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Health-Related Quality of Life Measures in Genetic Disorders: an Outcome Variable for Consideration in Clinical Trials

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Abstract

The field of medical genetics is rapidly advancing, and therapeutic options to treat genetic syndromes are becoming increasingly available. An understanding of the pathophysiology of various genetic disorders has provided researchers the opportunity to propose and test pharmacologic agents in preclinical murine models with hopes of translation to human trials. The development of clinical trials can be costly and time consuming, particularly for rare conditions. Pilot feasibility studies should be performed when designing clinical trials for genetic disorders. The development and selection of appropriate outcome measures are particularly paramount in the implementation of clinical trials. The selection of inappropriate outcome measures can lead to non-measurable differences or clinically insignificant findings. In addition, just as age appropriate measures are needed, some instruments may not apply to populations with specific genetic disorders that have significant cognitive and physical impairment, as the measures may not be sensitive enough to identify clinically significant changes. In the last decade health-related quality of life measures (HRQOL) have been increasingly included as an outcome measure in clinical trials. While traditional clinical outcomes are important, these newly developed instruments should be considered along with clinical indicators as measures of effect in clinical trials of interventions in genetic disorders.

Keywords

NF1; quality of life; clinical trials

INTRODUCTION

The field of medical genetics is rapidly advancing and therapeutic options to treat genetic syndromes are becoming increasingly available. The possibility of offering interventions that treat genetic disorders is an exciting prospect for medical geneticists and should provide incentive for medical students and trainees to consider careers in medical genetics. A recent understanding of the pathophysiology of various genetic disorders has provided researchers the opportunity to propose and test pharmacologic agents in murine models with hopes of translation to human trials. Examples include the use of angiotensin II receptor blocker medications in Marfan syndrome [Lacro et al., 2007], and the use of statins in neurofibromatosis type 1 (NF1) [Krab et al., 2008]. Opitz and Carey [2007] predicted that the participation of medical geneticists in designing and carrying out clinical trials in the

upcoming decade will be similar to the successful collaboration of medical geneticists with molecular biologists in identifying genes in the last two decades.

The decision of how to target each genetic condition varies. Conditions resulting in a complete deficiency of one enzyme potentially could be targeted through insertion of the normal gene, replacement of the enzyme, administration of a specific substrate or cofactor, or dietary supplementation. Although gene therapy has been used in ornithine transcarbamylase (OTC) and severe combined immune deficiency (SCID) syndromes, this approach has not become widely adapted primarily due to complications of delivery. Probably the most well established therapeutic approaches of genetic disorders historically have been dietary management such as in phenylketonuria and more recently in cystic fibrosis, and Smith-Lemli-Opitz syndrome. Enzyme replacement therapy has also advanced significantly the treatment of lysosomal storage diseases (e.g. Fabry disease, Gaucher disease, Pompe disease, mucopolysaccharidosis type 1) [Schiffmann et al., 2001], and bone-marrow transplantation has been utilized in Hurler syndrome [Field et al., 1994; Bjoraker et al., 2006]. Conventional pharmacology has also been used in genetic conditions such as the use of bisphosphonates in treating osteogenesis imperfecta [Plotkin et al., 2000], and growth hormone in Prader-Willi syndrome and Turner syndrome. As we develop a better understanding of the function of specific mutations and the mechanisms of their phenotypic impact, we are likely to identify more therapeutic options, which will need to be tested. However, we face the dilemma of not being ready to streamline potential beneficial therapies into the clinical realm. The development of clinical trials can be costly and time consuming, particularly for rare conditions. Therefore, the development and selection of appropriate outcome measures are paramount in the development stages of clinical trials.

The purpose of this paper is to identify the important themes in deciding upon outcome measures in clinical trials of genetic conditions by discussing potential outcomes in tibial dysplasia (TD) in NF1 as an illustration of the planning process. Additionally, we will report on the preliminary results of our ongoing multicenter study testing the use of a specific health-related quality of life (HRQL) measure in the NF1 population as an illustration of testing HRQL outcome measures in genetic disorders prior to clinical trials.

OUTCOME MEASURES IN TIBIAL DYSPLASIA IN NF1

Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder due to mutations in the *NF1* gene [Cawthon et al., 1990; Viskochil et al., 1990], with variable clinical manifestations including café au lait macules, intertriginous freckling, neurofibromas, optic pathway tumors, long bone bowing and pseudarthrosis (PA), and learning disabilities [Gutmann et al., 1997]. Because of our long standing interest in the skeletal abnormalities associated with NF1, we describe our approach to the development of outcome measures as an example of the thought processes involved in selecting such variables. Although NF1 is a common genetic disorder, long bone dysplasia is a rare manifestation of NF1, occurring in about 5% of patients [Friedman and Birch, 1997]. The tibia is the most commonly affected long bone and typically presents in infancy with anterolateral bowing [Stevenson et al., 1999; Crawford and Schorry, 1999]. The bowed tibia frequently sustains a fracture that does not heal resulting in a pseudarthrosis (PA). The morbidity of tibial pseudarthrosis is high, and therapeutic options are frequently unsatisfactory [Stevenson et al., 1999]. Perceptions of what therapeutic option is optimal have primarily consisted of retrospective reviews of various collections of patients. Despite many expert opinions and surgical series [Hefti et al., 2000; Coleman et al., 2005; Grill et al., 2000; Murray and Lovell, 1982; Traub et al., 1999; Tudisco et al., 2000; Anderson et al., 1992; Dobbs et al., 2004; Johnson et al., 1990; Friedlaender et al., 2001; Romanus et al., 2000; Ohnishi et al., 2005; Gilbert and Brockman, 1995; von Satzger and Herbst, 1981; Bara et al., 2007], there exists still a considerable lack

of consensus on the standard of care for the treatment of tibial pseudarthrosis. This is partially due to the challenge in the development of appropriate outcome studies using clinically relevant measurable outcomes within a reasonable time period.

Several factors have been identified in the literature as playing a potential role as a variable in outcome of TD. These include male gender, age of onset of bowing, ipsilateral fibular involvement, radiographic signs, and age of last surgery [Hefti et al., 2000; Grill et al., 2000; Stevenson et al., 1999]. All of these need to be taken into account as dependent variables in defining treatment groups and designing any intervention trial.

Clinical outcomes are the typical measure of the few outcome studies of TD and PA. One instinctively perceives that bony union would be the appropriate outcome to measure when studying interventions in PA. However, bony union does not necessarily mean that an individual will not sustain another fracture, require further surgical procedures, or have better physical function. Other clinical outcome measures for individuals with PA with or without NF1 to be considered could include leg length discrepancy, decreased range of motion, pain, limitation of walking distance, the presence of a valgus deformity, and gait disturbance. Moreover, about 20% of children with pseudarthrosis will end up with an amputation, an outcome that is usually perceived as a failure of the therapeutic interventions [Stevenson et al., 1999].

One must ask the question of what is the ultimate effect desired from a proposed treatment. Philosophically, one could argue that the ultimate effect is an improvement in the patient's quality of life. In recent years, investigators of outcome studies have adapted HRQL measures as a method to determine outcome along with clinical findings. These measures reflect a more holistic approach to management, and in recent years are becoming accepted in outcomes studies as measures of effectiveness of an intervention. The validation of these quality of life instruments has been reviewed and discussed in detail in recent years, and several measurement tools have been proposed for different diseases including chronic disorders of children [Elser and Morse, 2001; Wilson and Cleary, 1995]. Clearly clinical outcomes, (eg. height in Turner syndrome growth hormone studies, or number of surgeries to achieve union in tibial dysplasia/NF1 studies), are still included as expected outcome variables, but patient-centered outcome, which can be determined through HRQL measures, can also perform as primary or secondary outcome measures.

The impact of NF1 on quality of life has been investigated in a few reports [Wolkenstein et al., 2001; Page et al., 2006; Graf et al., 2006; Oostenbrink et al., 2007; Barton and North, 2000, Krab et al. 2009] utilizing a number of HRQL measures. However, the selection of appropriate measures to assess response to therapeutic interventions for specific manifestations still requires further thought. For example, some HRQL tools to assess response to therapies treating attention-deficit/hyperactivity disorder in NF1 may not be appropriate to assess response to therapy for tibial pseudarthrosis. Furlong et al. [2005] reviewed the assessment of patient-focused outcomes in pediatric orthopedic surgery. These authors discussed the selection of reliable and valid measures available for application to the targeted demographic of TD and NF1. Factors to consider in selecting outcome measures include study design, variability in study objectives, age range of subjects (i.e. TD and pseudarthrosis typically present in early childhood), assessment perspective, location and cultural characteristics of the study population, mode of data collection, assessment recall period, and burden of the instrument [Furlong et al., 2005]. One of the measures discussed by Furlong et al. [2005] was the Pediatric Outcome Data Collection Instrument (PODCI) [Daltroy et al., 1998; Vitale et al., 2001]. The PODCI has been validated in orthopedic investigations [Vitale et al., 2001]. The survey instrument consists of 117 questions requiring a grading of response on a Likert scale. The questions fall into five domains (see

Table I) and are answered by the parent proxy or by the child. It usually takes about 20 minutes to complete. We are currently analyzing the data on the application of the PODCI (and other HRQL instruments) in a multicenter investigation of the outcome of TD in NF1 patients. As an illustration of demonstrating that a particular HRQL measure is appropriate for a specific genetic disorder, and can detect differences in a particular manifestation of that disorder, we will present our preliminary data of this ongoing analysis. We show that there is a significant difference in the PODCI scores in children with NF1 and TD compared to control NF1 children. Our preliminary data suggest that the PODCI is an appropriate tool for evaluation of TD in the NF1 population, thus allowing the planners of a clinical trial for TD to consider choosing this instrument as a primary or secondary outcome in this group. (These data were presented in poster format at the 2007 American Society of Human Genetics meeting [Carey et al. 2007]).

MULTICENTER STUDY OF TD IN NF1: PRELIMINARY RESULTS

We have established a 5-year multicenter study to investigate the natural history of TD/PA, and determine outcome measures for TD for future therapeutic trials. The centers comprised 10 NF clinics and Shriners Hospitals for Children in North America [Carey et al., 2007]. The primary specific aim of the study was to assess the HRQL status in children and adolescents with TD and NF1 compared to NF1 controls without TD. The design was a case-control study, and clinical and HRQL data were gathered in the cases and controls from the various center when the patients attended their respective clinics on routine visits.

The study methods involved surveying patients and families with TD/PA and NF1 using several standardized HRQL instruments. Because of its known application to pediatric orthopedic conditions [Vitale et al., 2001], the PODCI was chosen as one of the instruments and forms the basis of our results in this preliminary presentation of the research in progress. In this analysis, we compared 24 children with NF1/ TD to 63 NF1 children without TD using the PODCI. Higher scores mean better outcomes in these measures. Since the distribution is skewed, we applied the Mann-Whitney U-Test, a nonparametric test, and demonstrated that the means of Global Functioning (23.5), Transfers and Basic Mobility (15.3), and Sports/Physical Function (13.7) were markedly different than controls (45.1, 46.7, 42.3 respectively) ($p < 0.001$) (see Table I). (These data are preliminary: the remaining 24 cases and over 100 controls are currently being analyzed.)

This study is the first QOL investigation of the orthopedic aspects of NF1. The overall purpose of the project is to obtain outcome data for the design of future medical/surgical therapeutic trials in patients with TD. These data - proof of principle - demonstrate that the PODCI detects differences in NF1/TD patients [Carey et al. 2007]. In summary, a HRQOL measure (PODCI) can be utilized effectively for a single manifestation (TD) of a specific genetic disorder (NF1). This information will be helpful in designing clinical trials for the treatment of TD in NF1.

DISCUSSION

We propose that most clinical trials should consider incorporating patient-focused health status and HRQL measures as outcomes. Anecdotally one would assume that most genetic disorders have an impact on quality of life, and this has been quantitatively assessed in a few genetic disorders [Wolkenstein et al., 2001; Miners et al., 1999]. A baseline assessment of HRQL in specific genetic disorders is helpful for their potential subsequent use as outcome measures in clinical trials. Although there are reliable and valid HRQL outcome measures available, they are typically reliable and valid for the general population and may not apply to a specific disease group. In addition, just as age appropriate measures are needed, some

measures may not apply to populations with specific genetic disorders who have significant cognitive and physical impairment as the measures may not be sensitive enough to identify clinically significant changes.

Feasibility and pilot studies (such as the preliminary data presented above), which select what is thought to be the most appropriate measures of HRQL for each specific disorder and their associated manifestations, are critical in avoiding potential pitfalls of clinical trials. Furlong et al. [2005] performed a pilot feasibility study of 8 NF1 patients using measures carefully selected after consideration of the study population and study design and showed that they were acceptable to patients' families and that results reflected the large variability in health related quality of life of the samples of patients. We posit that similar pilot feasibility studies should be performed when designing clinical trials for genetic disorders as these trials can be expensive and time consuming with a small number of subjects. Also our preliminary data mentioned above suggest that the PODCI is an effective HRQL outcome measure for TD in NF1 patients. The selection of inappropriate outcome measures can lead to non-measurable differences or clinically insignificant findings.

The addition of patient-focused outcomes allows for the patients and their representatives to provide meaningful measures of quality of life, which may be different than the clinician's perception. A clinician may interpret the improvement of a biochemical marker as a response to therapy, although there is no perceived benefit from the patient. Some studies have shown discordance between the physicians' assessment of physical outcomes compared to the patients' perception [Neville et al., 2000; Sztajn bok et al., 2007]. Other stressors involved in the actual therapy may outweigh the benefits as perceived by the patient in terms of their quality of life. This becomes even more complex when one recognizes the role of the caregiver as many genetic conditions require significant care management due to cognitive and physical impairments.

Recognition of the detailed phenotype of the various genetic disorders and the interacting pathways and mechanisms leading to the phenotype will direct the development of deliverable therapeutics. Many genetic disorders impact multiple organ systems resulting in a variety of manifestations which likely cannot be treated with just one intervention. Clinical trials may focus on one particular manifestation of a disorder, but selection of therapeutic agents based on knowledge of the impact of the genetic defect on biochemical pathways may have a positive outcome on more than one manifestation, whereas other agents will selectively target only one manifestation.

Medical geneticists are likely to become more intimately involved not only in the diagnosis of genetic disorders but their subsequent treatment. Genetic practitioners will need to decipher what therapies will be beneficial for their patients, and we suggest that the input of medical geneticists in the design of clinical trials in order to identify key outcomes that will be important in making evidence-based medical management decisions is critical.

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Biography

Bio sketches: John C Carey, MD,MPH, clinical geneticist, is a Professor of Pediatrics and the Vice Chair of Academic Affairs at the Department of Pediatrics, University of Utah Health Sciences Center. He is Editor-in-Chief of the *American Journal of Medical Genetics*.

David A Stevenson, MD, Assistant Professor of Pediatrics at the University of Utah, has been interested in the skeletal manifestation of NF1 since his freshman year of medical school when he embarked on a multicenter project studying tibial dysplasia. Dr. Stevenson currently has both NIH and Doris Duke Foundation funding to investigate this question.

Recently he has helped lead working groups on the osseous defects of NF1 both at the Salt Lake Shriners Hospital and The Children's Tumor Foundation.

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Table 1

Comparison of PODCI scores in the 5 domains of NF1 cases with tibial dysplasia vs. NF1 controls without tibial dysplasia

Domain	Group	N	Mean	STD	Mann-Whitney P-Value
Global Functioning:	Active	23	23.46	22.557	<.0001
	Control	62	45.14	12.970	
Extremity and Physical Function	Active	24	29.20	23.544	0.2309
	Control	62	32.31	26.534	
Transfers and Basic Mobility	Active	23	15.35	40.961	<.0001
	Control	63	46.78	11.718	
Sports/Physical Function	Active	23	13.68	24.879	<.0001
	Control	62	42.35	15.829	
Pain/Comfort	Active	24	43.44	14.683	0.0023
	Control	63	52.61	7.473	
Happiness	Active	21	49.61	12.197	0.2817
	Control	58	53.67	9.228	