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Quality of Life, Clinical Effectiveness, and Satisfaction in Pediatric and Young Adult Patients with Sickle Cell Disease Receiving Hydroxyurea Therapy

Hidroksiüre Tedavisi Alan Orak Hücre Hastalığı Olan Pediatrik ve Genç Erişkin Hastalarda Yaşam Kalitesi, Klinik Etkinlik ve Memnuniyet

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ABSTRACT Objective: Despite documented benefits of hydroxyurea (HU) for pediatric and young adults with sickle cell disease (SCD), there is still limited experience with the use of HU in these age groups and knowledge regarding its long-term efficacy, safety, and acceptance remains poorly defined. This study aims to evaluate quality of life, clinical effectiveness, and satisfaction in pediatric and young adult patients with SCD receiving HU. **Material and Methods:** In this study, 34 pediatric (7-11 and 12-17 years) and 16 young adult (18-22 years) patients with SCD receiving HU for at least a year were participated. The data for effectiveness of hydroxyurea therapy and parameters that may affect compliance to treatment and life quality of the participants were evaluated with using Demographic Data Collection Form, Life Quality Survey Short Form-36 (SF-36), Child Health Questionnaire-Parent Form 50, Case Report Form and HU Satisfaction Survey. **Results:** The patients aged 7-11, 12-17, and 18-22 years were being treated with HU at 15.3±4.0 (for 4.7±2.7 years), 14.4±3.7 (for 5.7±3.3 years), and 14.0±6.4 mg/kg/day (for 5.1±2.6 years), respectively. Correlation studies revealed that HU dose was not significantly correlated SF-36 summary scores in these patients. Duration of HU therapy was positively correlated with the SF-36 summary scores for physical functioning, physical role limitation, mental health, and general health perception in the young adult patients. However, duration of HU therapy was negatively correlated with the perceived effectiveness of therapy while positive correlations were observed between duration of treatment and burden of therapy/side effects. **Conclusion:** These findings suggest that the health quality and compliance of the pediatric and young adult patients to therapy might be low due to not sufficiently effective HU therapy in addition to comorbidities, concomitant drug use, and side effects.

Keywords: Hydroxyurea; anemia, sickle cell; compliance

ÖZET Amaç: Orak hücre hastalığı (OHH) olan pediatrik ve genç erişkin hastalarda hidroksiüre (HÜ)'nün yararlarının biliniyor olmasına karşın, bu yaş gruplarında HÜ'nün kullanımıyla ilgili deneyim hala sınırlıdır ve uzun süreli etkililiği, güvenliği ve kabul edilebilirliğine ilişkin bilgiler yetersiz kalmıştır. Bu çalışmada OHH nedeniyle HÜ tedavisi gören pediatrik ve genç erişkin hastalarda yaşam kalitesi, klinik etkinlik ve tedaviye uyum değerlendirilmiştir. **Gereç ve Yöntemler:** Bu çalışmaya, OHH nedeniyle en az 1 yıl süre HÜ tedavisi gören 34 pediatrik (7-11 ve 12-17 yaş) ile 16 genç erişkin (18-22 yaş) hasta katılmıştır. HÜ tedavisinin etkinliği ve katılımcıların tedaviye uyuncu ile yaşam kalitesine ilişkin veriler Demografik Veri Toplama Formu, Yaşam Kalitesi Anketi Kısa Form-36 (KF-36), Çocuk Sağlığı Anketi (Anne/Baba Raporu) 50, Olgu Rapor Formu ve HÜ Tedavisinden Memnuniyet Anketi kullanılarak değerlendirilmiştir. **Bulgular:** 7-11, 12-17 ve 18-22 yaş gruplarındaki hastalar sırasıyla 15,3±4,0 (4.7±2.7 yıl süreyle) mg/kg/gün, 14,4±3,7 (5,7±3,3 yıl süreyle) mg/kg/gün ve 14,0±6,4 (5,1±2,6 yıl süreyle) mg/kg/gün dozda HÜ ile tedavi edilmişlerdi. Genç erişkin hastalar için yapılan korelasyon çalışmaları, HÜ dozunun KF-36 özet puanları ile anlamlı olarak ilişkili olmadığını gösterdi. Bu hastalarda HÜ tedavisinin süresi ile fiziksel işlevsellik, fiziksel rol güçlüğü, ruhsal sağlık ve genel sağlık algısı için SF-36 özet puanları pozitif yönde ilişkiliydi. Öte yandan, bu hastalarda HÜ tedavisinin süresi algılanan etkinlik ile negatif yönde ilişkiliyken, tedavinin süresi ile tedavinin yükü/yan etkiler arasında anlamlı pozitif ilişkiler olduğu gözlendi. **Sonuç:** Bulgularımız, HÜ tedavisinin etkinlik algısının düşük olmasına ek olarak komorbiditeler, birlikte başka ilaç kullanımı ile yan etkilerden dolayı pediatrik ve genç erişkin hastaların yaşam kaliteleri ile tedaviye uyumlarının düşük olabileceğini düşündürmüştür.

Anahtar Kelimeler: Hidroksiüre; anemi, orak hücreli; uyum

Sickle cell disease (SCD) is an autosomal recessive disorder in the gene encoding the β-chain of hemoglobin causing a systemic syndrome characterized by chronic anemia, acute painful episodes, tissue ischemia, and chronic organ damage in addition to a significant reduction in life expectancy.[1-4] Sickle cell anemia (SCA) is the homozygoid form of SCD which includes a group of genetic disorders characterized by production of an abnormal hemoglobin S, hemolysis, and vasoocclusive phenomena with recurrent painful episodes, acute chest syndrome, splenic sequestration, stroke, and cholelithiasis that can lead to life-long disabilities and death. Since a significant amount of hemoglobin F interferes with hemoglobin S polymerization, the presence of fetal hemoglobin (hemoglobin F) seems to play a compara- tively protective role in the pathophysiologic mechanism of vasoocclusive symptoms of this condition.[1,2] As a disease-modifying medication for SCD, hydroxyurea (HU), a ribonucleotide reductase inhibitor, is a potent inducer of fetal hemoglobin (hemoglobin F) synthesis and antisickling chemotherapeutic agent. In the United states and many other countries, HU is approved for pediatric patients. Clinical trials have shown that HU is beneficial, safe, and cost-effective in reducing the frequency and intensity of painful events in as young as 9 months of age, infants, children, and adults with homozygous SCA (HbSS) and HbS/β^0-thalassemia (HbSβ^0).[1,5,6]

Despite documented laboratory and clinical benefits of HU for pediatric and young adults with SCD, there is still limited experience with the use of HU in these age groups and its long-term efficacy, safety, and acceptance remains poorly defined.[7,8] To better understand the potential impact of the therapeutic approach for SCD regarding use of inducers of hemoglobin F synthesis, it is important to understand the clinical effectiveness, patient acceptability, and side effects of HU in addition to patient's health related quality of life (HRQoL). Therefore, the aim of this single-center observational study was to evaluate quality of life, clinical effectiveness, and satisfaction in pediatric and young adult patients with SCD receiving HU therapy.

MATERIAL AND METHODS

Patients and study design: The single-center observational study was conducted among 34 pediatric (7-11 years [HbSS: n=7; HbSβ^0: n=2] and 12-17 years [HbSS: n=22; HbSβ^0: n=3]) and 16 young adult (18-22 years [HbSS: n=11; HbSβ^0: n=5]) patients with SCD who received HU (Hydrea®; Deva Holding, Istanbul, Turkey) for at least a year at the Hematology Unit of Department of Pediatrics, Faculty of Medicine, Mersin University, Mersin, Turkey from May to July 2016. Compliance to the therapy of chronic diseases such as SCD differs among pediatric patients aged 2-11 years, adolescent patients aged 12-17 years, and young adult patients aged 18-22 years. Therefore, we divided the patients into the three age groups to investigate the differences in terms of compliance to the HU therapy. The protocol of this study was approved by Mersin University Clinical Research Ethics Committee and Pharmaceuticals and Medical Devices Administration of Turkey (ClinicalTrials.gov identifier: NCT02868138). This study was conducted in line with Helsinki 2008 Declaration.

Participants were selected based on the inclusion and exclusion criteria. The inclusion criteria were patients willing to participate in the study, patients 2-24 years old, patients diagnosed with HbSS or HbSβ^0 SCD, and patients receiving HU for at least a year. The exclusion criteria were patients not meeting the inclusion criteria, patients diagnosed with other types of anemia except HbSS or HbSβ^0 SCD, patients having other conditions such as physical and/or mental difficulties which may affect their quality of life, and patients having any contrendication against HU.[6]

At the beginning of the study, all eligible patients and/or their parents were informed of the objectives of the study and assured that all information would remain confidential. After taking signed written informed consent from the patients and/or their parents, the following data were obtained through face-to-face survey methods: demographic and clinical characteristics of pediatric and young adult patients (using Demographic Data Collection Form and Case Report Form), health

status of pediatric patients (using Child Health Questionnaire-Parent Form 50; CHQ-PF50), quality of life of young adult patients (using Life Quality Survey Short Form-36; SF-36), and effectiveness and acceptance of HU therapy in pediatric and young adult patients (using Case Report Form and HU Satisfaction Survey).[6,8-15]

Statistical analysis: Qualitative variables were expressed as number and percent. Quantitative variables regarding health status of pediatric patients and compliance to HU therapy in pediatric and young adult patients were described in the form of mean±standard deviation (SD), median, and range. The other quantitative variables were expressed as mean±SD. Data were analysed by one-way ANOVA followed by Tukey test for multiple comparisons. Spearman's rank correlation coefficient and regression analysis were employed to assess the correlation of HU dose and duration of treatment with hematological and biochemical parameters obtained from patient's files, CHQ-PF50, SF-36, and HU therapy summary scores. A *P* value < 0.05 was considered to be statistically significant.

RESULTS

Demographic and clinical characteristics: The demographic and clinical characteristics of the patients are summarized in Table 1. HU dose was not significantly correlated, in particular, with the painful crisis, sequestration crisis, acute chest syndrome, stroke, and/or transfusion histories in the pediatric and young adult patients ($P>0.05$). In the patients aged 12-17 years complaining painful crisis >5 times/year, duration of HU treatment was significantly shorter than the patients having painful crisis <5 times/year ($P<0.05$) while significant correlations were not observed between duration of treatment and these parameters in the pediatric and young adult patients ($P>0.05$). In addition, HU dose and duration of treatment were not significantly correlated with the education of these patients and/or their parents ($P>0.05$). Overall, significant correlations were not observed between HU dose and duration of treatment and the parameters evaluated in the pediatric patients ($P>0.05$) while duration of HU treatment in the patients complaining acute chest syndrome was significantly longer than the patients not having this syndrome ($P < 0.05$).

Quality of life and effectiveness of HU therapy: Table 2 shows the CHQ-PF50 summary scores regarding HRQoL in HU-treated pediatric patients with SCD. In particular, the scores were ranged from 2.6±5.3 (n=9) for the general health to 24.8±3.7 (n=9) the self-esteem in the patients aged 7-11 years. The scores in the patients aged 12-17 years were ranged from 3.1±1.2 (n=25) for the bodily pain/discomfort - severity to 22.5±5.2 (n=25) the family activities. The difference between the scores in the pediatric patients were not statistically significant ($P > 0.05$). The SF-36 summary scores regarding quality of life in young adult patients with SCD who received HU are shown in Table 3. In particular, the scores in the patients were ranged from 70.6±32.6 (n = 16) for the physical functioning to 45.3±44.9 [50.0 (0.0-100.0)] (n=16) for the physical role limitation.

Dose of HU was not significantly correlated SF-36 summary scores in the young adult patients (Tables 1 and 3). In addition, duration of treatment was not significantly correlated CHQ-PF50 scores in the pediatric patients (Tables 1 and 2). However, duration of HU treatment was positively correlated with the SF-36 summary scores for physical functioning, physical role limitation, mental health, and general health perception in the young adult patients (r=0.636, $P < 0.05$; r=0.548, $P < 0.05$; r=0.687, $P < 0.05$; and r=0.684, $P < 0.05$) (Tables 1 and 3).

Table 4 details hematological and biochemical parameters in HU-treated pediatric and young adult patients with SCD. Regarding the normal ranges, ferritin, hemoglobin A2, F, and S, platelet, mean platelet volume (MPV), mean corpuscular volume (MCV), red cell distribution width (RDW), total bilirubin, direct bilirubin, and C-reactive protein values were higher while hemoglobin, hemoglobin A, hematocrit, and erythrocyte values lower in these patients. The values regarding other hematological and biochemical parameters measured were in their normal ranges. Blood creatinine levels were significantly higher in the young adult patients than the pediatric patients. The differences

TABLE 1: Demographic and clinical characteristics of HU-treated pediatric and young adult patients with SCD.

Age groups	**7-11**	**12-17**	**18-22**
Number of patients	9	25	16
Diagnosis[1]			
HbSS	7 (78)	22 (85)	11 (69)
HbSβ^0	2 (22)	3 (15)	5 (31)
Gender[1]			
Female	4 (44)	10 (40)	2 (13)
Male	5 (56)	15 (60)	14 (87)
Age (years)[2]			
Female	9.0±1.8	15.1±2.1	18.0±0.0
Male	8.4±1.3	14.4±1.7	19.1±1.2
Age at diagnosis (years)[2]			
Female	0.6±0.3	1.1±0.9	0.5±0.0
Male	0.8±0.7	1.3±0.2	1.3±1.1
Education[1]			
University	---	---	3 (19)
High school	---	14 (56)	11 (69)
Secondary school	1 (11)	10 (40)	1 (6)
Primary school	8 (89)	---	---
Illiterate	---	---	1 (6)
Home education	---	1 (4)	----
Maternal age[2] (year)	37.8±4.2	40.0±5.3	
Maternal education[1]			
University	---	2 (8)	---
High school	2 (22)	9 (36)	---
Secondary school	1 (11)	3 (12)	---
Primary school	6 (67)	9 (36)	---
Illiterate	---	2 (8)	---
Paternal age[2] (year)	41.3±5.5	45.5±5.03	---
Paternal education[1]			
University	---	1 (4)	---
High school	---	6 (24)	---
Secondary school	2 (22)	5 (20)	---
Primary school	7 (78)	13 (52)	---
Illiterate	---	---	---
Family history[1]			
No	1 (11)	2 (8)	0 (0)
Yes	8 (89)	23 (92)	16 (100)
Painful crisis history[1]			
No	1 (11)	0 (0)	1 (6)
Yes	8 (89)	25 (100)	15 (94)
<5 times/year	7 (78)	19 (76)	14 (93)
>5 times/year	1 (22)	6 (24)	1 (7)
Sequestration crisis history[1]			
No	9 (100)	24 (96)	16 (100)
Yes	0 (0)	1 (4)	0 (0)
Acute chest syndrome history[1]			
No	7 (98)	15 (60)	7 (44)
Yes	2 (22)	10 (40)	9 (56)
Stroke history[1]			
No	9 (100)	18 (72)	13 (81)
Yes	0 (0)	7 (28)	3 (19)
HU therapy[3]			
Age at onset of treatment (year)	4.7±2.7 (4.5 [2.0-8.0])	5.7±3.3 (6.0 [2.0-11.0])	5.1±2.6 (4.5 [2.0-10.0])
Total daily dose (mg/kg)	15.3±4.0 (16.0 [10.0-22.0])	14.4±3.7 (15.0 [8.0-22.0])	14.0±6.4 (14.0 [6.0-33.0])
Duration of treatment (year)	4.0±5.6 (4.0 [0.5-9.0])	9.1±3.5 (9.0 [2.0-15.0])*	14.3±3.0 (15.0 [8.0-19.0])*+

HU, Hydroxyurea; SCD, sickle cell disease. [1] Number of patients (%); [2] mean±SD; [3] mean±SD (median and range).* Significant difference compared with 7-11 age group ($P < 0.05$). + Significant difference compared with 12-17 age group ($P < 0.05$).

TABLE 2: CHQ-PF50 summary scores (%) in HU-treated pediatric patients with SCD.

Age group	7-11 (n=9)	12-17 (n=25)
Scale	Score	
General health	2.6±5.3 [3.0 (2.0-3.0)]	3.2±0.7 [3.0 (2.0-5.0)]
Physical functioning	16.6±4.0 [17.0 (8.0-22.0)]	14.3±5.7 [13.0 (7.0-24.0)]
Role/social limitations - emotional/behavioral	6.3±3.0 [6.0 (3.0-12.0)]	6.9±3.4 [6.0 (3.0-12.0)]
Role/social limitations - physical	4.0±2.7 [2.0 (2.0-8.0)]	5.0±2.4 [4.0 (2.0-8.0)]6
Bodily pain/discomfort		
Severity	3.7±1.0 [3.0 (3.0-6.0)]	3.1±1.2 [3.0 (1.0-6.0)]
Frequency	3.8±1.1 [4.0 (2.0-6.0)]	4.1±0.9 [4.0 (3.0-6.0)]
Behavior	16.6±4.3 [19.0 (10.0-22.0)]	19.4±4.4 [20.0 (9.0-25.0)]
Global behavior	3.2±0.7 [3.0 (2.0-4.0)]	3.4±0.8 [3.0 (2.0-5.0)]
Emotional state	17.2±3.3 [17.0 (13.0-23.0)]	16.4±3.9 [16.0 (9.0-23.0)]
Self-esteem	24.8±3.7 [26.0 (17.0-28.0)]	22.2±5.2 [23.0 (10.0-29.0)]
General health state	10.4±1.8 [11.0 (8.0-13.0)]	11.6±3.2 [10.0 (9.0-19.0)]
Health transition	3.8±1.2 [4.0 (1.0-5.0)]	3.7±0.8 [4.0 (2.0-5.0)]
Parent impact - emotional	8.2±2.5 [9.0 (5.0-13.0)]	8.8±3.3 [9.0 (3.0-14.0)]
Parent impact - time	6.6±3.4 [4.0 (4.0-12.0)]	7.1±2.8 [7.0 (3.0-12.0)]
Family activities	19.3±7.1 [20.0 (9.0-30.0)]	22.5±5.2 [22.0 (10.0-30.0)]
Family cohesion	3.2±0.8 [3.0 (2.0-5.0)]	3.6±0.6 [4.0 (3.0-5.0)]

CHQ-F50, Child Health Questionnaire-Parent Form; HU, hydroxyurea; SCD, sickle cell disease. Minimum and maximum scores are 0 and 100, respectively. Higher scores indicate better health. Data are expressed as mean±SD (median and range).

between the patient groups for the other parameters were not statistically different. As regarded the hematological and biochemical parameters, HU dose was positively correlated with the values of hemoglobin (r=0.747, $P<0.05$) and hematocrit (r=0.773, $P<0.05$) in the patients aged 7-11 years. In the young adult patients, HU dose was negatively correlated with the MPV values (r=-0.580, $P<0.05$) while values of MCV (r = 0.810, $P<0.05$) and mean corpuscular hemoglobin (MCH) (r=0.795, $P<0.05$) were positively correlated with the dose of HU. Moreover, duration of HU therapy was positively correlated with the creatinine values in the patients aged 12-17 years (r=0.695, $P<0.05$) while significant positive correlations were observed between duration of treatment and values of hemoglobin (r=0.501, $P<0.05$) and erythrocyte (r=0.532, $P<0.05$) in the young adult patients. In the patients aged 7-11 years, duration of treatment was not significantly correlated with the hematological and biochemical parameters.

Satisfaction with HU therapy: Table 5 shows HU therapy satisfaction summary scores regarding compliance level of HU-treated pediatric and young adult patients with SCD. In particular, the scores in the patients aged 7-11, 12-17, and 18-22 years were ranged from 15.3±2.8 (n=9), 17.5±4.5 (n=25), and 15.0±5.9 (n=16), respectively, for the perceived effectiveness of HU therapy to 79.9±13.5 (n=9), 83.6±11.3 (n=25), and 79.6±15.2 (n=16), respectively, the side effects of HU therapy. The difference between the scores in the patients aged

TABLE 3: SF-36 summary scores (%) in HU-treated young adult patients with SCD.

Scale	Score (n = 16)
Physical functioning	70.6±32.6 [85.0 (0.0-100.0)]
Physical role limitation	45.3±44.9 [50.0 (0.0-100.0)]
Pain	52.4±24.5 [52.0 (0.0-84.0)]
Mental health	57.8±6.5 [58.0 (44.0-68.0)]
Emotional role limitation	56.3±51.2 [100.0 (0.0-100.0)]
Social functioning	68.0±7.9 [68.8.0 (50.0-75.0)]
Vitality	60.3±6.7 [60.0 (45.0-70.0)]
Health transition over the past year	64.1±22.3 [75.0 (0.0-100.0)]
General health perception	54.1±25.4 [54.5 (0.0-100.0)]

HU, Hydroxyurea; SCD, sickle cell disease; SF-36, Short Form-36. Minimum and maximum scores are 0 and 100, respectively. Higher scores indicate better self-perceived health. Data are expressed as mean±SD (median and range).

TABLE 4: Hematological and biochemical parameters in HU-treated pediatric and young adult patients with SCD.

Age group	7-11	12-17	18-22
Parameter			
Ferritin (ng/ml) *(NR: 7.0-84.0)*	166.2±88.1 (n=9)	371.4±386.7 (n=25)	347.4±555.7 (n=16)
Hemoglobin (g/dl) *(NR: 11.5-12.0)*	9.2±1.2 (n=9)	9.1±1.1 (n=25)	9.6±1.2 (n=16)
Hemoglobin A (%) *(NR: 96.5-98.5)*	1.0±2.0 (n=4)	0.0±0.0 (n=10)	7.7±15.5 (n=8)
Hemoglobin A2 (%) *(NR: 1.5-3.5)*	5.3±1.6 (n=4)	5.4±0.8 (n=10)	5.3±1.5 (n=8)
Hemoglobin F (%) *(NR: < 2)*	12.9±10.4 (n=4)	14.4±6.2 (n=10)	7.4±5.4 (n=8)
Hemoglobin S (%) *(NR: < 0.1)*	80.8±9.0 (n=4)	80.21±6.0 (n=10)	79.6±14.2 (n=8)
Hematocrit (%) *(NR: 34.0-43.0)*	27.8±3.8 (n=9)	27.5±3.7 (n=25)	29.1±3.6 (n=16)
Platelet (x 10^3/µl) *(NR: 150.0-400.0)*	426.6±109.6 (n=9)	546.0±221.2 (n=25)	438.9±186.5 (n=16)
MPV (fl) *(NR: 7.4-10.4)*	8.3±1.3 (n=9)	8.3±1.1 (n=25)	8.5±1.5 (n=16)
Erythrocyte *(x 10^6/µl) (NR: 3.9-5.1)*	3.3±0.6 (n=9)	3.0±0.7 (n=25)	3.2±0.7 (n=16)
MCV (fl) *(NR: 75.0-87.0)*	87.7±16.9 (n=9)	93.3±10.3 (n=25)	95.2±16.3 (n=16)
RDW (%) *(NR: 11.6-14.8)*	20.8±5.2 (n=9)	20.7±3.1 (n=25)	22.1±4.8 (n=16)
WBC *(x 10^3/µl) (NR: 4.5-13.5)*	11.1±4.9 (n=9)	11.5±3.9 (n=25)	11.0±4.6 (n=16)
Creatinine (mg/dl) *(NR: < 0.9)*	0.3±0.1 (n=9)	0.4±0.1 (n=24)	0.5±0.1 (n=16)*
Urea (mg/dl) *(NR: 10.7-38.5)*	19.5±5.1 (n=9)	15.9±4.2 (n=23)	15.6±5.2 (n=16)
Total bilirubin (mg/dl) *(NR: < 1)*	2.4±1.5 (n=3)	3.7±3.9 (n=7)	4.2±2.8 (n=9)
Direct bilirubin (mg/dl) *(NR: < 0.5)*	0.5±0.2 (n=3)	0.7±0.2 (n=10)	1.1±0.9 (n=9)
ALT (U/l) *(NR: < 39)*	19.5±7.4 (n=9)	22.4±18.4 (n=24)	24.8±9.6 (n=16)
AST (U/l) *(NR: < 47)*	36.6±9.6 (n=9)	45.2±23.2 (n=24)	34.3±8.7 (n=16)
CRP (mg/l) *(NR: < 5)*	4.4±5.1 (n=7)	8.4±11.6 (n=20)	14.5±22.3 (n=14)

ALT, alanine aminotransferase; AST, aspartate transaminase; CRP, C-reactive protein; RDW, red cell distribution width; HU, hydroxyurea; MCV, mean corpuscular volume; MPV, mean platelet volume; NR, normal range; SCD, sickle cell disease; WBC, white blood cell count. Data are expressed as mean±SD. * Significant difference compared with 7-11 and 12-17 age groups (P < 0.05).

TABLE 5: HU therapy satisfaction summary scores (%) in pediatric and young adult patients with SCD.

Age group	7-11 (n = 9)	12-17 (n = 25)	18-22 (n = 16)
Concept		**Score**	
Perceived effectiveness of HU therapy	15.3±2.8 [16.0 (10.0-18.0)]	17.5±4.5 [20.0 (4.0-20.0)]	15.0±5.9 [18.5 (4.0-20.0)]
Acceptance of HU therapy	35.9±3.2 [37.0 (29.0-39.0)]	36.5±4.7 [38.0 (20.0-40.0)]	36.4±3.9 [37.5 (26.0-40.0)]
Burden of HU therapy	24.3±2.0 [25.0 (19.0-25.0)]	24.5±2.0 [25.0 (15.0-25.0)]	24.1±2.6 [25.0 (15.0-25.0)]
Side effects of HU therapy	79.9±13.5 [80.5 (51.6-94.4)]	83.6±11.3 [86.1 (51.1-94.4)]	79.6±15.2 [86.1 (36.6-91.6)]

HU, Hydroxyurea; SCD, sickle cell disease. Minimum and maximum scores are 0 and 100, respectively. Higher scores indicate better satisfaction. Data are expressed as mean±SD (median and range).

7-11, 12-17, and 18-22 years were not statistically significant (P>0.05).

HU dose was not significantly correlated with the HU therapy satisfaction summary scores in the pediatric and young adult patients (P>0.05) (Tables 1 and 5). In the pediatric patients, duration of treatment was also not significantly correlated with the scores (P>0.05). However, duration of HU therapy in the young adult patients was negatively correlated with the perceived effectiveness of HU therapy (r=-0.611, P<0.05) while significant positive correlations were observed between duration of treatment and burden of HU therapy (r=0.552, P<0.05) and side effects (r=0.683, P<0.05).

CHQ-PF50 summary scores for general health (r=0.889, P<0.05), bodily pain/discomfort-severity (r=0.841, P<0.05), bodily pain/discomfort-frequency (r=0.842, P<0.05), global behavior (r=0.918,

P=0.001), health transition (r=0.866, *P*<0.05), parent impact-emotional (r=0.847, *P*<0.05), and family cohesion (r=0.772, *P*<0.05) were also positively correlated with the HU therapy satisfaction summary score for perceived effectiveness of HU therapy in the patients aged 7-11 years (Tables 2 and 5). In the patients aged 12-17 years, CHQ-PF50 summary scores for general health (r=0.558, *P*<0.05), bodily pain/discomfort-severity (r=0.811, *P*<0.05), bodily pain/discomfort-frequency (r=0.806, *P*<0.05), global behavior (r=0.528, *P*<0.05), self-esteem (r=0.833, *P*<0.05), health transition (r=0.887, *P*<0.05), parent impact-emotional (r=0.775, *P*<0.05), and family cohesion (r=0.725, *P*<0.05) were positively correlated with the perceived effectiveness of HU therapy. In the young adult patients, SF-36 summary scores for pain (r=0.973, *P*<0.05) and health transition over the past year (r=0.874, *P*<0.05) were positively correlated with the perceived effectiveness of HU therapy (Tables 3 and 5).

Although CHQ-PF50 summary scores were not correlated with the acceptance of HU therapy in the pediatric patients (*P*>0.05) (Tables 2 and 5), SF-36 summary scores for vitality (r=0.749, *P*<0.05) and health transition over the past year (r=0.513, *P*<0.05) were also positively correlated with the acceptance of HU therapy in the young adult patients (Tables 3 and 5).

Table 6 details proportional distribution of satisfaction with acceptance of side effects of HU therapy observed in these patients. No serious side effects necessitating discontinuation or interruption of therapy in these patients were reported and no patients died during the study.

DISCUSSION AND CONCLUSION

HRQoL involves several aspects which includes domains related to emotional, physical, mental, and social functioning and focuses on the impact health status has on quality of life. The importance of the CHQ-PF50 and SF-36 questionnaires and the results of the individual scales on the actions that should be taken for pediatric and adult patients with SCD have been reported.[10,16-21] However, there is little published data on HRQoL in HU-treated pediatric and adult patients with SCD.[15,22-24]

HU treatment benefits include reduced frequency of acute sickle cell pain and acute chest syndrome, reduced need for blood transfusions and hospitalizations, and possibly improved survival. It is suggested that HU should be started 10 to 15 mg/kg/day to be initial dose and the dose should be adjusted upwards by 5 mg/kg/day increments every 6 to 12 weeks, to a target of approximately 30-35 mg/kg/day, as long as there is no major toxicity. Although we observed that our patients were receiving HU for a long time, HU dose was found to be almost at the starting dose because of the side effects of HU especially risk of neutropenia and did not reach maximum amounts in the patients. Yet, HU dose was positively correlated with the hemoglobin and hematocrit values in the patients aged 7-11 years and MCV and MCH values in the young adult patients. Hemoglobin and erythrocyte values were also positively correlated with duration of HU treatment in the young adult patients. These findings suggest that particularly increase in the hemoglobin and MCV values reflects to the compliance of the patients to HU therapy. Although the patients were receiving long-term HU therapy, we could not observed clinical outcomes of HU use almost all patient groups. Exclusively, duration of HU use was significantly longer in the patients aged 12-17 years having painful crisis <5 times/year. This finding suggests that prolongation of HU treatment leads to a decrease in the number of painful crises in these patients. Although positive effect of HU on the clinical findings of patients with SCD is well known, one of the reasons of unexpected findings in the present study could be treatment of these patients with quite lower doses of HU resulting in poor compliance.

Correlation studies revealed that duration of treatment was not significantly correlated CHQ-PF50 scores in the pediatric patients. HU dose was also not significantly correlated with the HU therapy satisfaction summary scores in the pediatric and young adult patients. However, duration of HU treatment was positively correlated with the SF-36 summary scores for physical functioning, physical role limitation, mental health, and general health perception in the young adult patients. These find-

TABLE 6: Proportional distribution of satisfaction with acceptance of side effects of HU therapy in pediatric and young adult patients with SCD.

Age group %	7-11 (n = 9)	12-17 (n = 25)	18-22 (n = 16)
90-100	Unusual bleeding or bruising, black tarry stool or blood in the stool, and/or purple raised patches of skin	Unusual bleeding or bruising, hallucination, difficulty or pain passing urine, black tarry stool or blood in the stool, rash, darkening of the skin, loss of skin and/or nail, and/or purple raised patches of skin	Hallucination and/or vomitting
80-90	Convulsion, numbness or formication in the hands or legs, rash, and/or loss of skin and/or nail	Convulsion, tremor, numbness or formication in the hands or legs, nausea, vomitting, and/or diarrhea	Infection, nausea, difficulty or pain passing urine, black tarry stool or blood in the stool, rash, loss of skin and/or nail, and/or purple raised patches of skin
70-79	Tremor, hallucination, difficulty or pain passing urine, and/or darkening of the skin	Abdominal pain	Unexplained fever, chill or sore throat, diarrhea, abdominal pain, and/or anxiety
60-69	Headache, drowsiness, diarrhea, sore/dryness on the lips or mouth, and/or hair loss	Increase/decrease in appetite, sore/dryness on the lips or mouth, and/or hair loss	Tremor, numbness or formication in the hands or legs, dizziness, and/or compliance problem with social environment
50-59	Infection, unexpected difficulty breathing or cough with fever, unexplained fever, chill or sore throat, anemia, somnolence, dizziness, increase/decrease in appetite, weakness or loss of energy, nausea, vomitting, abdominal pain, compliance problem with social environment, and/or anxiety	---	Convulsion, unexpected difficulty breathing or cough with fever, increase/decrease in appetite, sore/dryness on the lips or mouth, and/or hair loss
0-49	Lower back or flank pain	Infection, unexpected difficulty breathing or cough with fever, unexplained fever, chill or sore throat, lower back or flank pain, anemia, headache, somnolence, drowsiness, drowsiness, weakness or loss of energy, compliance problem with social environment, and/or anxiety	Lower back or flank pain, anemia, headache, somnolence, drowsiness, and/or weakness or loss of energy

HU, Hydroxyurea; SCD, sickle cell disease. Higher percentage values indicate better satisfaction.

ings suggest that satisfaction of these patients does not related with HU dose. Especially in the young adult patients, feeling better themselves regarding in particular physical issues seems to be due to long-term HU treatment. However, the patients at early ages appear not to correlate their satisfaction with HU therapy and complain burden of their treatment. Considering HU satisfaction summary scores, the scores for perceived effectiveness and acceptance of HU therapy were quite low in these patients. Similarly, CHQ-PF50 and SF-36 summary scores used for evaluation of HRQOL were also fairly low. However, the highest CHQ-PF50 or SF-36 summary scores were found to be for the general health, family activities, and physical role limitation in the patients aged 7-11, 12-17, and 18-24 years, respectively. Poor compliance to HU therapy in these patients is probably due to a complex combination of psychological/physical/social/demographic factors, living with a chronic disease,

concomitant diseases/conditions and drug use, and new challenges related to improved life expectancy in the diseases. It is also possible that problems with dose and duration of treatment in addition to comorbid diseases and concomitant drug use appear to be common causes of poor compliance to HU therapy in these patients.

As regarded HU therapy satisfaction summary scores, the highest scores in these patients were found to be for the side effects of HU therapy. Short term toxicities of HU are mainly those associated with myelosuppression. Other possible toxicities include renal and hepatic toxicity, gastrointestinal symptoms, cutaneous ulcerations, mucositis, and pancreatitis. Long-term toxicities of HU is not known related with to induce tumors, although concerns have been raised about an increased incidence of acute myeloid leukemia when used in patients with the malignant myeloproliferative neoplasms.[6,7,25-27] In the present study, we did not observed myelosuppression, nephrotoxicity, hepatotoxicity, and malignancy. Frequent emergency department visits and hospitalizations to manage pain and other complications, chronic medical treatment, inadequate nutrition, social limitations, increased dependence on family control, and economical and psychological problems of patients' families are the principal factors for the development of psychiatric disorders in the sufferers of SCD.[2-4] Due to these factors, the quality of life decreases and psychiatric problems such as depression, anxiety, and rejection of the therapy can be detected in patients with SCD.[3,4] The problems become clinically important especially in the adolescents and young adults. The positive correlation between perceived effectiveness and most of the concepts of CHQ-PF50 summary scores in the pediatric patients suggests that the increased rate of perceived effectiveness in these patients is related with feeling better themselves physiologically and psychologically. A similar correlation in the young adult patients were observed between pain and health transition over the past year scales of SF-36 summary scores. Also, in these patients, duration of HU treatment was negatively correlated with the perceived effectiveness of HU therapy while significant positive correlations were observed between duration of treatment and burden of HU therapy and side effects. These findings suggest that increased duration of therapy especially at older ages decreases expectations of patients from their treatments and complain burden of therapy. The positive correlation between duration of HU treatment and physical functioning, physical role limitation, and mental health is expected in the young adult patients. However, poor compliance of these patients to HU therapy seems to be due to the low rates of perceived effectiveness and acceptance of HU therapy. As expected, in the young adult patients, positive correlations were observed between duration of treatment and burden of HU therapy and side effects. Additional studies highlight higher hospitalizations, readmissions, and acute care utilization for young adults ages 18-30.[3,4]

In conclusion, the results of the present study suggest that the health quality and compliance of the pediatric and young adult patients to therapy might be low due to not sufficiently effective HU therapy in addition to comorbidities, concomitant drug use, and side effects. These findings are not surprising in the context of studies on poor compliance of patients with SCD to HU therapy.[6-8,12,13,15,24,25,27-29] With the increasing number of clinical studies that support HU use in the patients with SCD, a properly feasible strategy will likely be needed to effective use of HU in clinical practice.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Bahar Tunçtan, Selma Ünal;* ***Design:*** *Bahar Tunçtan, Selma Ünal;* ***Control/Supervision:*** *Bahar Tunçtan, Selma Ünal;* ***Data Collection and/or Processing:*** *Bahar Tunçtan, Selma Ünal, Furkan Cevher, Şefika Pınar Küçükkavruk;* ***Analysis and/or Interpretation:*** *Bahar Tunçtan, Selma Ünal, Bahar Taşdelen;* ***Literature Review:*** *Bahar Tunçtan, Selma Ünal;* ***Writing the Article:*** *Bahar Tunçtan, Selma Ünal, Bahar Taşdelen;* ***Critical Review:*** *Bahar Tunçtan, Selma Ünal, Bahar Taşdelen;* ***References and Fundings:*** *Bahar Tunçtan, Selma Ünal.*

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