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Hydroxyurea: Pattern of Use, Patient Adherence, and Safety Profile in Patients with Sickle Cell Disease in Oman

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ABSTRACT

Objectives: Many barriers contribute to the underutilization of hydroxyurea (HU) in the treatment of sickle cell disease (SCD), and adherence to its use is often reported to be suboptimal. It is important to have information on the safety of HU in patients with SCD. Our study assessed the pattern of use, patients' adherence to medication, discontinuation of use, and safety of HU in patients with SCD. ***Methods***: This cross-sectional study was conducted in the department of medicine of a referral hospital in Oman over five months and included a review of patient files and patient interview. Approval was obtained from the Regional Research and Ethics Committee of the A'Dakhiliyah Governorate and the hospital administration. The parameters were compared between groups using the chi-square test. ***Results:*** Of 298 patients studied, 128 (43.0%) had used HU at some points. The difference in the prevalence of HU use was statistically significant based only on age ($p = 0.014$), with younger patients more likely to be currently using HU or used HU in the past. The majority of patients were adherent (82.5%) based on self-reported adherence. The prevalence of discontinuation (temporary or permanent) of HU use was high (57.0%), and suspected adverse drug reaction (ADR) was the most common reason. Among those who had never used HU, 33.7% of patients had an indication for the initiation of HU. A quarter of patients who used HU developed a suspected ADR, with blood abnormalities being the commonest. The duration of HU use influenced ADR prevalence ($p = 0.015$). ***Conclusions:*** Among the current users of HU, the majority of the patients were adherent based on self-reported medication adherence. The prevalence of discontinuation of HU use and instances of non-initiation of HU among those indicated were high. A larger study, ideally of a prospective nature, in various governorates of Oman, would provide a wider picture at the national level.

Sickle cell disease (SCD) affects millions of people throughout the world.[1,2] It is a disease contributing to significant morbidity in the Arab world and the Middle East including Oman.[3,4] The prevalence of sickle cell trait and disease reported in Oman were 6% and 0.2%, respectively, in a 2003 report.[4] Treatment of SCD includes management of its acute and chronic complications and it comprises pain management, use of fetal hemoglobin inducers like hydroxyurea (HU), blood transfusion, and hematopoietic stem cell transplantation.[5] Other than HU, new therapeutic approaches for SCD treatment are being developed, and several studies are underway to determine the safety and efficacy of these new treatments.[6–8] The evidence supporting the expanded use of HU is increasing.[7] HU treatment is reported to produce several benefits in patients with SCD ultimately contributing to decreasing morbidity and mortality.[9–12] Reduced length of hospital stay and readmission rate are reported among patients on HU.[13] HU increased fetal hemoglobin is reported to translate to significant clinical benefits for patients.[14–16] Studies conducted within the Middle East region assessing the beneficial effects of HU in patients with SCD have also shown promising results as seen elsewhere.[9,13,17,18] Unfortunately, underutilization or suboptimal use of HU is a serious problem among patients with SCD.[6,19–24] Side effects and lack of patient adherence to treatment is a major concern associated with its use.[20,21,25] Its long-term safety profile is also a concern.[12,26–28]

Several barriers, including those related to the health care provider, patient, and health care system,

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contribute to the suboptimal use of HU. Involving patients and their families in treatment decision making is crucial because their concerns may or may not be the same as those of health care providers.[25,29] The identification of these aspects can form the basis of developing strategies for addressing the concerns, which might improve patient compliance and response to HU treatment.[30] Only limited studies have been conducted in Oman evaluating the use of HU in adult patients with SCD.[31] Most of the studies conducted have focused on the prevalence of SCD and its genetic determinants and other parameters.[3,4,32–34] Obtaining local data to understand the barriers is essential because this can form the basis of interventions based on regional needs. Moreover, assessing the level of patient adherence and factors contributing to it would be of additional value. Perceptions and misconceptions among patients regarding the use of HU must be identified.[29] The safety pattern of drugs may differ among medication users depending on the genetic influence, environment, and other factors. The literature on the pattern of adverse effects of HU among patients with SCD in this region is lacking. Therefore, our study was conducted to assess the pattern of use, patient adherence, and safety of HU predominantly in adult patients with SCD in the department of medicine of a referral hospital in Oman.

METHODS

This cross-sectional study was conducted over five months (January to May 2016) in patients with SCD from Nizwa Hospital, Oman. Patients with SCD were recruited from three different divisions; patients hospitalized in the department of medicine, patients visiting the outpatient clinic, and patients admitted to or visiting the emergency department for problems related to SCD. Patients from the emergency department were selected on a random basis based on the on-call duty of the data collector (one day per week during the study period). Patients aged ≥ 13 years old who sought treatment and medical care for SCD were referred to the department of medicine. Nizwa Hospital is located in the A'Dakhiliyah governorate, which is approximately 150 km away from Muscat, the capital city. Nizwa Hospital is a 350-bed referral medical facility that provides secondary (specialty) health care to the local population of the governorate of A'Dakhiliyah and its neighboring governorates including A'Dhahirah and AlWasta. According to the 2015 mid-year statistics, Nizwa Hospital catered for 650 000 people from the total Omani population of 4.16 million.[35] This study was conducted after obtaining approval from the Regional Research and Ethics Committee of the A'Dakhiliyah governorate and the hospital administration.

Individual patient files were reviewed, and the required details were documented. These included details on diseases, pattern of HU use (dose regimen, indication for use, and duration of use), reported medication adherence, and adverse drug reactions (ADRs) observed. The World Health Organization defines the ADR as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man."[36] In addition, we evaluated whether the dose of HU was increased from the initial dose during treatment. Individual patients were interviewed for details regarding their adherence to HU, ADRs observed, discontinuation of HU use, reasons for denying initiation of HU treatment, and any other relevant details required for the study. We identified and recorded suspected ADRs based on details collected from patients' interviews and/or medical records. These data were utilized to determine the prevalence of the suspected ADRs, classify the types of ADRs observed, and evaluate the action taken in response to the suspected ADRs. The prevalence of suspected ADR refers to the presence of an ADR at the time of data collection or a history of an ADR suspected to be caused by HU. Patients' medication adherence was assessed (with permission) using a scale published by Gehi et al.[37,38] In this scale, respondents could report their self-reported adherence as 'all of the time (100%)'; 'nearly all of the time (90%)'; 'most of the time (75%)'; 'about half of the time (50%)'; and 'less than half of the time (< 50%)'. Patients who responded as 'all of the time' and 'nearly all of the time' were categorized as adherent, whereas those who responded as 'most of the time'; 'about half of the time'; and 'less than half of the time' were classified as nonadherent. Verbal consent was obtained before interviewing and collecting details from patients. Depending on the feasibility, availability, and need, details obtained from electronic patient records, and those obtained from patient interviews were utilized.

Indications for the use of HU, which were generally considered in practice for the SCD patient population in our clinical setting and accordingly considered in this study,[39] encompassed SCD patients with any of the following indications; three or more sickle cell-associated vaso-occlusive pain crisis in a 12-month period, a history of acute chest syndrome, and severe symptomatic chronic anemia. In addition, on a case-to-case basis, frequent visits to the emergency department due to pain episodes but no hospitalization due to patient disinterest was also considered as an indication for the use of HU. Patients with SCD with the following genotypes were considered as candidates for HU treatment: SS, S beta 0, S beta +, SC disease, and HbS Oman.[40]

Statistical analysis was conducted using SPSS Statistics (SPSS Inc. Released 2007. SPSS for Windows, Version 16.0. Chicago, SPSS Inc.) to evaluate the relationship between patient demographics and the prevalence of HU use. Furthermore, the relationship between patient demographics and the duration of HU use with the instances of discontinuation of HU (by patients or physicians), and the occurrence of ADRs were evaluated. The parameters were compared between groups using the chi-square test. The difference was considered statistically significant for *p*-values < 0.050.

RESULTS

A total of 298 patients met the inclusion criteria from a patient pool of 387 patients with SCD aged ≥ 13 years who had visited the hospital during the study period. Approximately 1450 patients with SCD in the same age group were registered in hospital records during this period.

Table 1: Relationship between patient demographics and hydoxyurea (HU) users.

Demographics	HU use status at present/in past		
	Yes n (%)	No n (%)	*p*-value
Gender			0.373
Male	64 (46.0)	75 (54.0)	
Female	64 (40.3)	95 (59.7)	
Age, years			0.014
< 18	33 (50.0)	33 (50.0)	
18–30	65 (43.0)	86 (57.0)	
31–45	30 (42.3)	41 (57.7)	
46–60	0 (0.0)	9 (100)	
61–75	0 (0.0)	1 (100)	

Table 2: Self-reported adherence.

Adherence	n (%)
Self-reported adherence	
All of the time (100%)	40 (50.0)
Nearly all of the time (90%)	26 (32.5)
Most of the time (75%)	7 (8.8)
About half the time (50%)	2 (2.5)
Less than half the time (< 50%)	5 (6.3)
Total	80 (100)
Adherence category	
Adherent	66 (82.5)
Nonadherent	14 (17.5)
Total	80 (100)

A total of 128 (43.0%) patients had used HU as a form of treatment for SCD at any time during their disease. Eighty (62.5%) patients were using HU at the time of the study and data collection (current users). Forty-eight (37.5%) patients were past users; these patients had used HU at some time during their disease, but were not currently on HU as it was discontinued permanently either by the patient or their clinician. Current use or past use were considered for representing the prevalence of HU use. The number of hospitalizations due to vaso-occlusive crisis was the primary indication for HU use in the majority of patients. However, 170 (57.0%) patients never used HU.

The difference observed in the prevalence of HU use based on patient demographics was statistically significant based on age [Table 1]. The median age of the current and past users was 24.0 (interquartile range [IQR], 12) years. By contrast, the median age of the patients who had never received HU was 27.0 (IQR, 12) years. The difference in the median age between the groups was not significant ($p = 0.085$). The median duration of HU use in current and past users was 26.5 (IQR, 73) months calculated from a total of 124 patients. The data of four patients was not available. Among current HU users (n = 80), the initial dose was increased only in 52 (65.0%) patients.

The majority of patients were categorized as adherent (n = 66, 82.5%) based on self-reported adherence to HU [Table 2]. Patients who responded 'all of the time' or 'nearly all of the time' were considered adherent.[37,38] Among the 14 patients who

Table 3: Discontinuation of hydroxyurea use and prevalence of adverse drug reactions (ADRs) based on patient demographics and duration of use.

Demographics	Discontinuation			ADR present		
	Yes n (%)	No n (%)	*p*-value	Yes n (%)	No n (%)	*p*-value
Gender			1.000			0.066
Male	36 (56.3)	28 (43.8)		11 (17.2)	53 (82.8)	
Female	37 (57.8)	27 (42.2)		21 (32.8)	43 (67.2)	
Age, years			0.142			0.076
< 18	14 (42.4)	19 (57.6)		4 (12.1)	29 (87.9)	
18–30	40 (61.5)	25 (38.5)		17 (26.2)	48 (73.8)	
31–45	19 (63.3)	11 (36.7)		11 (36.7)	19 (63.3)	
46–60	-	-		-	-	
Duration of use, months			0.002			0.015
0–2	13 (86.7)	2 (13.3)		9 (60.0)	6 (40.0)	
> 2–≤ 6	9 (64.3)	5 (35.7)		4 (28.6)	10 (71.4)	
> 6– ≤ 12	9 (90.0)	1 (10.0)		3 (30.0)	7 (70.0)	
> 12–≤ 36	20 (55.6)	16 (44.4)		4 (11.1)	32 (88.9)	
> 36–≤ 60	8 (57.1)	6 (42.9)		4 (28.6)	10 (71.4)	
> 60	11 (32.4)	24 (68.6)		6 (17.1)	29 (82.9)	

were classified as nonadherent, the majority (n = 11, 78.6%) reported 'forgetting to take the medication' as the reason for nonadherence, followed by being 'too lazy to take' the medication (n = 6, 42.9%). In 11 of the 67 patients who used HU for more than two years, instances of missing follow-up in the outpatient department for more than two visits were observed.

Among the 128 patients currently taking HU or who had used it in the past, the instances of discontinuation, either temporary or permanent, were high (n = 73, 57.0%) [Table 3]. A significant difference in the instances of discontinuation of HU was observed based on the duration of HU use. The patients who used HU for a shorter period (0–2 and 6–12 months) tended to discontinue treatment at a higher rate than patients in the other time categories.

HU was more often discontinued by the physician (n = 39, 53.4%) than the patients (n = 36, 49.3%). Among the instances of the drug being discontinued by the physician, it was mainly stopped due to the presence of a suspected ADR (n = 17, 43.6%) [Table 4]. Similarly, the development of an ADR was the most common reason (n = 14, 38.9%) for the discontinuation of HU by the patients themselves. Among the 31 reports in which the drug was discontinued due to a suspected ADR, either by the physician or patient, the discontinuation was temporary in 13 with the drug reintroduced after recovery from the suspected ADR. Issues with regular follow-up were reported as a reason for self-discontinuation by nine patients.

Among the 169 patients who had never received HU treatment, the drug was not initiated despite

Table 4: Reasons for discontinuation.

Reasons	n (%)
Reasons for discontinuation by doctor	
Adverse drug reaction	17 (43.6)
Presence of caution/contraindication	12 (30.8)
No benefit	1 (2.6)
Others	4 (10.3)
No reason specified	5 (12.8)
Total	39 (100)
Reasons for discontinuation by patient	
Developed suspected adverse drug reaction	14 (38.9)
No benefit	3 (8.3)
No specific reason	2 (5.6)
Fear of side effects	1(2.8)
Other reasons	13 (36.1)
No follow-up	9 (69.2)
Forget to take	2 (15.4)
Feeling better after surgery	1 (7.7)
On regular exchange	1 (7.7)
No details on the reason	6 (16.7)
Total	36 (100)

Table 5: Reason for non-initiation of hydroxyurea in patients with an indication.

Reason	n (%)
Patient refused	17 (29.8)
Fear of side effects	7 (41.2)
Does not anticipate any benefit	2 (11.8)
Other reasons	4 (23.5)
No specific reason	7 (41.2)
No details on reason	-
Presence of contraindication/caution for its use	30 (52.6)
Pregnancy	8 (26.7)
Follow-up issue/non-compliance	20 (66.7)
Caution due to disease	2 (6.7)
No reason specified	1 (1.8)
No evidence that the drug was considered for use	9 (15.8)

having an indication for its use in 57 (33.7%) patients. The presence of a contraindication or caution for its use was the most (n = 30, 52.6%) common reason for not initiating HU by the clinician followed by patient refusal (n = 17, 29.8%) [Table 5]. Physicians were concerned that 20 of these patients might not be able to commit to a regular laboratory monitoring follow-up, do not have a regular follow-up with the SCD clinic of the hospital, or have issues of medication non-compliance. Eight patients were not initiated with HU treatment as a precautionary measure as they were pregnant. Among the 17 patients who refused the medication, fear of side effects was a leading factor (n = 7, 41.2%).

Among the 128 patients who used HU, 31 (24.2%) developed a suspected ADR. No significant difference was observed in the prevalence of ADR based on the gender and age group of the patients. However, the duration of HU use had a direct influence on the prevalence of ADR [Table 3]. The most common types of ADR observed in the patients were blood abnormalities (n = 19, 61.3%) followed by gastrointestinal disturbances (n = 5, 16.1%) and rashes (n = 2, 6.5%). Blood abnormalities observed in the patients were a decreased neutrophil count (< 1000 cells/mm^3; n = 14, 73.7%), a decreased thrombocyte count (< 80 000 cells/mm^3; n = 4, 21.1%), and anemia (n = 1, 5.3%). In all 19 cases of suspected ADRs identified as blood abnormalities, the drug was stopped. In 12 instances (63.2%), the drug was reintroduced after recovery of the blood abnormalities. Among the 12 patients in whom the suspected ADR was identified to affect other body systems, the drug was stopped in 10 and later reintroduced in one patient.

DISCUSSION

This study provided information regarding the pattern of HU use in patients with SCD and their level of self-reported medication adherence, instances of discontinuation of HU, reasons for non-initiation in those indicated, and crucial information on the safety of this drug.

HU use was not common in the 298 patients with SCD included in this study. The figures were lower than those reported in previous studies.[41,42] The prevalence of HU use was higher in patients aged < 18 years. The mean age of current HU users in a similar study was 33.3±11.9 years.[42] The median duration of HU use in our study was 26.5 (IQR, 73) months, which was higher than that reported in a study conducted in Nigeria (12 months).[41] Similarly, in another study, 84% of patients who used HU in the past had used the drug for < 1 year.[42]

The majority (82.5%) of patients were categorized as adherent. A study that assessed HU adherence and its associated outcomes among Medicaid enrollees with SCD reported that among 312 patients, only 35% were adherent, which was defined by a medication possession ratio of ≥ 0.80.[43]

Among the 14 patients who were classified as nonadherent, the majority reported 'forgetting to take the medication' as the reason. Forgetfulness by parents to administer the medicine was considered a common factor for medication nonadherence in children with SCD.[44] Various methods can be used to improve adherence to HU treatment including directly observed treatment, home visits, text message reminders, and electronic medication container-monitor-reminder devices.[45–50] Difficulty in obtaining medication refills from the pharmacy and visiting the clinic for follow-up as well as poor access to health care facilities were also reported as common reasons for nonadherence.[25,51,52] In a recent study conducted in Nigeria, barriers to the use of HU were the cost of medication, non-availability, follow-up visits, and drug restriction.[53] In our study, difficulty in adhering to the frequent follow-ups required while receiving HU treatment was a reason for the non-initiation of HU in some patients and the self-discontinuation of the medicine. In the

health care system in Oman, a patient started on HU is required to visit a hospital to perform follow-up for laboratory monitoring tests and meet the treating physician. However, if part of these visits are done in the local primary health centers and the major follow-up with the treating physician in regional or local hospitals, it might improve the willingness of patients to begin on HU, improve patient adherence, and reduce discontinuation. Efforts must be taken to reduce this system-based barrier. In the recent past, pharmacists in Oman have embraced a more active role in patient care. Accordingly, they should be actively involved in patient counseling to address the concerns of patients regarding HU as well as monitor and ensure appropriate medication adherence. This might bring a change in adherence, avoiding unnecessary discontinuation, and motivate patients to initiate the use of HU. Routine assessment of HU adherence and its related barriers is crucial because it can provide useful information to improve adherence rates and associated clinical outcomes.[52,54]

The prevalence of discontinuation of HU use was higher among those who used it for a shorter duration (0–2 and 6–12 months). A six-month trial on the maximum tolerated dose is required before considering discontinuing HU due to treatment failure.[55] Haywood et al,[42] reported that 50% of adult patients with SCD who had used HU previously reported use for < 6 months. Patients usually expect a rapid response to HU and failure of the same might contribute to early discontinuation of treatment.

HU was more often discontinued by the doctor than the patient, and the development of a suspected ADR was the most commonly reported reason. The most commonly reported reasons for stopping HU in the study conducted by Haywood et al,[42] were 'doctor's recommendation' or 'not liking the way it made me feel.' Montalembert et al,[56] reported that among 257 children on long-term HU treatment, 81 discontinued due to treatment failure or nonadherence.

Although there was an indication for HU use, the drug was not initiated in > 30% of patients with SCD. The eight patients who were not initiated on HU because of their pregnancy status were not started on HU after delivery mainly because they wished to breastfeed, subsequently became pregnant, and/or had improper follow-up with the clinic. The most common reason reported by patients who denied the initiation of HU was the fear of side effects. Haywood et al,[42] and Oyeku et al,[57] reported that the side effects of HU was a crucial factor that affected the patients' or caregivers' decision regarding the initiation of HU. Identifying health literacy and knowledge gaps in patients with SCD and their caregivers is important, and designing interventions, such as individual and group education sessions, to improve their knowledge and enhance the perception of HU usage are pivotal.[29,58] Having a system to foster a patient's and caregiver's involvement is important for facilitating shared decision making, because this can help reduce the barriers to HU initiation.[58–60] Targeted steps need to be initiated among providers to ensure appropriate initiation and continuation of this approved disease-modifying therapy.

One-quarter of HU users developed a suspected ADR, and the most common type was a blood abnormality. Blood abnormalities are common, dose-dependent, and reversible. The development of a blood abnormality reaching the threshold should result in withholding HU until the blood abnormality resolves.[5,61] The duration of HU use exerted an effect on the prevalence of ADRs. Nzouakou et al,[62] retrospectively studied HU-derived clinical and biological benefits and safety in 123 adult patients. They reported the occurrence of 56 adverse events, with leg ulcers being the most frequent. No major side effects of HU were reported in a study conducted on patients with SCD in Saudi Arabia.[63] With decades of accumulated evidence of using HU in patients with SCD, it is considered to have an acceptable long-term safety profile.[12] In our study, in 36.8% of the patients in whom the drug was discontinued due to a blood abnormality, it was not reintroduced at the time of evaluation. The contribution of a health care provider-based barrier should be considered in these instances because the guideline recommends that if thrombocytopenia or neutropenia develops, then HU can be reintroduced at a lower dose once the blood count recovers.[5]

Adherence to the use of HU was evaluated using self-reported adherence measures; thus, the presence of a higher percentage of patients in the adherent category should be considered with caution. There could have been situations in which a portion of patients have visited other health care institutions and accordingly chances of missing complete details in the patient records. Limitations of obtaining information from the already documented patient data as well as the vast amount of data to be assessed for an individual patient should be considered.

Recall bias while collecting information from the patients should not be overlooked.

Two sources of data records, namely electronic patient records and patient interviews, were used based on the evaluated parameters. Accordingly, there could have been instances of failure to obtain details from any one of the sources if data were already obtained from the other source. Since the data from the emergency department was collected only on one day in a week due to feasibility, a considerable number of patients with SCD who visited the emergency department on other days during the study period were automatically not included in the study.

CONCLUSION

The use of HU was not very common and was underutilized among patients with SCD. Non-initiation was noticed in many patients where there was a possible indication for its use. A commendable percentage of patients reported to be adherent to HU, but this should be interpreted with caution as it was assessed by self-reported medication adherence. The prevalence (history or present at the time of study) of an ADR with HU was high, blood abnormalities being the most common. Steps should be taken to facilitate the initiation in those indicated, reduce the rate of discontinuation, and improve adherence among patients with low adherence. Concerns on the use of HU among patients, especially regarding its side effects must be addressed. A larger study, ideally of a prospective nature, would provide a better picture of these important aspects.

Disclosure

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