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Assessment of the Efficacy and Tolerance of Drepanoalpha® in the Management of Sickle Cell Disease in Kinshasa (DR Congo): About Ten Cases

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BZG and KNN designed the study. Author DSTT performed the statistical analysis. Author PM wrote the protocol and author PTM wrote the first draft of the manuscript. Authors FMK and FLL managed the analyses of the study. Author GNB managed the literature searches. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Aims: The aim of this study is to assess the efficacy and safety of Drepanoalpha®, a nutraceutical used in the management of sickle cell disease in DR Congo.
Study Design: Drepanoalpha® to ten sickle patients, evaluation of parameters before and after treatment.

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Place and Duration of Study: Department of Biology, Science faculty, university of Kinshasa, between Sept 2015 and July 2016.
Methodology: The ten selected cases were submitted to Drepanoalpha® for two months and the following parameters were observed before, during and after treatment: The hemoglobin rate, the number of crises, biochemical parameters such as the rate of urea, creatinine, bilirubin (total and direct) and transaminases (SGOT and SGPT). A clinical evaluation and monitoring of product safety signs was also carried out.
Results: The results show an increase in hemoglobin in all patients ranging from 19.2 to 42.9% and a total stop of crises. The product does not disturb the indicators of liver function (transaminases SGOT and SGPT, total and direct bilirubin) nor those of renal function (urea and creatinine). No adverse effects event such as vomiting, urticaria, pruritus, itching and diarrhea were observed.
Conclusion: According to this study, Drepanoalpha® increases the hemoglobin level in subjects treated leading to a cessation of sickle cell crisis. This drug does not alter liver and kidney functions and does not induce side effects in treated subjects, thus ensuring its safety.

Keywords: Drepanoalpha®; nutraceutical; sickle cell anemia; hemoglobin rate; safety; Kinshasa.

1. INTRODUCTION

Sickle cell anemia is a genetic disease caused by a mutation at chromosome 11 which results in the substitution of glutamic acid by valine at position six on the beta chain. This unique substitution of a polar amino acid by a less polar one leads to the modification of hemoglobin affinity for oxygen and its solubility. In fact, in its oxygenated form, normal hemoglobin (HbA) and hemoglobin S (HbS) have the same solubility, but in the deoxygenated form, the solubility of HbA decreases by half while that of HbS decreases 50 times. This reduction leads to its precipitation and its intracellular polymerization leading to the modification of the structure of the red blood cells. Thus, from its normal biconcave form, the red blood cell takes the form of "banana" or "crescent" called "sickled form". Sickling conduct red blood cells to obstruct small blood vessels and block blood flow [1-3].

It can also be noticed that sickle-red blood cells have a short life span, therefore there is an early red blood cell hemolysis leading to anemia, henceforth the denomination Sickle Cell Anemia or SS Anemia [1,2]. Nowadays, this hemoglobin disease affects about 50 million people in the world mainly in Tropical Africa. The Democratic Republic of the Congo (DRC) has nearly a million and a half sickle-cell anemia patients [4-9].

Several therapeutic strategies have been tried to date in order to counteract the various mechanisms described above in order to improve life quality of sickle-cell anemia patients without success. Amongst these include analgesic and anti-inflammatory treatments for vaso-occlusive sickle cell crisis, antisickling therapy, blood transfusions, bone marrow transplantation and use of hydroxyurea. One of the staple obstacles to the application of these strategies in Africa remains their high costs [5,8,9]. So one of the best solutions in Africa is the development of phytomedicine based on the knowledge from the traditional pharmacopoeia. In fact, 80% of the African population uses traditional medicine for health care. Several plants used in traditional medicine have proved their effectiveness and several bioactive molecules have been isolated so far [10-14].

These last years, our research team have validated the antisickling activity of about 100 plants used in traditional medicine for the management of sickle disease, isolated some bioactive compounds and developed as well a phytomedicine based on food plants called Drépanoalpha® [4-9,11-22].

Some studies on acute and sub-acute toxicity, nutrient composition, antisickling, anti-haemolytic, free radical scavenging and antioxidant properties and the effect on the biochemical parameters of two animal models have been performed [19-22].

The aim of this study is to assess the efficacy and tolerance of Drepanoalpha® in ten sickle-cell patients by evaluating both biological and clinical parameters

2. MATERIALS AND METHODS

2.1 Study Area and Sampling

This study was conducted at the “Centre de Médecine Mixte et Anémie SS (CMMASS)” in

Kinshasa, DRC. Ten cases were selected on the basis of the following criteria:

- Being a known sickle cell subject, registered and regularly monitored at the "Centre de Médecine Mixte and Anemie SS and whose home addresses obtained are very clear and reliable;
- Have undergone one or more hospitalizations and consecutive transfusions for haemolytic and vaso-occlusive crises between June 2013 and June 2014;
- Accept to take the product and to be subjected to controls according to the protocol approved by the ethics committee of the department of Biology, Faculty of Sciences, University of Kinshasa.

There were no restrictions on age and sex and the selected subjects were also followed at their dwelling places.

2.2 Clinical Evaluation

Each pre-selected subject was subjected to a systematic physical examination before treatment with Drepanoalpha® and a regular medical check-up was performed every two weeks.

2.3 Biological Evaluation

Haematological and biochemical were also carried out in pre- and post-treatment with Drepanoalpha® in order to follow:

- The evolution of the hemoglobin rate relative to the initial rate, the rate during treatment and after ending the treatment.
- The subjects drug tolerance. The biochemical analyzes carried out were: total and direct bilirubin, transaminases (SGOT, SGPT), urea and creatinine.

2.3.1 Hematological analysis

The dosage of hemoglobin was performed by the well-known method of Sahli acid hematin [23,24].

2.3.2 Biochemical analyzes

Total and direct bilirubin, urea, creatinine, transaminases: serum glutamate oxalate transferase (SGOT) and serum glutamate phosphatase transferase (SGPT) were assayed according to standard methods as previously described [24,25].

2.3.3 Toxicity and adverse effects

The probable toxicity of Drepanoalpha® was assessed by following a few indicators of liver function (SGOT and SGPT transaminases, total and direct bilirubin) and renal function (urea and creatinine). As for the adverse effects, we searched for some manifestations such as vomiting, urticaria, pruritus, itching, diarrhea, metallic or unpleasant taste, etc. in the monitored subjects.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Socio-demographic characteristics of subjects, duration and cost of hospitalization

Table 1 gives the age, sex and education level of ten subjects who were subjected to the Drepanoalpha® intake, while Table 2 gives the duration (in number of days) of each subject's hospitalization at the "Centre de Medecine Mixte et Anemie SS " of Kinshasa as well as the average cost of the hospitalization in US dollars.

Table 1 shows that of the ten patients selected, nine are female and only one is male. The age of patients varies between 6 and 30 years. Three patients have a university degree, two have a secondary education and the other five are from the primary level.

Table 1. Assessment of socio-demographic characteristics

Patients	Age (Years)	Sex	Education level
SDC1	19	F	University
SDC2	9	M	Secondary
SDC3	18	F	University
SDC4	10	F	Primary
SDC5	6	F	Primary
SDC6	30	F	University
SDC7	20	F	Secondary
SDC8	11	F	Primary
SDC9	12	F	Primary
SDC10	7	F	Primary

Table 2. Cost and duration of hospitalization

Patients	Duration of hospitalization (days)	Cost (in USD)
SDC1	1	135.6
SDC2	2	145.2
SDC3	3	151.6
SDC4	4	200.0
SDC5	5	212.8
SDC6	6	220.2
SDC7	9	235.1
SDC8	10	301.0
SDC9	17	377.7
SDC10	25	484.0
Average	8.2	247.4

According to the CMMASS registers, the hospitalization time of ten subjects chosen for the period between June 2013 and June 2014 varies between 1 and 25 days, i.e. an average of 8.2 days while the overall cost of Hospital care varies between USD 136.6 and USD 484, an average of USD 247.4 per individual.

3.1.2 Hemoglobin level before and 60 days after treatment

Fig. 1 shows the hemoglobin level of patients before treatment with Drepanoalpha® and after 60 days of the treatment.

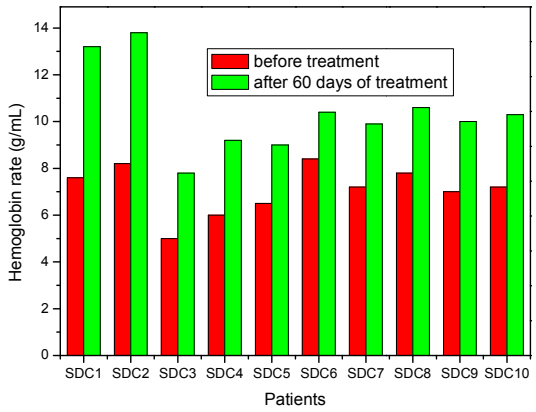

Fig. 1. Hemoglobin rate of patients before treatment with Drepanoalpha® and after 60 days of treatment

The hemoglobin level of patients subjected to treatment was between 5.0 and 8.4 g /100mL, i.e. an average of 7.1 g / 100 mL but after 60 days of treatment, the hemoglobin level of all the patients had increased and it was between 7.8 and 13.8 g / 100 mL (average of 10.4 g / 100 mL). It is known that in the case of anemia, one unit of the transfused blood restores between 1.5 and 2 g / 100 mL of hemoglobin [23,25]. By comparing the hemoglobin level before and after treatment with Drepanoalpha®, one can calculate the equivalent in blood units that the Drepanoalpha® intake saves (Fig. 2).

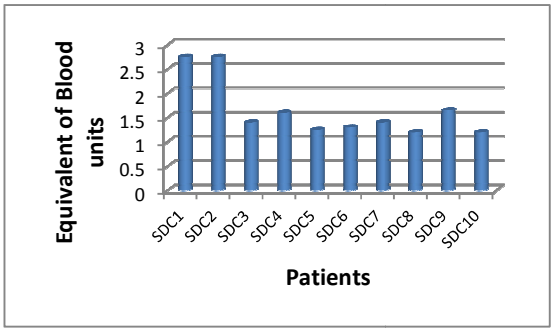

Fig. 2. Equivalent in blood units gained by patients after Drepanoalpha® treatment

It appears from this figure that SDC1 and SDC2 patients with the highest hemoglobin level have an equivalent in blood units of up to 2.75 while the lowest blood unit equivalent gain is SDC8 and SDC10 patients with 1.2 equivalent of blood units.

3.1.3 Effects of Drepanoalpha® on renal and hepatic functions

The content of urea, creatinine, SGOT, SGPT, direct bilirubin, indirect bilirubin and total bilirubin before and 60 days after treatment with Drepanoalpha® is given Table 3a and 3b.

It appears from Table 3b that 40% of subjects had bilirubin levels above 2 mg / 100mL before treatment and after treatment with Drepanoalpha®. There was an amendment in all subjects but only 20% showed a moderately higher rate than 2 mg /100mL. In general, two patients (SDC3 and SDC7) seem to have parameters out of normal limits.

3.1.4 Clinical observations

Tables 4 and 5 give the results of the observation before and after treatment with Drepanoalpha® respectively.

From Table 6, 100% of the cases showed jaundice of varying intensity and dark urine before treatment, while 60% had splenomegaly compared with 40% of hepatomegaly. But after treatment, 80% of the subjects treated with Drepanoalpha® showed an anicteric bulbar conjunctiva and their urine color normalized (pale yellow).

Table 3a. Effects of Drepanoalpha® on kidney and liver functions

Parameters	SDC1	SDC2	SDC3	SDC4	SDC5	SDC6	SDC7	SDC8	SDC9	SCD10	Standard
Before treatment											
Urea	23,6	10	23	19.6	32	28	16,8	32	21.2	18	10-50
Creatinine	0.8	1	0.7	0.52	0.61	0.58	0.55	0.42	0.62	0.66	0.5-1.5
SGOT	34.4	34.0	65	16.2	10.8	7	5.4	10.8	4.5	10,8	<40 UI
SGPT	16.1	9.1	28	14.5	12.4	12	5.4	14.4	4.5	16	<40 UI
Direct bil	0.82	0.26	5.8	1.02	0.26	1.63	4.33	0.31	0.7	0.8	< 1
Indirect bil	0.44	0.82	2.8	1.44	0.82	2.94	10.96	0.91	0.8	1.1	< 1
Total bil.	1.26	1.02	8.6	2.46	1.06	4.5	15.29	1.23	1.5	1.9	< 2
After treatment											
Urea	11	12	29	13	32	22	16	18	19	15	10-50
Creatinine	0.52	0.51	0.79	0.58	0.41	0.56	0.64	0.66	0.60	0.33	0.5-1.5
SGOT	30.5	12.4	59	16.3	10.8	7.4	4.4	10.8	5.1	12.4	<40 UI
SGPT	14.4	12.4	23.6	18.9	12.4	7.4	4.4	16	5.1	14.4	<40 UI
Direct Bil.	0.80	0.7	4.9	0.9	0.26	0.7	0.7	0.8	0.8	0.4	< 1
Indirect Bil.	0.46	0.8	2.6	0.8	0.86	0.6	1.8	1.1	0.9	1.1	< 1
Total Bil.	1.26	1.5	7.5	1.7	1.06	1.3	2.5	1.9	1.7	1.5	< 2

Table 3b. Effects of Drepanoalpha® on kidney and liver functions

Parameters	Urea		Creatinine		SGOT		SGPT		Direct bil		Indirect bil		Total Bil	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
SDC1	23.6	11	0.80	0.52	34.4	30.5	16.1	14.4	0.82	0.80	0.44	0.46	1.26	1.26
SDC2	10.0	12	1.00	0.51	34.0	12.4	9.1	12.4	0.26	0.70	0.82	0.80	1.02	1.50
SDC3	23.0	29	0.70	0.79	65.0	59.0	28	23.6	5.80	4.90	2.80	2.60	8.60	7.50
SDC4	19.6	13	0.52	0.58	16.2	16.3	14.5	18.9	1.02	0.90	1.44	0.80	2.46	1.70
SDC5	32.0	32	0.61	0.41	10.8	10.8	12.4	12.4	0.26	0.26	0.82	0.86	1.06	1.06
SDC6	28.0	22	0.58	0.56	7.0	7.4	12.0	7.4	1.63	0.70	2.94	0.60	4.50	1.30
SDC7	16.8	16	0.55	0.64	5.4	4.4	5.4	4.4	4.33	0.70	10.96	1.80	15.29	2.50
SDC8	32.0	18	0.42	0.66	10.8	10.8	14.4	16.0	0.31	0.80	0.91	1.10	1.23	1.90
SDC9	21.2	19	0.62	0.60	4.5	5.1	4.5	5.1	0.70	0.80	0.80	0.90	1.50	1.70
SDC10	18.0	15	0.66	0.33	10.8	12.4	16.0	14.4	0.80	0.40	1.10	1.10	1.90	1.50
Standard	10-50		0.5-1.5		< 40 UI		< 40 UI		< 1		< 1			< 2

Legend: Before treatment (BT), After treatment (AT)

Table 4. Clinical data before treatment

Patients	Status of conjonctiva	Color of urines	Status of the spleen	Status of the liver
SDC1	Icteric	Dark	Not felt	Not felt
SDC2	Icteric	Darker	2 cm SRCG	Not felt
SDC3	Icteric franc	Darker	5 cm SRCG	3 cm SRCD
SDC4	Icteric	Darker	2 cm SRCG	2 cm SRCD
SDC5	Icteric	Darker	Not felt	3 cm SRCD
SDC6	Icteric	Darker	2 cm SRCG	2 cm SRCD
SDC7	Icteric	Darker	4 cm SRCG	Not felt
SDC8	Anicteric	Darker	5 cm SRCG	Not felt
SDC9	Icteric	Darker	Not felt	Not felt
SDC10	Icteric	Darker	Not felt	Not felt

Table 5. Clinical data after treatment

Sujet	Status of conjonctiva	Color of urines	Status of the spleen	Status of the liver
SCD1	Anicteric	Light yellow	Not felt	Not felt
SCD2	Anicteric	Light yellow	Not felt	Not felt
SCD3	Icteric	Darker	6 cm SRCG	5 cm SRCD
SCD4	Anicteric	Light yellow	Not felt	Not felt
SCD5	Icteric	Darker	7 cm SRCG	Not felt
SCD6	Anicteric	Light yellow	Not felt	3 cm SRCD
SCD7	Anicteric	Light yellow	Not felt	4 cm SRCD
SCD8	Anicteric	Light yellow	Not felt	Not felt
SCD9	Anicteric	Light yellow	Not felt	Not felt
SCD10	Anicteric	Light yellow	Not felt	Not felt

Table 6. Clinical data before and after treatment

Patients	Status of conjonctiva		Color of Urines		Status of the spleen		Status of the liver	
	BT	***AT***	***BT***	***AT***	***BT***	***AT***	***BT***	***AT***
SDC1	Icteric	Anicteric	Dark	Light yellow	Not felt	Not felt	Not felt	Not felt
SDC2	Icteric	Anicteric	Darker	Light yellow	2 cm SRCG	Not felt	Not felt	Not felt
SDC3	Icteric franc	Icteric	Darker	Darker	5 cm SRCG	6 cm SRCG	3 cm SRCD	5 cm SRCD
SDC4	Icteric	Anicteric	Darker	Light yellow	2 cm SRCG	Not felt	2 cm SRCD	Not felt
SDC5	Icteric	Icteric	Darker	Darker	2 cm SRCG	7 cm SRCG	3 cm SRCD	Not felt
SDC6	Icteric	Anicteric	Darker	Light yellow	Not felt	Not felt	2 cm SRCD	3 cm SRCD
SDC7	Icteric	Anicteric	Darker	Light yellow	2 cm SRCG	Not felt	Not felt	4 cm SRCD
SDC8	Anicteric	Anicteric	Darker	Light yellow	4 cm SRCG	Not felt	Not felt	Not felt
SDC9	Icteric	Anicteric	Darker	Light yellow	5 cm SRCG	Not felt	Not felt	Not felt
SDC10	Icteric	Anicteric	Darker	Light yellow	Not felt	Not felt	Not felt	Not felt

Legend: Before treatment (BT), After treatment (AT)

3.2 Discussion

In this study, the age of patients ranges between 6 and 30 years, an average of 14.2 ± 6.0 years (Table 1). Age as an epidemiological factor is important to consider in the management of sickle cell anemia because it is known that fetal hemoglobin affects the severity of clinical signs of disease. In general, this rate remains below 20% after one year of age but a rate between 10 and 20% would be the basis of a late start of the symptoms of the disease and of a less severe clinical presentation characterized by low rate of transfusion and hospitalization [26].

Considering each patient's history of hospitalization (Table 2), the average number of hospitalization duration for the year before the study was 8.2 days per patient, and the average cost of Vaso-occlusive crisis taking into account all transfusion, medication and hospitalization costs for such a period would be around 247.4 USD after conversion to the local currency. This clinical management is very expensive when we consider the average income of the Congolese, which is among the lowest in the world [27]. Therefore, sickle-cell anemia contributes to the impoverishment of families that are already poor. A cure that would reduce the number of crises and hence the number and time of hospitalization would allow households to allocate these resources to other needs or to save, thus contributing to poverty reduction.

In sickle-cell anemia subjects, the hemoglobin level is generally low because of the short duration of sickle cell, which leads to hemolytic anemia [1,2]. The hemoglobin level of all the subjects examined is between 5.0 and 8.4 g / 100 mL confirming their anemic state. However, after 60 days of treatment with Drepanoalpha®, all patients showed an increase in hemoglobin with values even exceeding 13 g /100 mL for two patients (Fig. 1). The calculated rate of increase in hemoglobin ranges from 19.2 to 42.9%, i.e. an average of 31.4%. By comparing the mean values of hematocrit and hemoglobin before and after treatment by Drepanoalpha®, it was found that there was a significant difference ($p < 0.05$).

According Fig. 1, the results show that the treatment of sickle cell disease patients by Drepanoalpha® has the effect of raising the hemoglobin level conducting to the disappearance of the homolytic sickle cell crisis. These results confirm those already observed for this nutraceutical on two animal models, the WISTAR rats and the Guinea-pigs. In fact, Drepanoalpha® showed by two independent studies on rats and guinea-pigs that when these animals are subjected to a daily intake of this nutraceutical, they have growth rates of hemoglobin up to 50% [19,20]. A high value of hemoglobin was in patients SDC1 and SCD2 contrary to other patients for which values are comparable between them.

One of the ways to fight anemia in sickle-cell subjects is blood transfusion. But a good number of units of blood transfused to sickle-cell subjects especially in rural areas do not pass through the necessary control of a modern blood bank. This exposes sickle-cell subjects to other more serious infection such as HIV/AIDS and Hepatitis B.

We wanted to evaluate the equivalent in units of blood that the treatment by Drepanoalpha® would save in each of the patients examined (Fig. 2). Thus, the ten subjects are divided into three groups: four subjects who have gained 5.5 g of hemoglobin per 100 mL of blood (SDC1 and

SDC2) this is equivalent to a transfusion of 2.75 units of blood. Those with a gain between 2.5-3.9 g% would have gained 1.4 to 1.65 units of blood, while those with a gain range of 1.0 - 2.4 g% would have gained only 1.2 units of blood. Even if this value in units of blood has not been returned as a bolus, one can imagine the blood volume that Drépanoalpha® has provided to each subject thus avoiding the risks of contamination for the patients and an economy for the family.

It was recently shown that, Drepanoalpha® contains about 16% of proteins and a high iron content [22], apart from its antisickling activity due particularly it's anthocyanins and organic acids content [19,20], this could explain its effect on the increase in hemoglobin. In addition, it has been proposed that one of the beneficial effects of Drepanoalpha® is the consequence of epigenetic modulation of the hemoglobin gene by the bioactive secondary metabolites contained in this nutraceutical. In fact, it is not excluded that Drepanoalpha® could restart the gene for fetal hemoglobin whose expression is blocked during ontogenic development [21,28].

It can also be noticed that the increase in hemoglobin level is accompanied by the disappearance of typical inflammatory reactions of sickle cell disease (pain, etc.). This anti-inflammatory property of Drepanoalpha® would be attributed to the anthocyanins contained in this phytomedicine. In fact, it was reported that these secondary metabolites inhibit the transcription factor NF-KB which controls the genes involved in the inflammatory response [16]. These polyphenols may also strengthen the immune system of treated subjects [28-31].

In order to evaluate the toxicity of a drug, the study on renal and/or hepatic function is essential. In this study, before the treatment with Drepanoalpha®, 40% of subjects had bilirubin levels above 2 mg/dL, but after treatment, there was an improvement in all subjects although 20% of cases continued to present a rate moderately above 2 mg/dL (Table 3a, 3b). These results show that there was no renal alteration after treatment by Drepanoalpha® in 100% of the subjects treated. However, in two patients (SCD3 and SCD7) who had a history of decompensated and documented liver cirrhosis, there was a small improvement in the bilirubin level after treatment with Drepanoalpha®. As it was shown for most of the plants used in the management of sickle-cell anemia in Congolese traditional medicine [3-9,11-18], Drepanoalpha® would have, among other effects, the normalization of sickle cells form and the hemolysis prevention at the level of the reticuloendothelial system and this would result in a decrease in the level of bilirubin biogenesis which is a degradation product of hemoglobin. The decline in hemolysis is accompanied by that of the bilirubin level. The reticuloendothelial system, apart from its strong participation in immunity, plays a predominant role in the destruction of malformed, parasitic or aged circulating red blood cells. In sickle-cell anemia, during vaso-occlusive or hemolytic sickle cell crisis induced by various stress (dehydration, deoxygenation, infection and others), the sickle-shaped red blood cells are retained in the reticuloendothelial system by macrophages. This sequestration leads to an increase in the size of the spleen [2].

The results obtained in this study (Table 3a,b) indicate that Drepanoalpha® is effective in reducing the size of the spleen. After treatment with Drepanoalpha®, 66.7% of subjects who had splenomegaly at different individual values experienced a significant regression of the spleen volume compared to 33.3% of which the spleen remained palpable. In particular, there were two cases of decompensated and documented hepatic cirrhosis that were treated with Drepanoalpha®.

Safety of a drug is an important factor to consider when conducting clinical trials. Throughout the experiment, no adverse effects (hives, pruritus, itching, nausea, vomiting, diarrhea, dizziness, headache and unpleasant taste) associated with the treatment by Drepanoalpha ® were reported directly by patients or their surroundings during various visits of the research team. It should be remembered that Drepanoalpha® is a phytomedicine based on food plants, so it is a nutraceutical or a food-drug [18]. However, as a drug in the clinical evaluation phase, further study is envisaged on a large number of patients in order to reassure it safety. The possibility of a selection bias was estimated, following the situation at the individual pathological level of each participant selected for this case report. A definition of the diagnostic criteria was taken into account and the biochemical parameters of two groups were compared.

4. CONCLUSION

The aim of this study was to assess the efficacy of Drepanoalpha® in ten sickle-cell subjects.

According to this study, Drepanoalpha® increases the hemoglobin level in subjects treated with an average growth rate of 31% leading to a cessation of sickle cell crisis. This allows the families of patients to save nearly 247 USD representing the average cost of hospitalization. This drug does not alter liver and kidney functions and does not induce effects in treated subjects, thus positive for its safety. This study shows that Drepanoalpha® is not only able to relieve the suffering of the sick but also the burden of the families of the sick. Further works on the development of other galenic forms are needed. A second study on thirty other cases has just been completed, while a larger clinical study is being carried out in collaboration with the DRC's national sickle-cell disease program.

CONSENT

All authors declare that 'written informed consent was obtained from the patient for publication of this paper'.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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