (Hunter disease). Estimation of clinical effectiveness was done by using decision modeling. The model developed informed funding recommendations and ultimately led to an agreement with the manufacturer allowing funding of idursulfase in Ontario. Conclusions: This policy framework attempts to address the policy challenges of funding drugs for rare diseases. The framework will be used to assess other drugs in future and will inevitably require modification with experience. It is hoped that it may be of value to other policymakers. Keywords: cost-effectiveness, drug reimbursement, health policy, glycogen storage disease, mucopolysaccharidosis.

Introduction

In this article, we describe the development of a unique, evidence-based framework for the evaluation of drugs intended for the treatment of rare diseases. This framework was developed at the request and with the support of the Ontario Public Drug Programs of the Ministry of Health and Long-term Care in the province of Ontario, Canada. The purpose of the evaluation framework is to provide guidance for public drug-funding policy from the payer perspective. The framework consists of seven evaluative steps, each prerequisite for those that follow, and include steps of modeling of both effectiveness and cost-effectiveness. The evaluation framework was tested by using the case study of idursulfase for Hunter disease, and this is provided by way of example.

Background

Over the past decade, expensive enzyme replacement therapies for rare inherited metabolic enzyme deficiencies have emerged. These drugs are among the most expensive in the world (Table 1) and have created dilemmas for public drug payers [1–3]. Typically, data from adequately powered randomized clinical trials are required for both regulatory approval and public funding of most new drugs in Canada, which is decided at the provincial level. Escalating health care costs have led to greater provincial scrutiny of drug expenditures and increasing consideration of the cost of a drug to inform drug-funding decisions [4]. An approach considering health gain, incremental cost-effectiveness, and global budget impact has been adopted in Ontario.

To assess cost-effectiveness adequately as a part of such a process requires adequate information about the effectiveness of a new drug from randomized trials, and for rare conditions, such information is often limited, inadequate, or absent. There is little guidance available in the published literature or from other jurisdictions to guide the evaluation of drugs for funding in such situations [5]. The Canadian provinces and territories have attempted to develop a national strategy, but in the absence of a funding commitment from the federal government, this work has stopped, and so provincial funding recommendations considering efficacy and value for money in a conventional manner are typically negative [6].

The Ontario Public Drug Programs was formally established in April 2007, led by an Executive Officer who is invested with author-
that previously resided with Cabinet and the Minister of Health, including the mandate to administer Ontario’s $4.1 billion publicly funded drug programs [7]. The Committee to Evaluate Drugs (CED) makes recommendations for drug funding to the Executive Officer on the basis of clinical, safety, and cost-effectiveness data. Consistent with recommendations from the Canadian Drug Expert Committee, the CED had recommended against funding idursulfase for Hunter disease because it did not satisfy the usual criteria for clinical benefit and cost-effectiveness [6]. However, adherence to such criteria could appear unfair to patients stricken with a disabling and sometimes fatal condition, and who are often infants or children [8]. In view of the varied approaches taken in other Canadian provinces to the funding of idursulfase for Hunter disease and in an effort to address public demands fairly, the Executive Officer prioritized the development of a process for reviewing such drugs for funding in a fair, transparent, and consistent way.

A “Drugs for Rare Diseases Working Group” was created consisting of nine members selected by the Executive Officer: three representatives from the Ontario Ministry of Health and Long-term Care (the Executive Officer and two pharmacists), four members of the CED (two physicians, a pharmacist, and a health economist), and two other individuals, one with formal pharmacoeconomic training and an expert in the treatment of inherited disorders of metabolism in children. An ethicist was consulted ad hoc during the process.

### Development of the Framework

The Drugs for Rare Diseases Working Group had broad latitude to develop its own terms of reference and process. Several principles formed the basis of the development process. First, there was an expectation that the resulting policy product would be transparent and consistent and address the unique aspects of treatment of a specific rare condition while being adaptable to other rare but dissimilar conditions in future. Second, it was recognized that the framework should respect and be complementary with the current policies of the Ontario Public Drug Programs and the Ministry and that the perspective would be that of a public payer addressing requests for funding generated for a specific candidate drug rather than general treatment algorithms for a specific condition. Finally, as the overall aim was to develop a funding framework that considered the evidence available, patient need, and the current funding gap, it was specified that the conditions for “accountability for reasonableness” of Daniels and Sabin [9] for fair priority-setting be respected. These provide ethical guidance for making difficult decisions under constrained resources and include four domains: Publicity (decisions to limit health care and their rationales must be publicly accessible), Relevance (the rationales invoked must be based on evidence, reasons, and principles that fair-minded persons would affirm), Appeals (mechanisms for challenging allocation decisions must exist), and Regulation (public procedures must ensure the fulfillment of these three conditions). Appeal of drug-funding decisions in Ontario is available through the office of the Executive Officer.

### Policy Framework

No acceptable processes developed by other jurisdictions were identified for adoption, and so a seven-step framework was developed that addressed specific areas of uncertainty related to drugs for rare diseases that emerged early in Working Group discussions (Fig. 1). These included the following: Is the condition truly rare? Is it logical that patients could benefit from the treatment? What is the potential value of the treatment and to whom? It was also recognized that expert input was crucial and that the framework should be responsive to accumulating knowledge about the disease.

**Step 1: Confirm the condition for treatment with the candidate drug is truly “rare”**

In the context of this framework, it was considered of critical importance to define what constituted “rare.” It was agreed that the existence of such a policy process should not diminish the motivation to conduct randomized trials in conditions that were simply uncommon or difficult to study. Rare health conditions have been defined as liberally as a population prevalence of 1/1500 [10]. As well, with improved case finding and international collabora-

### Table 1 – The most expensive drugs in the world [1].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Annual cost</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soliris (eculizumab)</td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>$409,500</td>
<td>Alexion</td>
</tr>
<tr>
<td>Elaprase (idursulfase)</td>
<td>Hunter’s syndrome</td>
<td>$375,000</td>
<td>Shire</td>
</tr>
<tr>
<td>Naglazyme (galsulfase)</td>
<td>Maroteaux-Lamy syndrome</td>
<td>$365,000</td>
<td>BioMarin</td>
</tr>
<tr>
<td>Cinryze (C1 esterase inhibitor)</td>
<td>Hereditary angioedema</td>
<td>$350,000</td>
<td>ViroPharma</td>
</tr>
<tr>
<td>Myozyme (alguclosidase alpha)</td>
<td>Pompe disease</td>
<td>$300,000</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Arcalyst (nilonacet)</td>
<td>Cryopyrin-associated periodic syndromes</td>
<td>$250,000</td>
<td>Regeneron</td>
</tr>
<tr>
<td>Fabrazyme (agalsidase beta)</td>
<td>Fabry disease</td>
<td>$200,000</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Cerezyme (imiglucerase)</td>
<td>Gaucher disease</td>
<td>$200,000</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Aldurazyme (laronidase)</td>
<td>Hurler syndrome</td>
<td>$200,000</td>
<td>Genzyme, BioMarin Pharmaeutical</td>
</tr>
</tbody>
</table>

Note. From 2010 data provided by Forbes and Pharmaceutical Commerce (all prices in US dollars).
controlled trials are generally considered the gold standard of ev-
This step evaluates the theoretical value of the drug. Randomized
disease and the treatment.
and health of the patients. As these diseases are by definition rare,
natural history, and health effects of the condition under consid-
definition of an annual incidence of 1:150,000 live births in Can-
tion requires further methodological development. For the pur-
coherence when evaluating the efficacy of a new drug technology. If
randomized trials reporting clinically relevant outcomes were
was once considered to be a rare disease but have now been
It was the consensus that for the purpose of consideration for
exceptional funding, a “rare disease” should be one for which ran-
place of the drug in therapy. Ideally, the definition
Coherence
Observations of drug effects do not conflict with generally known facts of natural history and biology of the disease:
Plausibility
Drug mechanism addresses underlying disease pathophysiology:
Idursulfase therapy replaces the enzyme deficient in Hunter’s syndrome.
Biological gradient
Optimal disease improvements are associated with optimal drug doses:
Idursulfase 0.5 mg/kg infused weekly was associated with more benefit than alternate weekly infusions, which were
Associated with more benefit than placebo in a randomized trial.
Step 4: Model the potential clinical effectiveness of the candidate drug
From the data identified in step 3, clinical effectiveness can be
estimated by modeling by using clearly described methods includ-
ing estimates of the variability of treatment effects and acknowl-
edgment of the limitations of the data and techniques used. Deci-
sion modeling adopting a Bayesian perspective has some appeal in
this setting as it allows the synthesis of data of different degrees of
quality emanating from alternative sources. Other techniques to
estimate a candidate drug’s treatment effect, however, may be
quite reasonable and appropriate.
Step 5: Evaluate cost implications and generate a funding recommendation
Once estimates of clinical effectiveness are available, cost-effec-
tiveness can be theoretically calculated by using conventional
Step 3: Understand the potential value of the candidate drug
This step evaluates the theoretical value of the drug. Randomized
controlled trials are generally considered the gold standard of ev-

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Example</th>
</tr>
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<tbody>
<tr>
<td>Strength</td>
<td>Disease improvements strongly associated with drug exposure:</td>
</tr>
<tr>
<td></td>
<td>Hunter’s syndrome is inexorably progressive, and spontaneous improvements are not seen. Disease improvements</td>
</tr>
<tr>
<td></td>
<td>have been observed with idursulfase therapy.</td>
</tr>
<tr>
<td>Consistency</td>
<td>Disease improvements have been repeatedly associated with drug exposure despite variations in population, disease</td>
</tr>
<tr>
<td></td>
<td>stage, and therapy:</td>
</tr>
<tr>
<td></td>
<td>There are several reports of disease improvement with idursulfase therapy by different investigators in patients with</td>
</tr>
<tr>
<td></td>
<td>different disease burden treated with varying doses and schedules of therapy.</td>
</tr>
<tr>
<td>Specificity</td>
<td>Benefit with the drug is specific to the disease or disease mechanism:</td>
</tr>
<tr>
<td></td>
<td>Idursulfase has not been tested in other diseases.</td>
</tr>
<tr>
<td>Temporality</td>
<td>Disease improvements occur after drug exposure:</td>
</tr>
<tr>
<td></td>
<td>Benefits of idursulfase occur after prolonged drug exposure.</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>Optimal disease improvements are associated with optimal drug doses:</td>
</tr>
<tr>
<td></td>
<td>Idursulfase 0.5 mg/kg infused weekly was associated with more benefit than alternate weekly infusions, which were</td>
</tr>
<tr>
<td></td>
<td>associated with more benefit than placebo in a randomized trial.</td>
</tr>
<tr>
<td>Plausibility</td>
<td>Drug mechanism addresses underlying disease pathophysiology:</td>
</tr>
<tr>
<td></td>
<td>Idursulfase therapy replaces the enzyme deficient in Hunter’s syndrome.</td>
</tr>
<tr>
<td>Coherence</td>
<td>Observations of drug effects do not conflict with generally known facts of natural history and biology of the disease:</td>
</tr>
<tr>
<td></td>
<td>Idursulfase therapy is most effective for reduction of hepatosplenomegaly and appears ineffective in patients with</td>
</tr>
<tr>
<td></td>
<td>neurological involvement.</td>
</tr>
<tr>
<td>Experiment</td>
<td>Experimental data confirm disease improvement with drug exposure:</td>
</tr>
<tr>
<td></td>
<td>A single placebo-controlled randomized trial reported a statistically significant improvement in a composite end point</td>
</tr>
<tr>
<td></td>
<td>of 6-minute walk and percentage forced vital capacity at 1 y.</td>
</tr>
<tr>
<td>Analogy</td>
<td>Drugs of similar mechanism improve similar diseases:</td>
</tr>
<tr>
<td></td>
<td>Enzyme replacement therapy has been associated with clinical benefits in other inherited disorders of enzyme</td>
</tr>
<tr>
<td></td>
<td>deficiency, e.g., Gaucher’s disease.</td>
</tr>
</tbody>
</table>

Step 2: Understand the disease
This step invests time understanding the basic pathophysiology,
natural history, and health effects of the condition under consider-
ation. Such knowledge was considered essential to critically re-
view and fully understand the mechanism of action of the candid-
ate drug and its actual or potential effects on the natural history |
and health of the patients. As these diseases are by definition rare, |
this step requires engagement, participation, and collaboration |
with experts in the disease as well as supplemental information |
from the medical literature and other sources to address both the |
disease and the treatment.

Step 3: Understand the potential value of the candidate drug
This step evaluates the theoretical value of the drug. Randomized |
controlled trials are generally considered the gold standard of ev-
life-year or quality-adjusted life-year gained. In Ontario, the CED generally considers drugs to be cost-effective if the cost per quality-adjusted life-year gained is in the range of $40,000 to $60,000 or less, a threshold acknowledged as unlikely to be useful or achievable for most expensive drugs developed for the treatment of rare diseases. Estimation of budget impact, however, may be of particular importance at this step. The cost data generated can also be used to inform individual or group funding decisions, more precisely define the “funded” population, develop a budget for a rare disease portfolio, and identify areas for risk sharing to support price negotiations.

**Step 6: Review the drug evaluation with disease experts and stakeholders**

As the proposed process is unique, complex, and variable with the disease and drug under consideration, it is considered essential that independent disease experts not involved in the Working Group review the inputs, assumptions, and outputs to detect areas of significant disagreement or error. This helps to ensure validity of any modeling used. It is also essential that experts and other stakeholders including the public understand the process to facilitate acceptance of its conclusions.

**Step 7: Reassessment**

It is important to continuously review and incorporate new information regarding disease incidence, natural history, and the effectiveness or cost of candidate drug therapy. Potential impact on modeled effectiveness and/or cost-effectiveness estimates should trigger reanalysis with incorporation of the new data.

**Test of the Framework**

The evaluation framework was tested by evaluating idursulfase for mucopolysaccharidoses II (Hunter disease). Hunter disease has an estimated incidence of 1 in 170,000 male live births (1 to 2 births per year in Ontario), meeting criteria for a rare disease for public-funding purposes in Ontario [16] (step 1). It is an X-linked disorder caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase resulting in the accumulation of glycosaminoglycans in tissues and organs, causing the signs and symptoms of the disease [16]. Multiple organs are affected, and both age of onset and rate of progression are variable. Traditionally, Hunter disease patients have been categorized into two types: patients with type A, who have severe primary neurological involvement, which inevitably culminates in death by the end of the second decade of life, and patients with type B, who do not have primary neurological involvement and have reduced life expectancy because of the increased risk of respiratory, cardiac, and cardiorespiratory complications of the disease (step 2).

Idursulfase therapy replaces iduronate-2-sulfatase and satisfies eight of the nine modified Bradford Hill criteria (Table 2), confirming the potential of benefit to patients with Hunter disease. Clinical data have not shown benefit of idursulfase in patients with only musculoskeletal symptoms. However, the same treatment with idursulfase led to agreement with this recommendation against routine use as palliative therapy in patients with advanced multisystem disease. Idursulfase was considered potentially able to arrest or prevent multisystem morbidity and possibly even prolong life if initiated when disease effects were minimal early in childhood. It was also acknowledged that patients destined to develop severe neurological involvement would be unlikely to benefit significantly from therapy. A Markov modeling approach was developed to generate a model of the natural history of the disease incorporating estimates of small, moderate, and large effects of idursulfase therapy (Fig. 2) [17]. This demonstrated that idursulfase might lead to prolonged life expectancy for patients with type B Hunter disease (step 4). For example, if idursulfase treatment reduced disease progression by 10%, 20%, and 50%, life expectancy gains of 1.32, 2.93, and 10.66 years, respectively, were observed for an 11-year-old patient with type B Hunter disease and with only musculoskeletal symptoms. However, the same treatment resulted in life expectancy gains of only 0.03, 0.06, and 0.16 years, respectively, for an 11-year-old patient with type A Hunter disease with severe neurocognitive and respiratory problems.

The per-patient cost of idursulfase is in the range of $375,000 per year. Detailed cost analysis was not done because the drug was not considered cost-effective by conventional criteria even in the most extreme model scenarios. However, the potential life expectancy gains in type B patients were considered highly valued. This was reviewed and approved by the Executive Officer, and a funding algorithm was developed for negotiation with the manufacturer (step 5). A review of the Markov model by content expert physicians was conducted. This led to revision of some assumptions and general approval of the process and its results. The framework was also presented to and approved by the Ontario Public Drug Programs Citizens’ Council (step 6). Negotiations with the manufacturer led to the public funding of idursulfase in Ontario for patients 6 years or older without neurocognitive symptoms, while the manufacturer manages requests for funding for patients younger than 6 years of age in whom the potential effects on life expectancy were far less certain [18]. This has provided an estimate of the annual cost of idursulfase to Ontario Public Drug Programs prioritized to those patients most likely to benefit. No new information informing the model has been identified to date (step 7).

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**Fig. 2 – Schematic representation of Markov model for main health states in Hunter disease. (A) Progression of Hunter disease symptoms. (B) Progression of neurological deficit in Hunter disease.**
Discussion

Our evaluation framework has a number of limitations. It assumes the availability of adequate information about disease incidence and natural history. This may not always be the case. For the case study used to test the framework, a Bayesian approach using Markov modeling was employed to estimate ranges of clinical effectiveness on the basis of outcomes and clinical scenarios not studied in clinical trials. Critics of such an approach might suggest that such estimates are highly speculative and prone to error. However, we feel that this approach is defensible, because it is based on the most contemporary data and expert opinion available relevant to the disease, utilizes reasonable expectations of effectiveness at a point in the disease process when these are most likely to be realized, and can be adapted and updated to include new data about the disease and drug as this information becomes available.

The dilemma of funding drugs for rare disease is not unique to Ontario, and a number of strategies have been proposed [19]. The US Orphan Drug Act provides incentives for pharmaceutical companies to develop drugs; however, individual patients are left to rely on public or private reimbursement programs that are likely not to fund the drugs because of limited evidence and high cost. It has been argued that a more utilitarian approach should be used when it comes to orphan drugs and that rarity of a disease is a limited justification. For example, in the United Kingdom, the primary care trusts of West Midlands commissioned a report on the ethical issues, clinical efficacy, cost-effectiveness, and public perspective on whether to reimburse patients with Fabry disease and other rare diseases for the costs of treatment [20]. It was agreed that rarity was not significant enough a factor to override all other considerations in developing a decision. As a principled argument could not be made to distinguish patients with rare diseases from those with common diseases who also had unmet treatment needs, along with poor cost-effectiveness, the trust denied reimbursement of treatments for Fabry disease and also discontinued reimbursement of treatment for new cases of Gaucher disease. A balance between pure utilitarianism based on cost-effectiveness and patient nonabandonment must be struck, but how this should be done in an evidence-based public health context is uncertain [19].

Conclusions

Our evaluation framework attempts to systematically address the many challenges raised when considering funding new drugs for rare diseases—many of which are expensive—within an evidence-based publicly funded drug program. If it is accepted that it is truly impractical to perform adequately powered randomized clinical trials, then we believe that funding decisions must be addressed in a consistent, fair, and transparent manner. In the case study we have described, modeling of effectiveness supported potential benefits including prolonged life expectancy in a subgroup of patients. This advice led to a unique funding algorithm for this drug in Ontario. This framework is an iterative process that inevitably will require modification with experience. Feedback will be obtained through a series of meetings with patient, physician, and stakeholder groups, the pharmaceutical industry, and other interested parties. This evaluation framework attempts to identify an evidence-derived “middle ground” that is an improvement over arbitrary decisions based on either the absence of specific data or political expediency. It is hoped that it can be of value for the assessment of other drugs in future; however, it cannot be considered a cipher for uncritical assignment of drug therapy.

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REFERENCES