Health-related quality of life and treatment practice in cystic fibrosis in Hungary

PhD thesis

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1. Introduction

Cystic fibrosis (CF) is one of the most common rare, genetic disorder in Hungary. The CF gene mutation, a defect of an anion channel is developed and in every organ where this channel exists, transport of chloride (Cl^-), sodium (Na^+) ion and water is disturbed, hereby adds up to production of thick mucus. This thick mucus is leading to obstruction in the affected organs hereby, cystic-fibrotic destruction of the parenchyma. The most common affected organs include the lung, gastrointestinal, hepathobiliar and reproductive tracts, as well as sweat glands meaning the basic of the diagnostics. Currently, causal therapy of the disease is not known, however, due to the multi-organ failure the symptomatic treatment is very complex which can cause significant burden for patients as well as for caregivers. Nowadays, with the development of the scientific research CF patients not only live to adulthood but also survive it. Generally they can live 30-35 years but this age approaches the 40 years in the Western European Region. However, with increasing life expectancy, another viewpoint of patients gets priority. Today, not only survival but also quality of life is important. In the last decade, the rapid development in pharmaceutical research and management of CF is observed in western countries, as compared to arrear of Eastern Europe.

2. Objectives

The aim of my PhD thesis was to measure the Hungarian treatment practice and health-related quality of life of children and young adults in CF.

2.1. Estimation of the real case number of Hungarian CF patients:

a) Comparison of the annual patient number registered in the Hungarian Cystic Fibrosis Registry to the data of the annual patient number of the Hungarian Health Insurance Fund,

b) Estimation the rate of the CF patients who receiving adequate therapy.

2.2 Evaluation of health-related quality of life (HRQoL) of children and young adults suffering from CF:

a) To measure the HRQoL of Hungarian children and young adults with CF between 8 and 30 years with a disease-specific questionnaire,

b) To determine the most impacting factors on CF patients' HRQoL with a disease-specific questionnaire,

c) To determine the relationship between objective parameters of lung function and subjective HRQoL,

a) To determine who is the relevant person to evaluate the child's HRQoL.

2.3 Comparison of HRQoL among Hungarian and Polish children with CF:

a) To determine CF patients' HRQoL aged 6-18 years using disease-specific questionnaire,

b) To identify the clinical, social and parental factors and differences affecting HRQoL.

2.4 Comparison of HRQoL of children suffering from asthma to the HRQoL of CF patients:

a) To measure 8-18-year old children's HRQoL suffering from asthma and CF using a generic questionnaire,

b) To assess the level of agreement of HRQoL scores between children and their parents,

c) To investigate the relationship between objective clinical parameters and subjective HRQoL.

3. Methods

3.1. The annual number of Hungarian CF patients was analysed by comparing retrospective analysis based on the data of the Hungarian Cystic Fibrosis Registry and the data of the Health Insurance Fund between 2010 and 2012.

Records on health care utilization and pharmacy-dispensing records (for patients with CF diagnosis code of the diagnoses-related groups – DRG, including one patient once a year to the

analysis identified by a unique Social Security Number) were required from the Hungarian Health Insurance Fund. Pharmacy refill records of dornase alpha and pancreas enzyme replacement therapy (PERT) were provided by the Hungarian Health Insurance Fund for three consecutive years (2010-2012). The dispensing records of oral and inhaled drugs (number of drug boxes per a year) were received based on CF diagnosis code of DRG. Then I separately estimated the drug release habit depending on participating oral or inhaled therapy. Following this, I compared the annual pharmacy-dispensing records of the Health Insurance Fund to the hypothetic pharmacy-dispensing data calculating on the basis of the annual, patient number of the Hungarian CF Registry and Hungarian Health Insurance Fund.

3.2. I carried out a prospective and cross-sectional study in outpatient units of five CF centres between September 2010 and October 2011. Children and young adults with CF (aged 8-30 years) filled out the Hungarian version of *The Cystic Fibrosis Questionnaire-Revised* (CFQ-R) disease-specific questionnaire. To measure disease severity, *Shwachman-Kulczycki* score, FEV_1 (Forced Expiratory Volume in 1 second) and BMI (Body Mass Index) was considered. I

recorded patients' infection status with *Pseudomonas aeruginosa* (PA) and history of hospitalization in the last year.

3.3. During the one-year period, part of the Hungarian-Polish cooperation, a questionnaire-based, non-invasive, cross-sectional, prospective study was carried out in outpatient units of five Hungarian and one Polish CF centres. We measured the 6-18-year old children's HRQoL with the Hungarian and Polish versions of CFQ-R disease-specific questionnaire. Disease severity was assessed measuring FEV_1 and BMI z-score. Basic demographic data, school attendance habits and parents' employment status were asked.

3.4. I measured HRQoL of children (aged 8-18 years) suffering from asthma or CF with a prospective, cross-sectional study in outpatient units of five CF centres and the pulmonological ambulance of Törökbálint Pulmonological Institute between September 2010 and October 2011. HRQoL was measured with a generic questionnaire, using the Hungarian version of the *Pediatric Quality of Life Inventory™ Version 4.0 (PedsQL™ 4.0).* Spirometry was carried out as part of the study.

4. Results

4.1. Results were the following if comparing data of the Hungarian Health Insurance Fund with the data of the Hungarian CF Registry:

a. The number of patients with the diagnosis code of CF was almost double comparing to the patient number of the Hungarian CF Registry, during the investigated three years (2010: 597 vs 1077; 2011: 592 vs 1078; 2012: 579 vs 1017).

b. Based on the number of CF patients reported in the Hungarian CF Registry, 2.7-2.9 time lower patients received dornase alpha and on the basis of the data of the Hungarian Health Insurance Fund six time lower patients collected dornase alpha as it would be expected.

According to my calculations, 3.5-3.9 time lower PERT were collected, year by year, considering only adult CF patients, since they this treatment need according to the case number of CF patients.

4.2.a, During the study period, 59 CF patients (average age: 14.03 years; 47.5% male, average FEV_1:77.93%) were included in the study. *Respiratory symptoms* (CFQ-R=67.8$\pm$18.0) had the highest impact and *Eating* (CFQ-R=83.1$\pm$22.2) the lowest on CF patients' HRQoL according to patient report. Parents evaluated with the lowest score the

Weight (CFQ-R=60.4±38.3) and *Treatment burden* (CFQ-R=60.4±21.5) domains and with the highest score *Emotional functioning* (CFQ-R=78.3±14.6).

4.2.b, Only *Eating* (r=0.28) and *Treatment burden* (r=-0.26) showed a significant, weak correlation with age. Moderate correlations were identified between **disease severity** and *Physical functioning* (r=0.55, R^2=0.35, p<0.01), *Body image* (r=0.41, R^2=0.28, p<0.01) and *Respiratory symptoms* (r=0.43, p<0.01) domains, by child-self report. In most of the domains, patients non-infected with PA evaluated their HRQoL better than **PA infected** patients, except in *Social functioning*, *Eating* and *Digestive symptoms* domains. Significant differences were detected in *Body image* (p<0.01) and *Respiratory symptoms* (p<0.05) domains between the CFQ-R scores of PA infected and non-infected groups. Only in *Physical functioning* domain was detected a significant difference between **hospitalised** (CFQ-R=62.91±30.16) and non-hospitalised (CFQ-R=80.98±18.01) groups, by child-self report (p<0.05). Children with **malnutrition** assessed their HRQoL with lower scores in the *Physical functioning*, *Eating*, *Body image* and *Respiratory symptoms* domains, than their adequate weighted patient mates, by self report (p<0.05). According to parents' perception, *Physical functioning*, *Eating*, *Weight* and

Respiratory symptoms domains had lower HRQoL scores in the case of children with malnutrition than in children with adequate weight ($p<0.05$).

4.2.c, Moderate correlations were identified between *Physical functioning* and FEV_1 ($r=0.42$, $p<0.01$); *Respiratory symptoms* and FEV_1 ($r=0.37$, $R^2=0.17$, $p<0.01$), by child-self report. A weak correlation was measured between *Body image* and FEV_1 ($r=0.30$, $p<0.05$).
A weak correlation was found between *Digestive symptoms* and FEV_1 ($r=-0.27$, $R^2=0.08$, $p<0.05$); and a moderate between *Physical functioning* and FEV_1 ($r=0.56$, $p<0.01$), by parent-proxy report.

4.2.d, A good agreement was measured in *Physical functioning* domain between parents' and children's answers (ICC=0.77), a moderate relationship was found in *Eating* (ICC=0.51), *Body image* (ICC=0.54) and *Respiratory symptoms* (ICC=0.49) domains. A low agreement was detected in *Emotional functioning* (ICC=0.07), *Treatment burden* (ICC=0.21) and *Digestive symptoms* (ICC=0.40) domains between parents' and children's answers.

4.3. 141 (Hungarian n=43, Polish n=98) children with CF and 102 caregivers (in the case of 6-13 year-old children)

participated in the study. Polish children's average age was 14.41±2.61 years, and Hungarian's was 11.86±2.87 years (t=5.17; p=0.01).

4.3.a, Both Hungarian (CFQ-R=82.4±23.9) and Polish (CFQ-R=76.8±22.2) children assessed their HRQoL with the highest score in *Eating* domain, by child-self report. Hungarian children rated their HRQoL with the lowest score in *Respiratory symptoms* (CFQ-R=66.2±20.9) domain and Polish children in *Treatment burden* (CFQ-R=64.4±18.2). Hungarian children rated with higher scores *Treatment burden* domain (t=3.30; p<0.05) than their Polish mates. According to the Polish parents' answers, *Eating* (CFQ-R=78.41±18.9) affected at least their children's HRQoL whereas Hungarian parents evaluated *Emotional functioning* (CFQ-R=78.33±14.6) with the highest score. In both patient groups, *Treatment burden* (Poland=46.3±23.2; Hungary=60.4±21.5) had the lowest score. Generally, Hungarian parents rated their children's HRQoL with higher scores in the following domains: *Emotional functioning* (t=3.18; p <0.01), *Eating* (t=2.03;p<0.05) and *Treatment burden* (t=3.00;p<0.01) than Polish caregivers. Contrarily, Polish parents assessed their children's HRQoL with higher scores in *Digestive symptoms* (t=2.16;p<0.05), compared to their Hungarian mates.

4.3.b, Significant relationships were detected between **FEV_1** and *Physical functioning* (β=0.31; $p<0.001$ and β=0.52; $p<0.001$); FEV_1 and *Respiratory symptoms* (β=0.20; $p<0.05$ and β=0.41; $p<0.001$), by both child-self report and parent-proxy report, in the two country groups. Furthermore, a significant relationship was measured between FEV_1 and *Health perception*, by proxy report, too (β=0.36; $p<0.001$). A significant impact of **BMI z-score** was identified on *Body image* and *Treatment burden*, by child-self report and on *Eating* and *Weight* by parent-proxy report. Either FEV_1's nor BMI z-score's significant impact could identify on *Emotional functioning* and *Digestive symptoms*, by both self report and proxy report. Significant relationships were detected between **school attendance** and the following HRQoL domains: *Physical functioning* (F=10.73; p=0.01), *Social functioning* (F=8.10; p=0.01), *Body image* (F=5.33; p=0.02), *Eating* (F=10.45, p=0.00), *Respiratory symptoms* (F=7.43; p=0.01) and *Emotional functioning* (F=3.91; p=0.05). Parents who do not work, evaluated their children's HRQoL with higher scores only in the *Digestive symptoms* domain (F=4,60; p=0,04) than who were employed.

4.4. 172 children (CF=39, asthma=133; average age: 11.6$\pm$2.56 years, 54.7% male) participated in the study.

4.4.a, HRQoL of CF patients was worse in almost all of the domains, than children's suffering from asthma, by child-self report, except the *Physical Functioning* and *Social functioning* domain ($p<0.05$). There was no significant difference in HRQoL between the two patient groups according to the parents' opinion ($p>0.5$).

4.4.b, A moderate correlation was measured in every HRQoL domains between parents' and children's answers in CF (ICC_{CF}=0.39-0.59), contrary to asthma, where only a weak relationship was detected (ICC_{asthma}=0.29-0.37).

4.4.c, In CF, *Physical functioning* showed a moderate association with lung function ($p<0.05$) in 8-12-year old patient group as well as in 13-18-year old patient group. Among children suffering from asthma, a weak and negative correlation was found between *School functioning* and FEV_1 ($p<0,05$), however, generally there was no relationship between lung function and HRQoL of children with asthma.

5. Conclusions

5.1.a, According to the result of my PhD thesis, the data of the Hungarian CF Registry reported underestimated data about the patient number of Hungarian CF patients. My study noticed first this discrepancy.

5.1.b, The aim of my study was to estimate how many CF patients receive adequate therapy in Hungary. It was identified that every 6th Hungarian CF patient collected inhaled dornase alpha and every 4th adult patient received PERT, on the basis of pharmacy-dispensing records of inhaled respiratory therapy and PERT. My results are much worse than it was previously published in the literature.

5.2. My investigation was the first multicentre, disease-specific HRQoL evaluation among Hungarian children and young adults with CF.

5.2.a, I identified first the most impacted HRQoL domains of CF patients. *Respiratory symptoms* caused the most significant problem for CF patients', by self report. *Weight* and *Treatment burden* meant the highest problem, by proxy report.

5.2.b, I identified first the factors affecting Hungarian CF patients' HRQoL. A weak relationship was identified between age and HRQoL. Moderate relationships were detected

between disease severity and observable HRQoL domains, by both child-self report and parent-proxy report. *Pseudomonas aeruginosa* infection, hospitalization and malnutrition deteriorated HRQoL of CF patients.

5.2.c, Moderate correlations were identified between lung function (FEV_1) and *Physical functioning* and symptoms scores, by self-report. However, there was no relationship between psychosocial domains and lung function. Hereby highlighting an important issue, that during the holistic CF care, it is not enough to consider only objective parameters but also monitoring subjective HRQoL is needed.

5.2.d, Only in the observable HRQoL domains could I detect a good or moderate agreement between children's and parents' answers. However I could not identify any relationships between parents' and children's perception in emotional domains. According to the results of my research, both children's and parents' perception should be considered to manage a HRQoL measure below 14-year old children in CF.

5.3. My comparison study was the first which compared Hungarian CF patients' HRQoL to another nation CF patients' HRQoL.

5.3.a, Based on the results, there were no significant differences between CF patients' HRQoL of the two countries, by child-self report.

5.3.b, It was identified that disease severity as pulmonary or nutritional status has substantial impact on CF patients' HRQoL. My research highlighted a non-recognized relationship between school attendance and CF patients' HRQoL. I identified first that children with CF who participated in individual education have significantly worse HRQoL than those who are regularly going to school.

5.4.a, My research identified that HRQoL of CF patients is worse, than the HRQoL of children suffering from asthma. However, the very different HRQoL estimation of parents highlighted the fact that in paediatric HRQoL measurement, it is not enough to consider only parents' evaluation about their children's HRQoL.

5.4.b, A weak relationship was detected between child-self report and parent-proxy report in asthma, contrary to CF, which observation verifies the above mentioned conclusion.

5.4.c, Nor in CF, neither in asthma could not be detected a significant association between psychosocial domains and lung function. Based on this result, to assess lung function

alone is not enough while providing holistic care of children suffering from chronic respiratory illness.

6. List of own publications

6.1. Publications related to the topic of the PhD thesis

Articles in English:

1. **Bodnar R**, Kadar L, Szabo L Hernadi M, Mikoczi M, Meszaros A. (2014) Health related quality of life of children with chronic respiratory conditions.Adv Clin Exp Med,in press **IF_{2013}:0.333**
2. **Bodnar R**, Kadar L, Holics K, Ujhelyi R, Kovacs L, Bolbas K, Szekely Gy, Gyurkovits K, Solyom E, Meszaros A. (2014) Factors influencing quality of life and disease severity in Hungarian children and young adults with cystic fibrosis.Ital J Pediatr,40:50. **IF_{2013}:1.236**

Articles in Hungarian:

3. **Bodnár R**, Holics K, Ujhelyi R, Kovacs L, Bolbas K, Szekely Gy, Gyurkovits K, Solyom E, Meszaros A. (2013) Cystás fibrosisban szenvedő betegek életminőségének felmérése Magyarországon. [Quality of life in Hungarian patients with cystic fibrosis] Orv Hetil,154(20):784-791.
4. **Bodnár R.** (2012) Az inhalációs antibiotikumok életminőségre gyakorolt hatása cystas fibrosisban. [Impact of inhaled antibiotics on quality of life in cystic fibrosis] Med Thorac,LXV(4):254-259.
5. Ágh T, **Bodnár R**, Ágh L. (2010) Az életminőség-mérés szerepe asztmás betegek gondozásában. Med Univ,43:(5):179-181.
6. **Bodnár R**, Németh Á. (2009) Életminőség-vizsgálat gyermekkori asthma bronchialéban. Tüdőgyógyászat,3(10):2-11.

6.2. Publications independent from the topic of the PhD thesis

Articles in English:

7. **Bodnar R**, Kadar L, Somoskovi A, Meszaros A. (2011) Cost of Tuberculosis in Childhood. Mycobact Diseases,1:2. doi:10.4172/2161-1068.1000102

Book chapter in English:

8. **Bodnar R**, Kadar L, Meszaros A. A Reemerging Bacteria: Cost analysis of care and treatment of tuberculosis (TB) in childhood – Hungary. In: Robinson JS, Walid MS, Barth ACM (szerk.), Toward Healthcare Resource Stewardship. Nova Science Publishers, New York, 2011:217-225. **ISBN:** 978-1-62100-182-9

Articles in Hungarian:

9. **Bodnár R**, Kádár L, Mészáros Á. (2010) A gyermekkori tuberkulózis kezelésének költségelemzése. Tüdőgyógyászat,4(9):2-10.

10. **Bodnár R**, Mészáros Á, Kádár L. (2010) Tuberkulózis kezelése során felmerülő direkt költségek elemzése gyermekkorban. Acta Pharm Hung,80(2):67-73.

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