REFERATE GENERALE

A new model for Cystic Fibrosis Management: Control Concept

Hasan Yuksel, Ozge Yilmaz

Celal Bayar University Medical Faculty, Dept of Pediatric Allergy and Pulmonology, Manisa, Turkey

REZUMAT

Un nou model pentru managementul fibrozei chistice: conceptul de control

Îngrijirea medicală tradiţională consideră simptomele şi constatările obiective ale unei boli drept principalele măsuri ale rezultatului. Totuşi, practica medicală modernă defineşte sănătatea ca o stare de bine completă, incluzând statusul fizic şi percepţia pacientului cu privire la starea de bine socială şi psihologică. Prin urmare, principalul obiectiv al managementului terapeutic trebuie să fie „controlul bolii legat şi nelegat de starea de sănătate în termeni de stare de bine funcţională şi emoţională". Aceasta necesită evaluarea statusului de control la cazurile de fibroză chistică prin evaluarea simptomelor şi a elementelor obiective prin tehnici de laborator şi instrumente psiho-somatice. Obiectivul acestui referat general este să definească cei trei indicatori principali ai controlului şi să ofere ideile iniţiale pentru dezvoltarea unui nou instrument care să acopere toate aspectele.

Cuvinte-cheie: *fibroză chistică, concept de control, măsura rezultatului raportat de pacient*

ABSTRACT

Traditional medical care considers symptomatic and objective findings of disease as the main outcome measure. However, modern medical practice defines health as a complete state of well being including physical state and patient's perception of social and psychological well being. Therefore, the main aim of therapeutic management needs to be "the control of disease related and unrelated to the health condition of the individual in terms of functional and emotional well being". This necessitates evaluation of control status in cases with cystic fibrosis via evaluation of symptomatic and physical findings with laboratory techniques and psycho-somatic instruments. The aim of this review article is to define the three main indicators of control and to provide initial ideas for development of a new instrument that covers all.

Keywords: *cystic fibrosis, control concept, patient reported outcome measures*

Introduction

Conventional health care and medical practice considers mainly symptomatic relief and prevention of complication in treatment of chronic diseases. This approach applies to cystic fibrosis (CF) that has a chronic and complicated course. Management of CF is mainly based on clinical symptomatology because of the difficulties encountered during the treatment of acute exacerbations, continuous revision of the therapy plan and the very active chronic nature of disease. However, merely symptom control is not adequate in this chronic disease that shortens the life expectancy of the patient. Psychosocial state and control in respect to this state needs to be determined, too. All these factors lead to exhaustion syndrome of both the family and physician. However, elimination of clinical symptomatology is not sufficient as a final target in the concept of therapeutic health care [1]. Achievement of the optimal health condition of the organism via optimal control of the disease state is the target outcome. The definition of health includes the individuals' feeling of complete well being [2]. Therefore, the therapeutic target of CF management needs to be a union of physical state, patient's perception of social and psychological well being and elimination of clinical symptomatology. Defining the therapy step required to achieve this target is possible via "the control of disease related and unrelated to the health condition of the individual in terms of functional and emotional well being". Therefore, determination of the control status is essential in cases with CF and this evaluation requires completion of symptomatic and physical findings with laboratory techniques and psycho-somatic instruments. At this point of modern clinical approach to health care, control concept in CF emerges integrating physical-organic, psychological and social well being of the patient with CF [3]. The ideal target is the development of an instrument that includes all these aspects. The aim of this review article is to define the three main indicators of control and to provide initial ideas for development of a new instrument that covers all.

Which Instruments Can Be Used In Evaluation of Control?

Cystic fibrosis that is a genetically transmitted disease decreasing the life expectancy has a phenotype with multi-organ involvement with changing severity due to the mutation type [4]. Therefore, there is no aggreement on an instrument (parameter, questionnaire, biochemical analysis etc.) that will determine the clinical status or more importantly that will demonstrate the control status.

Respiratory status is the main determinant of survival time and quality of life (QoL) clinically, therefore, lung function tests and FEV1 is accepted as the parameter that is most correlated with clinical findings and severity of disease [5,6]. Determination of clinical status reflects the functional capacity. However, detection

Contact: Hasan Yuksel, Prof, 116/17 sokak No:7 C blok Daire:3 Bornova-IZMIR; e-mail: hyukselefe@hotmail.com

of a deterioration in functional capacity in CF implies the initiation of irreversible changes in the organs such as the lungs. Therefore, only clinical and functional evaluation is not adequate to reflect the disease status in the aspect of "control concept". Therefore, CF lack the clear and definite criterion to follow up on the basis of "control" in contrast to asthma which has led to the development of the concept of control [7]. Thus, recent guidelines base asthma treatment on disease control but the control phenomenon has not been incorporated into CF management. Many international medical organizations (World Health Organization), local medical organizations (Cystic Fibrosis Federation, National Institute of Health of America) and specialists are working collaboratively on development of ideal instruments for evaluation of patients with CF.

The first instrument used in evaluation of disease severity in CF was the Shwachman-Kulczycki clinical scoring system validated in 1958 [8]. Various other scales have been developed during the last 20 years to improve this and a modified Shwachman-Kulczycki clinical score including the radiological severity has been developed cosidering that absence of radiological scoring in the original one was a shortfall [9].

Recent data point out to three aspects of CF control:

- Clinical scoring (severity and status);
- Radiological scoring;
- Measurement of quality of life.

The first two areas have been of interest during the last 50 years but measurement of QoL has gained interest only recently.

Clinical Scoring

Until recently, main interest of physicians dealing with CF has been the clinical status of disease. This included the answers to the questions such as "how are the symptoms of the patient?", "to what extent are the physical examination findings pathological?" and "are the functional parameters (biochemical tests, lung function tests) that are the indicators of their status well?". The answers to these questions reflect the success of the physician and efficacy of the prescription based therapy. With these endpoints that can be measured physically, we get an opinion about the treatment of disease and the efficacy of medications.

"Symptom score scales" are the simplest tools in evaluation of clinical status. In most of these, status of acute exacerbations is the most valued part by clinicians [3]. However, they do not reflect psychological or social weighing of the patient although they provide objective criteria for physical evaluation and therefore symptom score scales are not adequate for management according to control status [3].

Main symptoms and signs used in clinical scoring of CF are summarized in table I [9]. Multisystem nature of CF is an important obstacle in clinical score scales that have been developed. All these criteria are used in routine medical practice and aid in evaluation of the patient with CF physically as an object. However, it is nearly impossible to gather all the symptoms of CF in one symptom score format. Even the symptoms of the respiratory and gastrointestinal tracts that have been widely included in these scales are not covered adequately. Moreover, symptoms and signs of other common clinical conditions such as pancreatic insufficiency, diabetes, infertility, chronic hepatic disease, clubbing etc are not included in these scales. On the other hand, inclusion of all these would have made the scale too crowded for routine use.

Table I. Main Clinical Symptoms and Signs used in Clinical Scoring Scales for CF

System	Symptom and Sign
Pulmonary	Dyspnea Exercise intolerance Cough (day/night) Cough frequency Sputum expectoration Jugular filling Wheezing Hemoptysis Amount of sputum Change in the appearance of sputum Change in sputum color Change in sputum consistency Increased respiratory rate Impairment of lung function tests
Upper airway	Sore throat/rhinorrhea Pain in the sinuses Purulent nasal/sinus ostium discharge
Gastrointestinal	Abdominal pain Diarrhea/greasy stool Others
Activity	School absenteeism Difficulty in walking/running/ swimming
General	Fever (>38ºC) Lack of apetite Fatigue/weakness Weight loss Nutritional status

Therefore, none of the clinical scores developed upto date are adequate to give a numeric value to the clinical status of the patients with CF.

Shwachman-Kulczycki Score: The scale developed in 1958 based on the findings of patients in a five year follow up study aims to estimate morbidity and mortality as well as disease severity. Four main domains include general activity, physical examination findings, nutritional status and chest X-ray findings, each containing five items. Each item is scored over the maximum score of 5. Highest score is 100 and score above 88 denotes a very good clinical status. Validity and reliability has not been analyzed by comparisons with an objective instrument. Moreover, there are items classified under different titles though they have similar meanings and some others are classified under titles that are not exactly correlated. Another major defect is the exclusion of lung function tests.

Shwachman-Kulczycki Score is the most commonly used clinical scoring system that has been found correlated with clinical and laboratory parameters in more that 200 reliable research despite all the defects listed above [8].

Modified Shwachman-Kulczycki Score: Patient history findings has been added to the activity domain, cough status to the physical examination findings and growth status and stool characteristics have been added to the nutritional status. However, international authorities have stated that the subjective characteristic of the Shwachman-Kulczycki score as well as the intra-scale overlaps persist. Moreover, inability of the scale to sense "mild" findings prevents its use as an outcome measure for monitoring treatment and follow up plan [10].

Cooperman Score: Developed to provide a simple method of evaluation in 1971, it includes five main domains (activity, chest X-ray, growth-development, complications, clubbing) and an eat

item is scored 0 to 2. Its use is as easy as the Apgar score. However, it has not been validated [11].

NIH (National Institute of Health) Score: This scale developed by Taussig in 1973 aims to evaluate past and present clinical status. It is composed of five main categories of 12 sub-items. The categories include lung function test, physiological characteristics, psychological characteristics, chest X-ray and history characteristics. It has been validated clinically and statistically by two important studies. However, scoring between one to three leads to decreased sensitivity and may not reflect transitional states and mild findings. Moreover, it can detect changes in time. Although it is a commonly used scale, comprehensibility by children is low [12].

Bernese Score: It has been developed by Kraemer et al. in 1979 as a test that will also detect the correlation between clinical findings, chest X-ray, lung function tests and arterial blood gas values. Sputum characteristics are included. Each item is scored 1 to 5. However, it has not been validated, can not detect differences between patients and it is invasive [9,13].

Huang Score: It was developed by Huang in 1976 to compare therapeutic regimens and antibiotic efficacy because NIH and Shwachman-Kulczycki scores could not detect changes over short time periods. Each of the twenty main categories (10 clinical, 5 pulmonary, 5 radiological) are scored between 1 and 5. Main disadvantage is that it can not be used by the children. This scoring system was modified by Matouk et al in 1997. Domains were expanded and respiratory failure as well as many other details were added. However, it can still be used only in adult patients and is complex and time-consuming [14].

Cystic Fibrosis Clinical Score: It has been published by Kanga et al. in 1997. Scoring is done over cough, apetite, sputum expectoration and 5 different clinical findings (fever, respiratory rate, weight, gas exchange and pulmonary auscultation findings). The results have been correlated with NIH score in a couple of studies. It is easy to use but has not been used in children commonly. Validity has been demonstrated, however reliability has not been studied yet. However, it is a promising scoring format [15].

Others: There are a couple more scoring systems. Most were developed for specific purposes like evaluation of acute exacerbations. For example, Rosenfeld et al published a scale in 1997 that evaluates acute findings as "present" and "absent", thus does not reflect disease severity [16]. Similarly, Rabin et al has developed another scale in 2004 specifically to compare treatment results of acute exacerbations. However, it can not be used in children [17]. Moreover, Borg Scale has been developed only to demonstrate the severity of dyspnea and exertion tolerance and the recently developed Respiratory-Systemic Symptom Score scale can only be used to measure acute exacerbations in the aspect of respiratory tract.

Moreover, scales such as Borg dyspnea scale, UCSD-SOBQ (University of California at San Diego and Shortness of Breath Questionnaire), BCSS (Breathlessness, Cough, and Sputum Scale) and SGRQ (St. George's Respiratory Questionnaire) can also be used in CF [18]. However, none of these scales, except SGRQ, are validated. Moreover, they are not specific for CF.

In conclusion, clinical scoring systems developed until today are not adequate to evaluate the status of the patient globally. Despite providig valuable information for the physical status of the patient, additional instruments are required both to improve physical evaluation and to include patient reported outcomes in order to achieve a global evaluation of the patient.

Radiological Scoring

Radiological imaging techniques have been proposed as markers in many diseases and some were validated. Among these, most research has focused on computerized tomography (CT) [9]. Similarly, the most efficient radiological technique to use in scoring for CF seems to be CT since Magnetic resonance imaging (MRI) is inadequate to visualize the parenchyme due to the air filled structure. There are many studies indicating a correlation between CT findings and lung function tests both in adults and children [19-24]. Furthermore, CT has been proposed to detect bronchial and parenchymal changes before lung function tests deteriorate. Therefore, it has been suggested to obtain CT images before early lung disease develops and in follow up. CT has been used for evaluation of dornase alpha treatment efficacy in a couple of studies [25]. Improvement in radiological stage as well as the clinical symptom score was reported in one of these. However, radiation exposure and side effects in the diseased lung parenchyma needs to be investigated thoroughly especially in children.

Computerized tomography seems to be rational for evaluation of clinical (physical and functional) control status in CF patients when the side effects are overlooked. The most important characteristic of CT in this aspect is the opportunity for numerical staging which allows follow up of the progressive course of CF. The staging system used in CF is summarized in figure 1. Moreover, this staging system has been linked with management strategy plans [26].

Radiological staging is associated with lung function tests, mucus clearance rate and quality of life however optimal use of CT in CF control requires longitudinal data with recurrent CTs at intervals. This has many disadvantages such as high radiation exposure and cost. Moreover, timing of CT needs to be carefully specified since images obtained during an acute exacerbation may be misleading. Technological progress in CT imaging decreasing the radiation dose will place radiological scoring among frequently used CF control instruments in future [26].

Quality of life Measurement

During the last 20 years, quality of life measurement has been a rapidly developing field of medical practice considering the description of health as "combined state of physical and mental well-being".

Conventional medical practice did not tend to consider patient reported outcomes, therefore "psychological health" has not been in focus until the last 20 years. In this aspect, traditional medical practice seems to be "physician" focused instead of "patient" focused. Physician is successful to the extent that he can ameliorate the symptoms of the patient and the medicine sector that provides the mediator for this is profitable. However, in this "physician" focused practice, patient is viewed only as "organs" that can be examined and the presence of his mental and social status are overlooked. Expression of mental and social status of the patient as well as the symptoms by himself or his family and consideration of these in evaluation of treatment will be an approach of modern medical practice. "Patient focused" follow up including these three main concepts of health will be the "patient reported outcome" (PRO) [3].

Most developed forms of the PRO systems are the "quality of life questionnaires" [1]. In the patient based modern medical prac-

tice, "health related quality of life" (HRQoL) and questionnaires will be important. However, for PRO approach other psychometric instruments that are used to measure the psychological status (child behaviour check list, anxiety-depression scales, hospital depression scale etc., can also be used.

There are two aims of the HRQoL instruments: one is to measure the status of quality of life of the patient irrespective of the specific disease state or organ involvement. These are called generic or general QoL questionnaires [27]. For example, KINDL (QoL questionnaire developed by Ravens-Sieberer & Bullinger only for childhood), PedQoL (pediatric quality of life questionnaire), CHQ (child health questionnaire) and SF-36 for adults (short form of 36; HRQoL questionnaire of 36 questions), WHOQoL (World Health Organization HRQoL questionnaire) are examples to these. Second aim is to measure the HRQoL that is influenced directly by the disease. These are the "disease specific" HRQoL questionnaires [27,28]. These aim to measure PRO in the aspect of symptoms, mental health and social well-being related to the specific disease. The best example for this is the CFQ-R (cystic fibrosis questionnaire-revised) that is mainly the only questionnaire that is accepted world-wide and validated.

The most appropriate use of HRQoL questionnaires for patients with CF includes both thee generic and disease-specific HRQoL questionnaires at the same time. Moreover, "parents forms of HRQoL questionnaires" can be used for children.

The ideal result in determination of the control status in CF can be accomplished by the use of clinical scoring (symptom score and physical findings) and functional parameters (FEV1, FVC etc., 6-minute walking test etc.) as well as the HRQoL measurements [3].

Why should the quality of life questionnaires be used "to determine the control status" in CF? For all the clinicians, the most important end result in patient follow-up of patients is the control of disease. Conventionally, this includes clinical scoring, radiological findings etc., however in the light of the above information, these are not adequate for the concept of control. When the clinical and radiological scoring systems that are suggested for use today are reviewed, it is noticed that they provide limited information about this multi-system involving disease. However, when CFQ-R is reviewed, it provides information about symptomatology, clinical information and psychometric results that are important indicators of control (table II) [1,3,28]. Moreover, another advantage is that it provides minimal clinically important difference (MCID) for children and adults which is not provided by other scales. Therefore, quality of life questionnaires that are important instruments of PRO are the most rational methods to determine the control status of CF.

Quality of life questionnaires can be used in "control based CF follow-up" as in asthma. Currently, both pediatric and adult asthma follow up is based on "control". Both control question-

Table II. Scores, Quality of Life Questionnaires and their constituents used in CF

System	Syptom and Findings	SK*	NIH	RSSQ	Radiology	CFQR
Pulmonary	Dyspnea					
	Exercise intolerance	x	X			x
	Cough (Day, Night)	x				x
	Cough frequency	x	x			x
	Sputum expectoration	x	x	x		x
	Jugular filling			x		
	Wheezing			x		
	Hemoptysis			x		x
	Sputum amount	x				x
	Sputum appearance Change in sputum color	x				x
	Sputum consistency			x		x
	Increase respiratory rate			x		
	Retractions		x			x
	LFY impairment	x	x			
Upper airway	Sore throat/rhinorrhea					
	Sinus pain			x		
	Purulent nasal/sinus discharge			x		
Gastrointestinal	Abdominal pain					x
	Diarrhea/greasy stool			x		x
	Other					x
Activity	School absenteeism					x
	Difficutly walking/running etc.					x
General	Fever (>38°C)					
	Lack of apetite		x			
	Weakness/fatigue		x			x
	Weight loss			x		x
	Nutritional status		x	x		x
Mood						x
Well-being			x			x
Psychosocial						x
Chest Xray/CT			x		x	

**: Shwachman-Kulczycki Score*

naires and control tests have been developed for this aim and under-use. Quality of life questionnaires, among which CFQ-R is the main one, can be used in control based follow-up. Validity and reliability studies revealed successful results for all CFQ-R questionnaires [1].

Other Instruments To Use in Evaluation of Control

There are two additional sub-titles in the evaluation of control status in CF. These are "feeling of pain" and "depressive mood". There are many instruments for measuring these and this area requires a more detailed examination psychometrically. These scales can be done via scoring or VAS (visual analog scale; for example grading of the condition from 1 to 10 by the patient). However, the instrument that will be used by the physician encountering with the patient must be included in the control concept.

Feeling of is a perception that is not paid much attention in patients with CF. Research with "faces pain scale" and likert scale has demonstrated that majority of school aged and adolescents and nearly all of the older aged patients have increased feeling of pain. Moreover these are associated with low scores in CFQ-R [29,30].

Depressive symptoms increase with age and needs to be considered in patients with CF. Although CFQ-R shows the level of well-being, it can not demonstrate the contribution of mood in this overall results. CESD (Center for Epidemiologic Studies Depression Scale), HAD and other similar instruments may be used for this [31,32].

In conclusion, a global evaluation system is required for patients with CF and the model of control concept that has long been used in asthma patients might provide clues for this. A new istrument that covers clinical scoring, radiological scoring and patient reported outcome measures needs to be developed in order to achieve this goal.

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