Steroid treatment in children with sickle-cell disease

Given the controversy concerning the effects of steroids in patients with sickle cell disease (SCD), we evaluated the tolerability of long-term steroid treatment in 16 children with SCD and autoimmune and/or systemic diseases. The steroid treatment was poorly tolerated.

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There is controversy concerning the effects of steroids in patients with sickle cell disease (SCD).[1-5] We, therefore, evaluated the tolerability of long-term steroid treatment in patients with both SCD and autoimmune and/or systemic diseases. The study population consisted of 16 SCD patients, less than 18 years of age, who were treated with steroids between January 2000 and December 2005. Clinical data were provided by their treating institutions: all centers belonging to the French study group on sickle-cell disease, one Belgian center and II African centers were contacted to assess the tolerability of steroid treatment for periods of up to 6 months from the start of this treatment.

Prednisone was initiated because of systemic and/or auto-immune diseases, and was given together with immunosuppressive drugs to seven patients (Table 1). Five patients received hydroxyurea before the initiation of steroids. Fifteen severe complications were observed in ten of the 16 patients (62%) (Table 1). Eight patients experienced severe vaso-occlusive events (VOE) within the 2 months following the initiation of steroid treatment, including a two-fold increase in the frequency of painful crises, occurrence of a very severe pain episode, acute chest syndrome, stroke, and renal infarction. Severe infections and avascular necrosis of the femoral head occurred in three and one patients, respectively. Complications occurred in all seven patients who received other immunosuppressive drugs in combination with steroids, but in only three of eight patients who did not receive immunosuppressive drugs. Among patients for whom leukocyte counts were available, the mean leukocyte count increased from 12.4×10^9/L to 28×10^9/L in the five patients with severe VOE, and from only 17.1×10^9/L to 20.3×10^9/L in the three patients who did not experience VOE after initiation of steroids. The

Table 1. Demographic characteristics of the study patients.

Patient/ gender/ age at onset	*Type of SCD*	*Nature of systemic and/or autoimmune disorder*	*Dosage of prednisone (mg/kg/day)*	*Other treatments at onset of steroids*	*Leukocyte count before/after** the initiation of steroid treatment ($x10^9$/L)*	*Adverse events (delay from onset of steroids to the occurrence of adverse event)*	*Modification of treatment after the initiation of steroid treatment*
1/F/13.3	SS	SLE	1	HU	NA	None	–
2*F/17	SS	SLE	1	CYC, HU	15.7/24.2	Increased frequency of pain episode, staphyloccocal septicemia, intracranial hemorrhage and death (1 y)	–
3/M/9	SS	SLE	1	CYC; HU	15.5/24	Increased frequency of pain episodes, ACS, stroke, hypertension	ETx
4/M/11.3	SC	SLE	0.5	Plaquenil	2.8/7.9	Renal infarct (2 months)	–
5/F/4.2	SS	SLE	1	–	NA	None	HU
6/F/10	SS	AIH	1.3	AZA, URSO	7.6/22.1	Very severe pain episode (1 month)	Decrease of steroid dosage from 1.3 to 0.5 mg/kg/d
7*/F/7	SS	AIH	1	AZA, URSO	NA	Increased frequency of pain episodes, recurrent cholangitis, staphylococcal septicemia	ETx
8/F/6	SS	AIH	1	AZA, URSO	NA	Osteomyelitis	–
9/M/13	SS	Sarcoidosis	1	Chronic Tx	16.9/27.2	None	–
10/F/16.9	SS	Sarcoidosis	1	–	11.1/16.7	Very severe pain episode (one day)	CS stopped
11/M/18.3	SS	Crohn's disease	0.7	HU	9.4/15.7	None	–
12/F/18.2	SS	Polyarthritis	1	–	NA	ACS (15 days)	CS stopped
13/F/15.4	SS	Polyarthritis	1	MTX	NA	Avascular necrosis of the femoral head (5 months)	–
14/F/8.2	SS	Polyarthritis	0.5	–	NA	None	–
15/M/0.9	SS	AIHA	2	–	25/18.2	None	–
16/M/5.8	SS	AIHA	2	AZA, HU	12.4/53	Very severe pain (5 days)	CS stopped

*SLE : systemic lupus erythematosus, AIH: autoimmune hepatitis; AIHA: autoimmune hemolytic anemia, SCD: sickle cell disease, ACS: acute chest syndrome; CYC: cyclophosphamide, AZA: azathioprine, MTX: methotrexate, URSO: ursodeoxycholic acid, TX: transfusion, ETx : exchange transfusions, CS : steroid, HU : hydroxyurea NA: not available *: indicates that the patient has a central line; ** : leukocyte count was measured within the week preceding the initiation of steroid therapy and within 1 month following the start of this treatment.*

occurrence of severe pain episodes led to withdrawal of steroid treatment (three patients) or to reduction of its dosage (one patient). Treatment with hydroxyurea and exchange transfusion programs led to the regression of pain episodes in two patients each. Among the five patients who received hydroxyurea before the initiation of steroid treatment, three experienced pain episodes. Steroids were well tolerated by the only patient who was on a chronic transfusion program prior to the treatment.

The present study emphasizes the poor tolerance of steroids in SCD patients, especially when associated with other immunosuppressive drugs. Sixty-two percent of the patients experienced severe complications, in particular, worsening of the course of the SCD, and infections. However, this small retrospective study has several limitations. Firstly, we cannot exclude that immunosuppressive drugs administered in combination with steroids contributed to the occurrence of complications, although two patients, one who had severe pain episodes and the other with acute chest syndrome, received only steroid treatment. Secondly, VOE events observed during steroid treatment might have been triggered by the systemic/autoimmune condition itself rather than by steroids but the fact that they occurred shortly after the initiation of steroids and that they did not occur during a flare of the underlying disease argues against this hypothesis. Treatment with hydroxyurea administered before steroid treatment did not prevent the occurrence of VOE in three of five patients. On the other hand, a chronic transfusion regimen may have beneficial effects in preventing such episodes, although the number of transfused patients was too small to allow any definite conclusion to be drawn in our series.

There is controversy concerning the effects of steroids in SCD patients. Dexamethasone has been shown to have short term beneficial effects in patients with painful crises and moderate acute chest syndrome by reducing the duration of hospitalization and analgesic therapy,[1,2] but the high frequency of rebound attacks finally argues against the use of dexamethasone in these patients. Severe pain episodes and stroke were reported to have occurred in four SCD patients after administration of steroids for rheumatoid arthritis[3,4] and autoimmune hepatitis.[5] These episodes may be hypothetically explained by the increased leukocyte and neutrophil counts induced by steroids. There is strong evidence of an association between neutrophil counts and crisis rates,[6] and higher leukocyte counts are associated with an increased risk of stroke and early death in children with sickle cell anemia.[7] In the present study mean leucocyte counts increased more in patients who experienced severe VOE after the initiation of steroids, than in patients who did not, but the small number of patients limits the significance of this result.

This study suggests that long-term administration of steroids results in severe side effects in most of the patients with both sickle cell disease and systemic and/or autoimmune diseases, especially if given in combination with immunosuppressive drugs. In order to prevent or reduce complications, a chronic transfusions regimen should be considered before starting steroid therapy in SCD patients.

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