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REVIEW

A journey of hope: lessons learned from studies on rare diseases and orphan drugs

M. WÄSTFELT[1], B. FADEEL[2] & J.-I. HENTER[3]

From the [1]Strategy and Development Office, Karolinska Institutet, Stockholm; [2]Division of Biochemical Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm; and [3]Childhood Cancer Research Unit, Department of Woman and Child Health, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden

Abstract. Wästfelt M, Fadeel B, Henter J-I (Strategy and Development Office, Institute of Environmental Medicine, and Department of Woman and Child Health, Karolinska Institutet, Stockholm, Sweden). A journey of hope: lessons learned from studies on rare diseases and orphan drugs (Review). *J Intern Med* 2006; **260**: 1–10.

Rare diseases are frequently life-threatening or chronically debilitating and the impact on the quality of life of affected patients and their family members is thus significant. However, drug development for these conditions has been limited by a lack of understanding of the underlying mechanisms of disease and the relative unavailability of subjects for clinical trials, as well as the prohibitive cost of investing in a novel pharmaceutical agent with poor market potential. Nevertheless, the introduction of Orphan Drug legislations has provided important incentives for the development of orphan drugs (i.e. drugs that have been abandoned or 'orphaned' by major drug companies). Moreover, recent studies on rare diseases, including inherited immunodeficiencies and metabolic disorders, have served not only to alleviate the plight of patients with rare diseases, but also yielded valuable information on biological processes of relevance for other, more common conditions. These lessons, along with the crucial importance of cooperation between academic institutions, pharmaceutical companies, patient advocacy groups and society in the elucidation of rare diseases, are highlighted in the present review.

Keywords: familial hemophagocytic lymphohistiocytosis, hereditary type I tyrosinemia, orphan drugs, patient advocacy groups, rare diseases, severe combined immunodeficiency.

Introduction

Rare diseases are not so rare. An estimated 25 million North Americans and 30 million Europeans are currently affected by one of the 5000–6000 known rare diseases, most of which are of genetic origin [1]. However, rare diseases have often been neglected by pharmaceutical companies and patients suffering from rare diseases thus have less access to relevant therapy. This situation dates back to the 1960s when amendments were made to existing federal laws in the United States, mandating that all drugs must be shown to be safe and effective through 'adequate and well-controlled studies' before receiving market approval [1, 2]. This condition raised the cost of drug development, and resulted in drugs for small disease

populations being 'orphaned' by many major drug companies. It is thus a paradox of modern society that the lack of options for the treatment of patients with rare diseases results, at least in part, from society's increasing demands for the protection of public health through extensive and expensive testing of novel drugs.

No single definition of orphan diseases exists. The European Union (EU) criterion is a disease with a prevalence of five or less cases per 10 000, whereas in the United States, a disease or condition that affects less than 200 000 individuals in the country is considered to be 'rare' [3]. Rare diseases are often chronic, progressive, disabling, and even life-threatening, and most of these diseases have no effective or curative treatment. Moreover, rare diseases are becoming less and less rare, an apparent conundrum that is explained by our increasing understanding of the underlying pathophysiological mechanisms, resulting in the separation of broad disease categories into smaller and more well-defined disease entities. Hence, about 250 new rare diseases are described each year. This process of fragmentation of disease categories is expected to increase in the future as genomic and postgenomic approaches allow us to further explore the nature of human diseases. Rare diseases, therefore, are not so rare when considering the total number of affected individuals and attention should thus be devoted to the specific problems related to these patients.

In the present review, we will discuss the incentives provided by orphan drug legislations in Europe and the United States, the challenges facing clinical trials for rare diseases, along with a few illustrative examples of rare, hereditary, and life-threatening conditions for which successful therapeutic interventions have been accomplished in recent years. The latter examples will also serve to highlight the importance of cooperation between academic institutions, pharmaceutical companies, patient advocacy groups, and society in the quest for improved diagnosis and treatment of patients with rare diseases.

Orphan drug legislations: incentives for the development of drugs for rare diseases

In order to stimulate the development of orphan drugs, several countries have implemented legislations and directives that provide incentives to drug companies to develop medicinal products for rare diseases. These incentives may include market exclusivity up to 10 years, tax credits and fee reductions, accelerated marketing procedures, and scientific and technical support (Fig. 1). Importantly, orphan exclusivity is often considered to be a more comprehensive incentive than a patent (which requires that a drug is novel and its production 'nonobvious'); drugs that would ordinarily not be eligible for patent protection might thus be eligible for orphan exclusivity pending orphan drug designation and product approval [2].

The Orphan Drug Act (ODA) was passed by the United States congress in 1982 and signed into law in 1983, and has had a significant impact on public health [1]. Hence, in the 24 years since this

Fig. 1 European Union incentives for orphan drug development. Figure reprinted with permission from Thomas Lönngren (European Agency for the Evaluation of Medicinal Products).

pioneering law was passed, more than 280 drugs have become available to patients with rare diseases in the United States, whereas in the 8–10 years prior to the orphan drug legislation, only 10 treatments for rare diseases were approved by the Food and Drug Administration (FDA) and brought to the market [2]. The two largest groups of orphan drug designations are for rare forms of cancer and metabolic disorders, which account for approximately 30% and 10%, respectively, of all such designations; an estimated 50% of all orphan products approved to date are for paediatric use [2]. The success of the ODA has inspired the implementation of orphan drug legislations in other countries in order to address the needs of patients suffering from rare diseases. Similar legislations are thus in force in Singapore (1991), Japan (1993), Australia (1998), and more recently, within the EU (2000). The 1st International Conference on Rare Disease and Orphan Drugs (ICORD), jointly organized in 2005 by the European Commission, the Office of Rare Diseases (ORD) at the National Institutes of Health, and Karolinska Institutet (Stockholm, Sweden) was aimed at disseminating and sharing experiences within the field of orphan drug development in the United States and other countries, and a second conference in this series is scheduled for 2007.

The ODA has not only had a positive impact on the lives of patients and families with rare diseases, but has also contributed to the development of innovative biotechnology products such as diagnostic and therapeutic monoclonal antibodies and gene therapies [discussed below, in the context of severe combined immunodeficiencies (SCID)], as well as to the growth of the biotech industry and the evolution of numerous small and medium-sized enterprises (SMEs). There are currently more than 110 pharmaceutical companies in the United States that have received FDA marketing approval for at least one orphan drug, and several well-known biotech companies, including Genentech, Amgen and Genzyme Corporation, have started out with an orphan drug as their first drug to receive marketing approval [1]. Moreover, amongst the 10 best-selling biotech drugs worldwide in 2001, five were originally approved as orphan drugs (erythropoeitin for anemia, interferon-β for multiple sclerosis, rituximab for non-Hodgkin's lymphoma, somatotropin for growth disorders and infliximab for Crohn's disease), and three others were approved for orphan indications in addition to the original use [4, 5].

A drug or medical product intended for use in the treatment of rare diseases becomes an orphan drug when it receives designation as an orphan medicinal product or orphan drug from e.g. the Committee for Orphan Medicinal Products (COMP) at the European Agency for the Evaluation of Medicinal Products (EMEA) or the Office of Orphan Products Development at the FDA in the United States. Orphan drug designation qualifies the sponsor to receive the benefits, including market exclusivity, specified above. The request for orphan drug designation can be made at any stage of drug development, as soon as sufficient scientific evidence is available. The drug may thus be in the preclinical stage (not yet tested on human subjects) or may have reached the stage of clinical trials (discussed below). Pharmaceutical companies may also seek orphan status for a drug which is already in clinical use for a more frequently occurring disease, if efficacy of this drug in the treatment of a rare disease can be demonstrated. Patient access to orphan drugs is sometimes complicated by the fact that marketing approval, e.g. in the EU, does not mean that the drug is necessarily available in all EU countries. However, early access to an orphan drug prior to marketing authorization can be granted in the EU under certain conditions and for a specific patient group. Moreover, the FDA can enable manufacturers of orphan drugs to provide for expanded access to patients who may benefit from treatment, even when the patients in question do not qualify for clinical trials.

Orphan drug legislations are not limited to drugs for rare diseases. Hence, orphan drug incentives may also be implemented for conditions that are not classified as being 'rare' but for which the cost of drug development and marketing would not be economically viable without such incentives. For instance, tropical diseases and other diseases that specifically affect populations in developing countries, including several major diseases linked to poverty, may fall into this category [6]. These diseases are neglected, but not rare, and development and distribution of drugs for such conditions remains an important challenge.

Clinical trials for rare diseases: platforms for cooperation are provided by public networks for rare diseases

Clinical trials for drugs in orphan populations are subject to the same requirements for ethical conduct, efficacy and safety as other drugs. However, investigators performing trials of orphan drugs are faced with several challenges that are not usually encountered in clinical trials of larger populations [1]. Obvious drawbacks include the small size of the trial population and the fact that patients are often geographically dispersed. In Europe, obstacles also include problems of coordination in a multi-lingual and multi-cultural continent with a diversity of healthcare systems. On the other hand, orphan drugs may often receive priority review status as most orphan drugs are intended for the treatment of life-threatening conditions; moreover, the smaller number of patients enrolled in these clinical trials results in less data to be reviewed and might account for a more rapid approval time, at least for some orphan drugs.

Randomized, double-blind, placebo-controlled studies (i.e. the gold standard of clinical trials) are not always possible to perform in the setting of rare diseases, and alternative study designs are often required. Moreover, to show efficacy in a study with a very small number of patients, products might need to show a more robust treatment effect than in large studies. To recruit a sufficient number of patients for investigations of an orphan drug, these clinical trials often need to be conducted at multiple sites. Such multi-centre studies require careful coordination and harmonization through national or international networks of centres or clinics. The Rare Diseases Act, signed into law in the United States in 2002, provided a legislative mandate to establish the ORD within the National Institutes of Health. The ORD provides support for the Rare Diseases Clinical Research Network (RDCRN), consisting of 10 clinical research consortia and a Data and Technology Coordinating Center (Fig. 2). The aim of the RDCRN is to facilitate collaboration amongst experts on several groups of rare diseases and create platforms for collaboration in order to identify biomarkers for disease risk, disease severity and activity, and clinical outcome. These consortia also encourage the development of new approaches to diagnosis, prevention and treatment of rare diseases. In addition, the ORD provides support for basic and clinical research on rare diseases and supports the activities of patient advocacy groups such as the Genetic Alliance and the National Organization for Rare Diseases (discussed below). The European Clinical Research Infrastructures Network is a similar initiative aimed at creating European networks of clinical research centres and

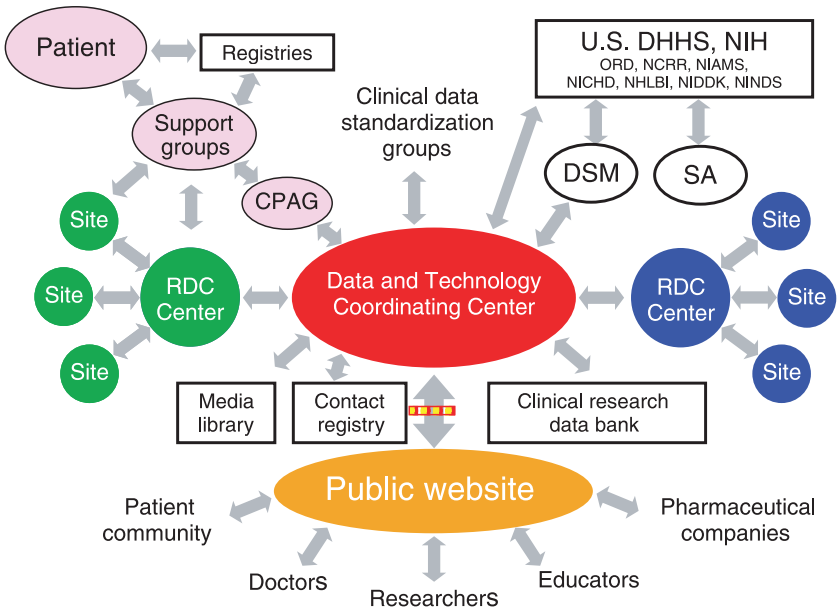

Fig. 2 Organization of the Rare Disease Clinical Research Center Network in the United States. Figure reprinted with permission from Dr Stephen Groft (Office of Rare Diseases, National Institutes of Health).

clinical trial units spanning all fields of medicine. These centres are closely associated with scientific associations and investigators and act through specific networks of practitioners to recruit patients to clinical studies, in particular in the field of rare diseases.

Most of the companies that file applications for orphan drug designation are SMEs. These companies often have a limited geographical reach with poor access to patients and limited regulatory and clinical trial experience. The European Center for Clinical Trials in Rare Diseases is a nonprofit organization that provides services for drug development for SMEs and other companies, as well as training in good clinical practice (GCP) and good laboratory practice (GLP) adherence. http://clinicaltrials.gov, a website developed by the National Library of Medicine, provides updated information on clinical research in humans. http://centerwatch.com is a for-profit organization in the United States which collects information on clinical research and clinical trials as a resource for research professionals as well as patients interested in participating in such trials. EudraCT is a database of all clinical trials within the EU, and is accessible only to the competent authorities of the Members States, the EMEA and the European Commission.

Disseminating information to patients and to professionals in health care, academia and the pharmaceutical industry remains an important issue, in order to continue the quest for safe and efficient drugs for all patients with rare diseases. There is also an urgent need for more international concerted actions in clinical research in this field. In addition, a simplification of the procedures for clinical trials might enable further investigations of drugs for patients affected by very rare disorders.

Lessons learned from studies of severe combined immunodeficiencies: the long and arduous path from basic science to novel therapeutic approaches

Studies on rare diseases may have several beneficial effects, apart from facilitating the diagnosis and treatment of the specific condition in question. First, rare diseases are often of genetic origin, i.e. they are caused by inherited deficiencies of normal human biology; revealing the underlying cause of a rare disease may thus teach us more about normal biological processes. Secondly, novel therapeutic approaches that are developed for a rare disease may turn out to be applicable also in the treatment of other, more common diseases. In addition, the establishment of partnerships between academic researchers/clinicians, pharmaceutical companies, patient–parent support groups and government agencies to solve problems related to rare diseases may also serve as a paradigm for the studies of other diseases. Some examples of basic and clinical investigations that have resulted in the successful treatment of patients afflicted with rare diseases are discussed in the following sections.

Inherited human immunodeficiencies represent a formidable challenge for both clinicians and scientists; however, refined and persistent investigations of these conditions may nurture new avenues in basic immunological research and serve as a disease model for novel therapies targeting the immune system [7]. Indeed, there are few short cuts in the field of rare diseases; each of these uncommon conditions requires meticulous molecular and clinical studies including a detailed description of the natural history of the disease, delineation of the underlying pathophysiology, and finally the development of new therapeutic approaches, and studies on human immunodeficiencies may serve as a template for such investigations. SCID, with an approximate incidence of 1 child in 1×10^5 live births, are characterized by a genetically determined arrest of T-cell differentiation and early death in the absence of therapy; 11 distinct SCID phenotypes have been identified to date along with 10 distinct underlying molecular defects [8]. Transplantation of allogeneic haematopoietic stem cells (HSCT) can restore T-cell development, thus saving the lives of these SCID patients. In fact, SCID was the first disease to be successfully treated by HSCT more than 35 years ago [9]. Furthermore, recent studies have indicated the possibility of gene therapy-based cures for SCID, as an alternative to stem cell transplantation.

Severe combined immunodeficiency-X1 (SCID-X1), also known as gamma chain (γc) deficiency, is an X-linked inherited disorder characterized by an early block in T and natural killer lymphocyte differentiation. Researchers/clinicians at the Necker Hospital (Paris, France) initiated a gene therapy trial for SCID-X1 in 1999, based on retrovirus-mediated γc gene transfer into autologous $CD34^+$ bone marrow cells. Amongst the first 10 treated patients

with typical SCID-X1, T-cell development occurred in nine [10]. Similar results were obtained in a study of four additional patients treated in London (UK) according to a similar protocol [11]. These gene therapy studies have provided hope of sustained T-cell immunity in SCID patients, which could potentially be of much longer duration than what is observed after HSCT in these children [8]. Of course, long-term monitoring of the immune status of SCID patients who have undergone gene therapy will be necessary to validate this prediction. The efficacy of gene therapy has also been reported in the treatment of four patients with adenosine deaminase (ADA) deficiency, a variant of SCID in which premature lymphocyte apoptosis is triggered by a purine metabolism defect [12].

There are, however, some limitations to gene therapy of SCID. Two patients from the original SCID-X1 gene therapy trial developed an uncontrolled clonal proliferation of mature T cells almost 3 years after treatment. It was subsequently determined that this was caused by insertion of the retrovirus within the LMO-2 locus, leading to aberrant transcription and expression of the proto-oncogene LMO-2 [13]. The development of safer vectors for gene therapy therefore remains an important task for scientists/clinicians in this field. Studies of SCID nevertheless represent a major breakthrough in modern medicine insofar as a novel therapeutic tool (gene therapy) has been made available through the detailed and systematic study of these rare patients. Furthermore, studies of the underlying molecular defect in SCID patients with ADA (a condition resulting in the accumulation of toxic purine metabolites) have led to the development of a new cytotoxic drug, 2-chlorodeoxyadenosine, that is now used to treat more common diseases, including certain leukaemias and lymphomas [8].

Detailed investigations of rare patients with inherited breaches in immune homeostasis have thus yielded numerous important lessons. These studies serve to underscore the need for clinical reference centres of expertise on rare diseases, as well as the importance of international collaborative efforts, a multi-disciplinary approach to research, and interactions between scientists/clinicians and dedicated pharmaceutical companies. The European Rare Disease Therapeutic Initiative, through which academic researchers are provided access to compounds of interest developed by pharmaceutical companies [14], provides an illustrative example of the emerging partnerships between academia and industry.

Lessons learned from studies of familial haemophagocytic lymphohistiocytosis: role of patient–parent advocacy groups in promoting research on rare diseases

There are few areas in medicine in which patient–parent advocacy groups play such a central role as in the field of rare diseases and orphan drugs. Indeed, patient–parent support groups were instrumental for the introduction of the ODA in the United States, and these organizations remain key players in providing patient–parent perspectives on rare diseases.

The two largest patient–parent advocacy groups in the United States are the National Organization for Rare Disorders (NORD) and Genetic Alliance (see Table 1 for the websites of these advocacy groups). NORD is a federation of voluntary health organizations dedicated to helping people with rare orphan diseases. Since the inception of its research programme, NORD has awarded approximately 4.5 million USD to fund 110 grants and fellowships. The programme aims to provide 'seed money' to academic researchers studying new treatments or diagnostics for rare diseases. Researchers can then use the preliminary data to apply for larger multi-year government grants or to attract a commercial sponsor in order to produce and market novel orphan drugs. Genetic Alliance is a coalition of more than 600 patient organizations, and serves to leverage the voices of millions of individuals who are affected by genetic diseases, in part by increasing the awareness of rare diseases in congress and government agencies. The organization has also sponsored the Genetic Alliance BioBank, which aims to make biological samples and data available to academic researchers.

The European Organization for Rare Diseases (EURORDIS) is a patient-driven alliance of patient organizations, covering over 1000 rare diseases and representing millions of individuals living with a rare disease. A partnership is evolving between patient advocacy organizations and European regulatory authorities, and patient representatives thus play an active role in COMP and also contribute to

Table 1 Some useful websites related to rare diseases

http://www.centerwatch.com	A for-profit website listing more than 40 000 active industry and government-sponsored clinical trials
http://clinicaltrials.gov	A website developed by the National Library of Medicine, to provide information on federally and privately supported clinical research in human volunteers
http://www.emea.eu.int	Website of the European Agency for the Evaluation of Medicinal Products, with information on COMP, the Committee for Orphan Medicinal Products
http://www.erditi.org	Website of the European Rare Diseases Therapeutic Initiative, providing access to academic researchers of compounds developed by pharmaceutical companies
http://www.eudract.emea.eu.int	A database of all clinical trials commencing in the European Community from 2004 onwards
http://www.euorphan.com	Website providing information services in support of the orphan medicine market in the European Union
http://www.eurobiobank.org	Website of the European network of DNA, cell and tissue banks for rare diseases, financed by the European Union under the Fifth Framework Programme for Research and Development
http://www.eurocat.ulster.ac.uk	Website of the European network of population-based registries for the epidemiological surveillance of congenital anomalies
http://www.eurogentest.org	Website for the European network for genetic test development, harmonization, validation and standardization
http://www.europabio.org	Website of the European Biotechnology Industry Association, representing 40 globally operating biotechnology companies and 24 national associations
http://www.eurordis.org	Website of the European Organization of Rare Diseases, an alliance of more than 200 patient associations
http://www.fda.gov/orphan	Website of the Office of Orphan Products Development at the US Food and Drug Administration
http://genetests.org	Website funded by the NIH, providing medical genetics information for physicians, researchers, and other health care providers
http://www.geneticalliance.org	Website of Genetic Alliance, a US-based consortium of national voluntary organizations for individuals and families who have genetic disorders
http://www.histio.org	Website of the Histiocytosis Association of America, with links to numerous other national patient-parent organizations devoted to the histiocytoses, and to the professional Histiocyte Society
http://www.icord.cc	Official website of ICORD 2005, the 1st International Conference on Rare Diseases and Orphan Drugs
http://rarediseases.info.nih.gov	Website of the Office of Rare Diseases at the National Institutes of Health, with numerous resources on rare diseases
http://www.rarediseasesnetwork.org	Website of the Rare Diseases Clinical Research Network, a US-based network of clinical research consortia
http://www.rarediseasetesting.org	Website of the National Laboratory Network for Rare Disease Genetic Testing, with member laboratories in the United States and Canada
http://rarediseases.org	Website of the National Organization for Rare Disorders, a federation of voluntary health organizations dedicated to helping people with rare diseases
http://www.orpha.net	The European database of rare diseases and orphan drugs, with an encyclopaedia of 1000 rare diseases, and a directory of services available in Europe
http://www.orphanxchange.org	A directory of academic research projects seeking industrial partnership, in the field of rare disease therapy and diagnosis
http://www.who.int/medicines	The World Health Organization website for essential drugs and medicines

protocol assistance and risk benefit assessments within the frame of the EMEA. EURORDIS also directly fosters patient-centred research on rare diseases, and were involved in the organization of the European Conference on Rare Diseases held in Luxembourg last year.

The Histiocytosis Association of America (HAA) was founded in 1986 by the parents of an affected child, and serves to further illustrate the impact of patient–parent advocacy groups on basic and clinical research on rare diseases. This partnership of patients, families, doctors and friends currently has more than 5000 registered members and aims to support patients and their families, to promote education related to the childhood histiocytoses, and to foster research directed at finding a cure for these rare conditions. Remarkably, over 80 research projects to date have been funded, at least in part, by this association. HAA also serves as the administrative secretariat for the Histiocyte Society, an international professional society of clinicians and researchers devoted to these particular childhood disorders.

Familial haemophagocytic lymphohistiocytosis (FHL) is a rare autosomal recessive disease, and is invariably fatal when untreated with a median survival of only 1–2 months after diagnosis [15]. FHL has an estimated incidence of approximately two children in 1×10^5 live births, and it may thus appear difficult to perform meaningful clinical studies on this disease. However, under the auspices of the Histiocyte Society and with the support of the HAA, successful international studies have been performed in recent years. FHL was first described as a clinical entity in the 1950s, and three different underlying molecular defects (affecting the genes encoding perforin, Munc13-4 and syntaxin proteins respectively) have been revealed in the last 5 years or so. Importantly, each of these inherited deficiencies has served to shed light on the role of pro-apoptotic responses in the regulation of normal immune homeostasis [16]. However, 10–15 years ago almost all children with FHL died of their disease, sometimes without receiving an appropriate diagnosis. The Histiocyte Society, founded in 1985, developed diagnostic guidelines for FHL, and initiated the first prospective international therapeutic study of this disease in 1994. The treatment protocol combined chemotherapy and immunotherapy regimens, followed by HSCT. A total of almost 240 eligible patients from more than 20 countries were included between 1994 and 2003, and the estimated 3-year probability of survival for these children is now more than 50% [17, 18]. Hence, although FHL is a rare disease, large series of patients and meaningful statistical analyses are feasible through international collaboration within the framework of clinical studies that are supported, in part, by active parent organizations.

Finally, based on the remarkable success of the treatment protocol for primary as well as virus-associated secondary forms of histiocytosis syndromes [19], it was recently hypothesized that a similar protocol of cytotoxic therapy might also be beneficial in the treatment of severe avian influenza A (H5N1) infection [20]. Although not tested to date, this proposal nevertheless illustrates how clinical studies on rare diseases may generate unanticipated ideas and hypotheses of potential relevance for diseases in other fields of medicine.

Lessons learned from studies of hereditary type I tyrosinemia: importance of cooperation between academic institutions and biotech companies

The EU Orphan Drug regulation, inspired by the success of the ODA in the United States, has had a promising start: more than 250 orphan drug designations thus far when compared with nearly no EU-developed products before the regulation was in force. Orphan drugs are often developed by small biotech enterprises, and are at the basis of many biotech companies, as mentioned in a previous section. The discovery of the orphan drug nitisinone for treatment of tyrosinemia type I, a metabolic childhood disease, serves as an intriguing success story in the field of rare diseases, and also provides an instructive example of drug development supported by orphan drug legislations, and of the importance of close interactions between clinicians/academic researchers and pharmaceutical companies.

Tyrosinemia type I is an inherited, life-threatening disease caused by a deficiency of fumarylacetoacetase (FAH), the last enzyme of the tyrosine degradation pathway [21]. The disease is characterized by progressive liver disease, and preclinical studies suggest that this is associated with an accumulation of pro-apoptotic metabolites in FAH-deficient hepatocytes [22]. In children who do not succumb to liver failure, there is an increased risk for

hepatocellular carcinoma (HCC) and survival beyond adolescence is extremely rare. Tyrosinemia type I was recognized as a disease entity during the 1960s, but the primary cause of the disease was unknown until the 1970s. Dietary and supportive therapy may be life saving in acute cases, but does not prevent a progressive course of the disease and liver transplantation remains the only cure. During the late 1980s, the ICI Central Toxicology Laboratory discovered that a group of herbicidal chemicals were potent inhibitors of tyrosine degradation. Importantly, it was noticed that rats exposed to these chemicals developed corneal lesions, a hallmark of elevated blood tyrosine levels in both rats and humans. Soon thereafter it was realized that such a chemical might be an effective drug for the treatment of tyrosinemia type I. The rationale for this approach is to stop the flux through the tyrosine catabolic pathway at an early step in order to prevent the production of toxic metabolites that accumulate due to the inherited enzyme deficiency [23]. Thus, in 1991, a critically ill infant was given NTBC [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, or nitisinone]. The response to treatment in this patient was dramatic, and the trial was soon extended to include four other subacute or chronic cases, all of whom responded well, with an improvement of liver function [24].

Based on these promising results, a long-term clinical study was initiated by academic researchers/clinicians with the intention to evaluate whether nitisinone treatment could serve as an alternative to liver transplantation. Approximately 400 patients worldwide have now been included in the study and 320 of these have ongoing nitisinone treatment [23]. Nitisinone has been shown to be most effective in patients when treatment is initiated early during the course of the disease. In patients identified by neonatal screening and with an immediate start of nitisinone treatment there have been no deaths to date and no development of HCC. Moreover, adverse events are few and have in no case required interruption of therapy [23]. Of note, nitisinone was developed, marketed and distributed by a small biotech enterprise (Swedish Orphan) founded in 1988 as a direct result of the financial incentives provided by the Orphan Drug legislation in the United States, and was approved by the FDA in 2002. The drug also received orphan drug status in the EU in 2005 (i.e. some 15 years after the first patient had received this treatment).

Nitisinone, originally deemed an unsuccessful herbicide, has thus improved the outcome of a rare and devastating childhood disorder [25]. Importantly, as in the case of development of novel and life-saving therapies for SCID (discussed above), these important advances in the management of patients with tyrosinemia type I were based on persistent and detailed studies of the underlying pathophysiological mechanism of the disease, and on international clinical trials, in the latter case with support from a small orphan drug company.

Concluding remarks

Several goals in the area of rare diseases and orphan drugs have been fulfilled in recent years. For instance, rare diseases are now on the political agenda, there are active and well-organized patient–parent advocacy groups, pharmaceutical companies including small biotech enterprises committed to the development of orphan drugs have emerged, and public funding is becoming available for basic research as well as clinical trials on rare diseases. However, there are also some remaining challenges. Dissemination of the awareness of the generous financial incentives provided both to academic institutions and biotech companies by orphan drug regulations remains an important task. Similarly, it is important to also embrace the development of treatments for neglected diseases in developing countries. International networks and partnerships such as those described herein will be particularly valuable for such conditions. Along these lines, the ICORD organized recently by the European Commission, the ORD at the National Institutes of Health, and Karolinska Institutet (Stockholm, Sweden), has provided an important platform for academia, patient organizations, pharmaceutical companies, and public authorities and policymaking bodies working towards the common goal of improved diagnosis and treatment of rare diseases. Future perspectives in this field include increasing the awareness of rare diseases throughout society, as well as increasing the equitable and timely access to orphan treatments for these conditions. Finally, as emphasized in the present review, further basic and clinical studies on rare diseases may not only facilitate the diagnosis and

treatment of the specific condition in question, but are also likely to yield important lessons of considerable relevance for our understanding of normal biological processes and the treatment of more common diseases.

Conflict of interest statement

The authors have no conflict of interest to declare.

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Correspondence: Jan-Inge Henter, Childhood Cancer Research Unit Q6:05, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden.
(fax: +46 8 5177 3184; e-mail: jan-inge.henter@ki.se).