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HEADING: DRUG AND ORPHAN DISEASES

Collaboration between academics, small pharmaceutical company and patient organizations in the development of a new formulation of cysteamine in nephropathic cystinosis: A successful story.

A successful collaboration in rare disease clinical research

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Summary Rare diseases usually concern small and disseminated population. Implementing clinical research with the right design, outcomes measures and the recruitment of patients are challenges. Collaborations, training and multidisciplinary approach are often required. In this article, we provide an overview of a successful collaboration in nephropathic cystinosis (NC), focusing on what was the key of success, the interactions between academics, the pharmaceutical company and patients organizations. NC is considered as a very rare disease. In 2010, a new formulation of cysteamine, the only available treatment to improve renal outcome of the disease, was proposed by a small American company. Studies were implemented in France under the coordination of an expert of the disease and the clinical investigation center of Lyon. The collaboration resulted in a good recruitment and retention of the patients in the study and most of all in the availability of the new formulation in France. Patients could have facilitated the research by being involved in the early stages of the studies. Involving patients and public early in the process is particularly important in rare diseases as the patient is a great source of knowledge and has his own expectations. Priorities of research, design, conduct and reporting of clinical trials can be defined in collaboration with adults but also with young patients or public, the first concerned in rare diseases. This concept is still to be developed and improved especially with paediatric patients.

KEYWORDS

Rare diseases; Multidisciplinary approach; Patient advocacy; Nephropathic cystinosis; Clinical research

ABBREVIATIONS

CIC: clinical investigation center

EC: European Commission

EMA: European Medicine Agency

ESRD: end-stage renal disease

FDA: Food and Drug Administration

NC: nephropathic cystinosis

PD: pharmacodynamic

PK: pharmacokinetic

US: United States

WBC: white blood cell

Introduction

Rare diseases are defined as conditions affecting 1 out of 2000 people or less. The currently known rare diseases affect about 30 million people in Europe, a number probably underestimated [1, 2].

Rare diseases usually concerned small and disseminated populations. Thus, implementing clinical research is challenging. Design and outcome measures should be adapted to small population and appropriate outcomes should be defined to meet patients 'expectations and competent authorities' requirements [3]. Another issue is about patient recruitment which often requires multicenter, multinational trials and a complex logistic approach for the implementation of clinical trials [4]. In addition, there are few medical experts of one particular disease so not many potential investigators for clinical research. Funding remains also an issue as few budgets are dedicated to the development by pharmaceutical companies and few institutional budgets are available. Also coordination of the budgets should be at a larger scale than national level [5, 6].

Collaborations are often needed at different levels: investigators experts of the disease, sponsors, trained clinical research staff and patients themselves [7, 8]. A multidisciplinary approach is also required by the condition affecting the patients so implementation of research may require different categories of physicians or healthcare professionals on one site.

Objectives

The objective of this article is to provide an overview of a successful collaboration in the field of rare diseases: nephropathic cystinosis (NC). We present here the context and the way the development was performed and how studies were implemented in France trying to focus on what was the key of success and what could be improved.

Context

Development of a new formulation of cysteamine in nephropathic cystinosis

Cystinosis is an inherited autosomal recessive disease (Gahl et al [9]). It is considered as a very rare disease with a prevalence estimated around 1 case per 100 000 to 200 000 living births in developed nations [10]. It has been identified as a generalized lysosomal storage disease linked to a molecular defect of a transport protein, cystinosin [9]. The diagnosis of NC is confirmed by increased cystine levels in leukocytes (above 2 nmol half-cystine/mg proteins, normal < 0.2) and genetic analyses [9].

Patients usually present during the first six months of their life with a Toni-Debré-Fanconi syndrome leading to a progressive chronic interstitial nephritis and then to end-stage renal disease (ESRD) in the first decade of life [11, 12]. Since the 1980's, cysteamine therapy has improved renal outcomes by delaying progression of ESRD and other extrarenal complications to the second and third decade of life [10,13].

Until the 2010s, the only available treatment was a short acting formulation to be taken 4 times a day, every 6 hours strictly. The main side-effects of this treatment were breath and body odour, nausea, vomiting, drowsiness. Because of these side effects, the daily regimen (4 times a day) and the need for a life-long treatment, the patient's adherence to the treatment was not good [14]. Levtchenko et al demonstrated that only about 25% (5 of 22) of patients were actually compliant with the 4 times a day regimen [15]. Moreover, there is evidence that failure to adhere to this strict 4 times a day regimen results in rapid deterioration of kidney function [16]. Thus, improving patient adherence should ultimately delay the time to kidney failure or the morbidity and mortality associated with renal replacement therapy such as dialysis or transplant, and hence greatly improves both the patient's quality and quantity of life.

In 2010, a small American company (Raptor pharmaceuticals) launched a program to develop a new formulation of cysteamine. The pharmaceutical company developed a delayed-release formulation of cysteamine as encapsulated, beaded, enteric-coated, bitartrate salt of cysteamine for oral administration.

Seven clinical studies were part of the development plan discussed with the American Food drug Administration (FDA) to allow marketing authorization of this new formulation in the United States (US) and in Europe. The first study was performed on a restricted number of subjects in the US to determine pharmacokinetic (PK) and pharmacodynamic (PD) parameters as well as potential safety and tolerability of the treatment compared to the existing formulation [17]. Four bioequivalence studies were performed in fasted and fed healthy volunteers in the US only to demonstrate bioequivalence of open capsules versus whole capsules and interactions of food or Proton Pump Inhibitors with the new formulation of cysteamine [18, 19].

Two main studies were performed in NC patients worldwide, including France. The first one was an open-label randomized cross over trial to evaluate the non-inferiority of the delayed release

formulation compared to the short acting cysteamine, for the maintenance of leukocyte cystine levels under 1 nmol half-cystine/mg protein. The second one was an open label, single-arm long term safety study [20, 21].

Coordination of the study and collaboration between sponsor and academics

As few specialist physicians were available worldwide, the study needed to be multinational and multicenter. The site of Lyon was selected to be an investigation site among 8 other sites worldwide. A greater collaboration was decided based upon the experience of Lyon in NC and the lack of experience of the company in clinical research performed in Europe, at that time. The clinical investigation center (CIC) of Lyon was selected to coordinate the study in France, with the local physician (Pr Pierre Cochat). Three other sites were implemented in France (2 in Paris and 1 in Montpellier), all having a CIC as supporting research structure. A CIC is a structure which allows physicians and sponsors to perform research projects, providing resources to perform clinical research [22].

All sponsor study activities, except submissions to competent authorities, were delegated to CIC, including submissions to the French central ethic committee, adaptation of the study protocol and documents to local requirements, pharmacovigilance (through the hospital vigilance unit in the University hospital of Lyon), coordination and monitoring of the four French sites, ensuring the study was conducted in conformity with GCP and French law.

The recruitment rate in the first randomized controlled crossover trial was very good: 43 patients were randomized in one year. Under CIC coordination, France enrolled 13 patients i.e. 30% of the patients randomized in the study, in 2 months. Twenty-three (38%) out of 60 patients entered the long term safety study in France.

Discussion

Coordination was performed with CIC network procedures following local regulation and good clinical practice guidelines [23]. The advantage of working with CIC of Lyon was: (1) its knowledge of the French regulation and experience in coordination; (2) its connections with other French CIC which participated as local investigation centers, helping investigators to perform the study on sites.

A good recruitment was possible through collaboration between the investigators and the clinical investigation centers (CIC) network offering access to research facilities to investigators and sponsors. As a result of these collaborations, the audit from the FDA which was performed during the course of the study resulted in no notes for the audited site in Paris. The CICs make it possible to carry out studies satisfying the quality standards required by the authorities. Also, two publications resulted from this collaboration.

Moreover, coordinating these studies in France and collaborating with patients and investigators allowed the CIC team and the coordinating investigator to propose a research to better understand adherence to cysteamine and late complications of the disease: the CrYSTobs clinical research. This study enrolled 17 French patients, most of them already included in the studies on the new formulation of cysteamine. The study visits were proposed at the same timing in order not to add any constraints for the patients. Examinations specifically performed for the CrYSTobs study (adherence measurements, MRI, neuropsychological testing, blood samples, urinary samples...etc...) were proposed when patients were already scheduled at hospital for the main studies. This system allowed the participation of a rather important number of patients in our physiopathological study. Participation would have been more difficult in the CrYSTobs study which did not propose any therapeutic solution to the patients but only explorations to better understand the disease and its complications. Preliminary results of this study, particularly on neurological complications, were presented to patients and their families as well as the community. Exploring neurological complications and providing new information was expected by the NC population who is currently facing this late complication of the disease (first results submitted).

Involvement of patients and collaboration with an academic coordination centre

The recruitment in the study was greatly facilitated because the expectations of the patients were very high. The twice daily formulation was highly demanded by patients and their families because of the difficulties in adherence and the reality of the progression of the disease. With the previous formulation, patients had to be awakened in the middle of the night to take their medication to maintain adequate white blood cell (WBC) cystine levels. Emerging from the University of California Los Angeles, the sponsor was directly collaborating with the physicians on the new formulation of cysteamine. Even though patients and patients' organizations worldwide were not involved in the design of the project, the recruitment rates in both studies were very good.

As there were few sites per country, patients wishing to participate had to travel sometimes more than 100 kilometers away from home. At the beginning of the cross-over study, patients had to come to hospital 8 times in the first month, staying up to 4 days in a row for some visits. After that, their visits were scheduled every three months until availability of the product in the patients' country. There are several challenges with this type of organization: (1) Because of the distance, travel advances could be prohibitive for patients. A system had to be found to allow patients' reimbursements in a timely manner. A research organization independent from the sponsor was chosen by the investigators and the coordination center; (2) Patients and their families had to engage to come every three months for study visits at hospital, on a long term. Psychological considerations had to be taken into account. Some patients did not have a regular follow-up before their enrollment in the study, some had left their standard of care follow-up for several years before volunteering for a research, others had high expectations related to this new formulation: better tolerance, greater quality of life...etc...This has been previously highlighted in the literature as an issue for the retention of patients in a study. In this case, the new formulation did not have a better tolerance profile nor resolved the side effects of cysteamine. Two French patients early-terminated the study however most of them remained with the new formulation until availability in France.

As for many rare diseases, the evaluation of the new formulation marketing authorization application by French health Authorities was considered quite long by the patients. One reason was that the studies were not designed to assess properly the impact of the new formulation on quality of life and patient related outcomes. Complementary analyses of adherence to treatment provided by an ancillary study performed only in French patients helped providing more information to resolve the issue. The patients' organizations also played an important role by pushing further the discussion to express the patient's point of view, the impact on quality of life, insufficiently taken into consideration into the studies [24].

Keeping patients aware, informed and collaborating with them was the objective of the coordination center. Information on study progress were sent through specific newsletter, social media of the patients' organizations and through several meetings with patients and patients' organizations scheduled during the study. During these meetings dedicated to NC, patients were involved by presenting their experience with the new formulation or discussing other aspects of the disease or their participation in the study. Information on study progress and drug availability were given. When available, study results were presented [7].

Conclusion

This example of collaboration between sponsor, academics and patients was a success with the marketing authorization obtained for the new formulation of cysteamine in 2013 and most of all its availability in France in 2018. This was a long process during and after the studies. It could not have been a success without these collaborations. The availability of the new product in France could have been facilitated with patients' related outcomes such as quality of life, adherence to treatment more clearly defined and assessed in the studies. The patients and public themselves could have been of a great help in the conception of the protocol [24]. Personally, this successful approach and collaboration contributed to the PhD I'm currently doing on the involvement of young persons advisory groups in paediatric clinical research.

Involving patients and public early in the process, particularly in rare diseases as the patient is a great source of knowledge and has his own expectations is needed [25]. Priorities of research, design, conduct and reporting of clinical trials can be defined in collaboration with adults but also with young patients [25, 26] as they are the first to be concerned by rare diseases. Patients and public, whatever their age, can be involved as early as possible in clinical development: from prioritization of research to dissemination of study results and Health authorities' evaluations.

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Disclosure of interest

Authors have no competing interest to declare

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