Figure 13.21: Effect of treatment with HU + rHuEpo
Hb F level in SCD patients

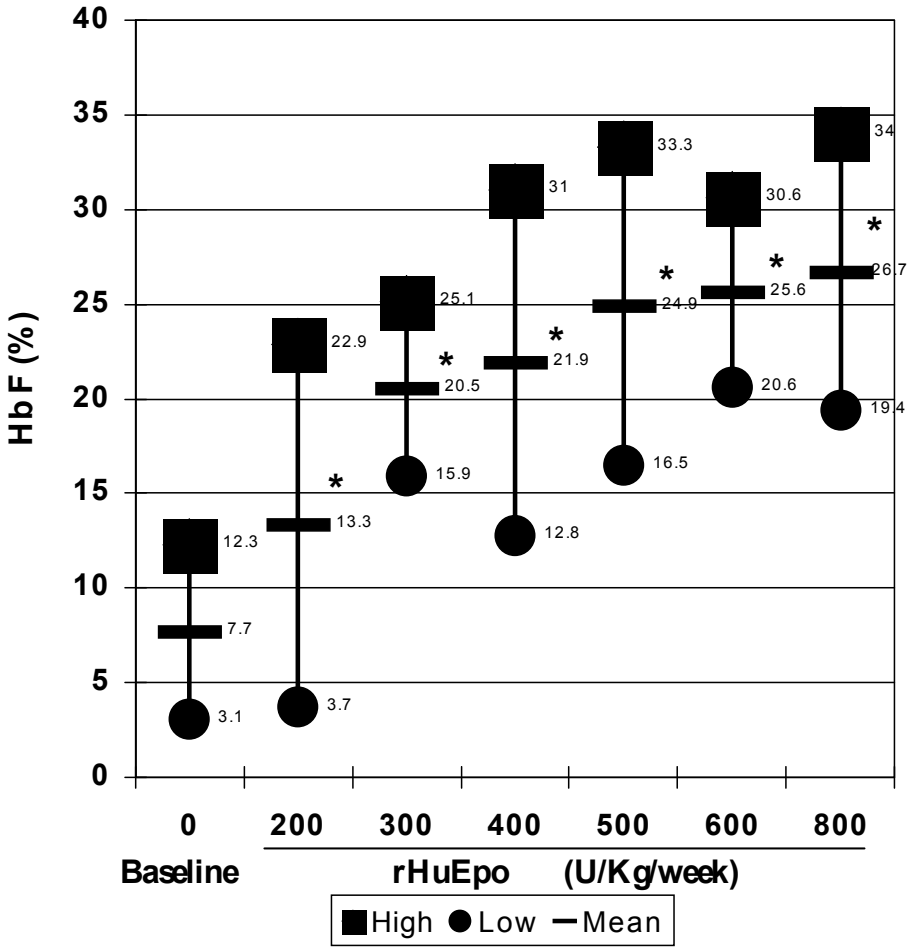


Figure 13.22: Effect of treatment with HU + rHuEpo
Hb F Cells in SCD patients

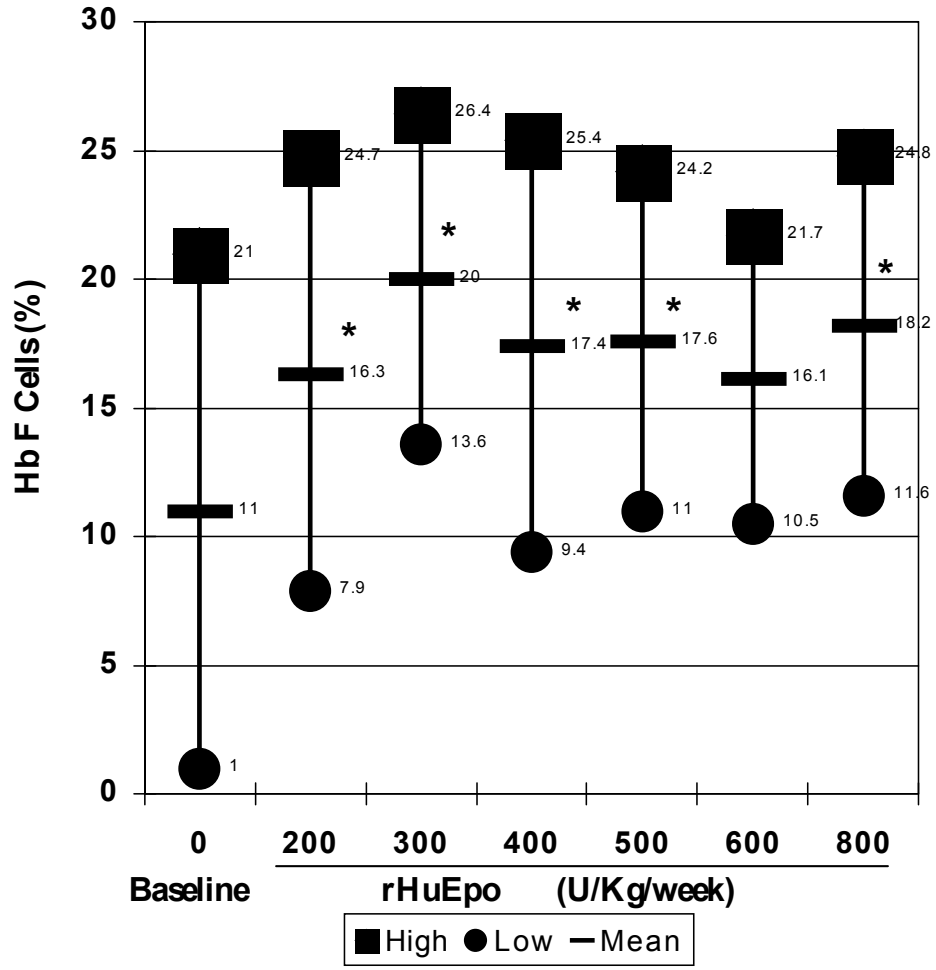


Figure 13.23: Effect of treatment with HU + rHuEpo
Hb level in SCD patients

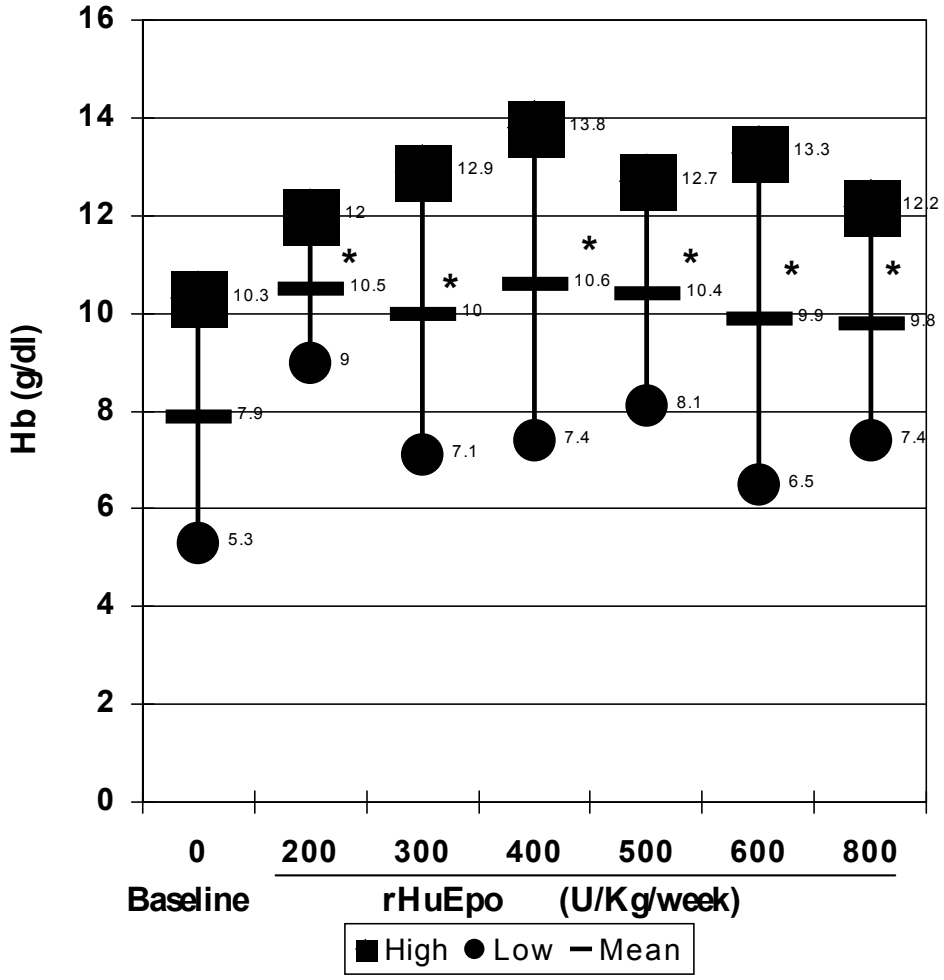


Figure 13.24: Effect of treatment with HU + rHuEpo
MCV level in SCD patients

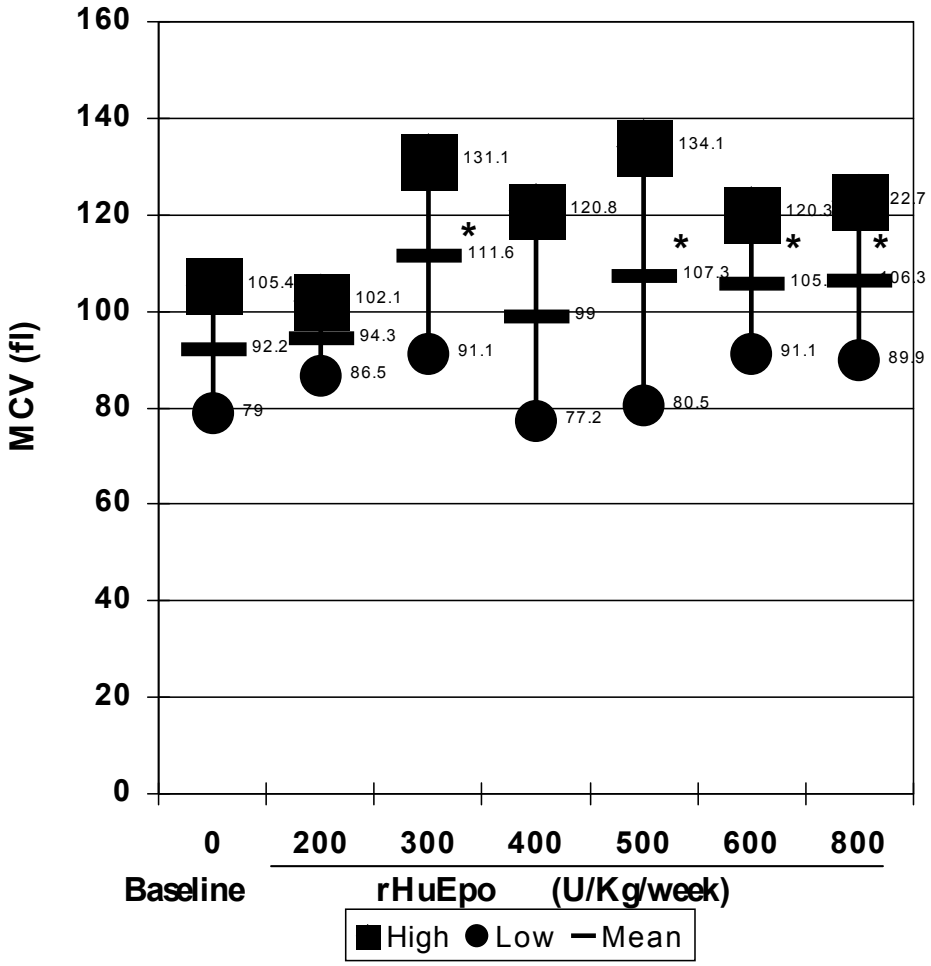
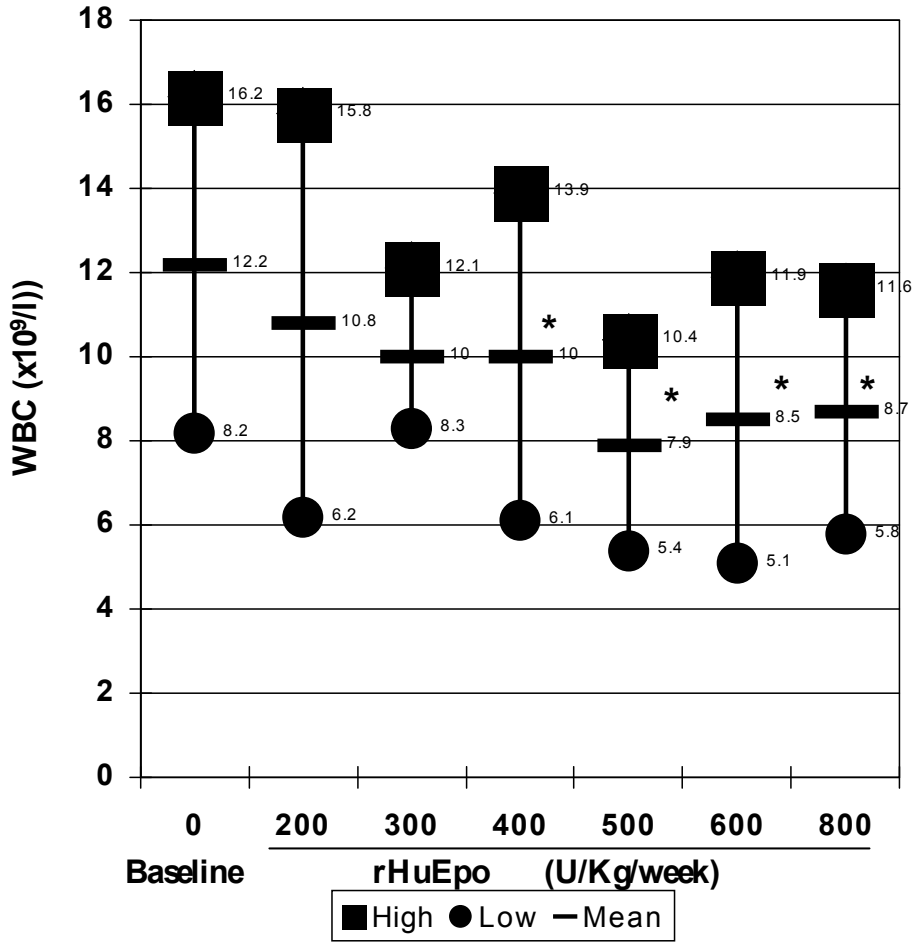


Figure 13.25: Effect of treatment with HU + rHuEpo
WBC level in SCD patients



increased.

13.2.6. Patients on HU+rHuEpo therapy for 4 weeks maintained on HU alone

Four patients who were maintained a combination therapy of HU and rHuEpo for 4-8 weeks followed by HU treatment alone showed a significant improvement in the value of haematological parameters concomitant with the significant improvement in Hb F level and Hb F cells.

The initial treatment with HU+rHuEpo acts as a booster to improve the haematological and biochemical values (Figure 13.26 to 13.31) and decrease the disease severity, which can then be maintained on HU alone (Figures 13.32 and 13.33). In one 18 years old male, doses of rHuEpo were given during HU treatment. Change in Hb F level is shown in Figure 13.34.

13.2.7. Withdrawal of HU therapy

Two patients were followed for a period of 12 months after HU withdrawal. The Hb F and Hb F cells decreased to the original baseline value within 6 months and most haematological parameters showed a significant disease, while WBC count, reticulocyte count and total bilirubin increased to the baseline value.

13.2.8. Discussion

Taken together our results showed a beneficial influence of HU alone and with rHuEpo in dose of the range 400-600 U/kg body weight/week. The improvement in the haematological parameters was significant, the parameters indicating haemolysis showed a considerable decrease and clinically the patients improved significantly, thus confirming our earlier observation of a beneficial influence of combination therapy. An interesting finding was that if the patients were initially started on a combination therapy of daily oral

Figure 13.26: Effect of HU treatment:
Hb level in patients treated with HU/HuEpo for 4 weeks

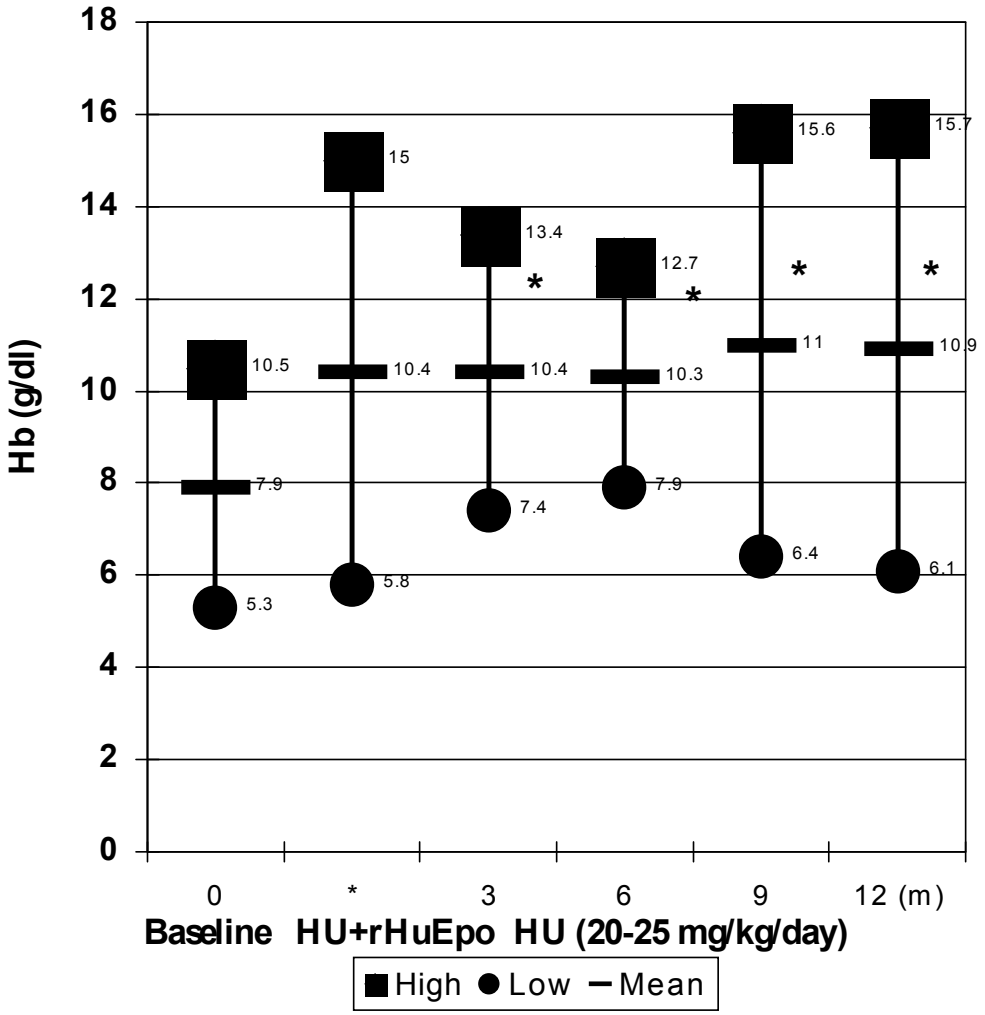


Figure 13.27: Effect of HU treatment:
Hb F level in patients treated with HU/HuEpo for 4 weeks

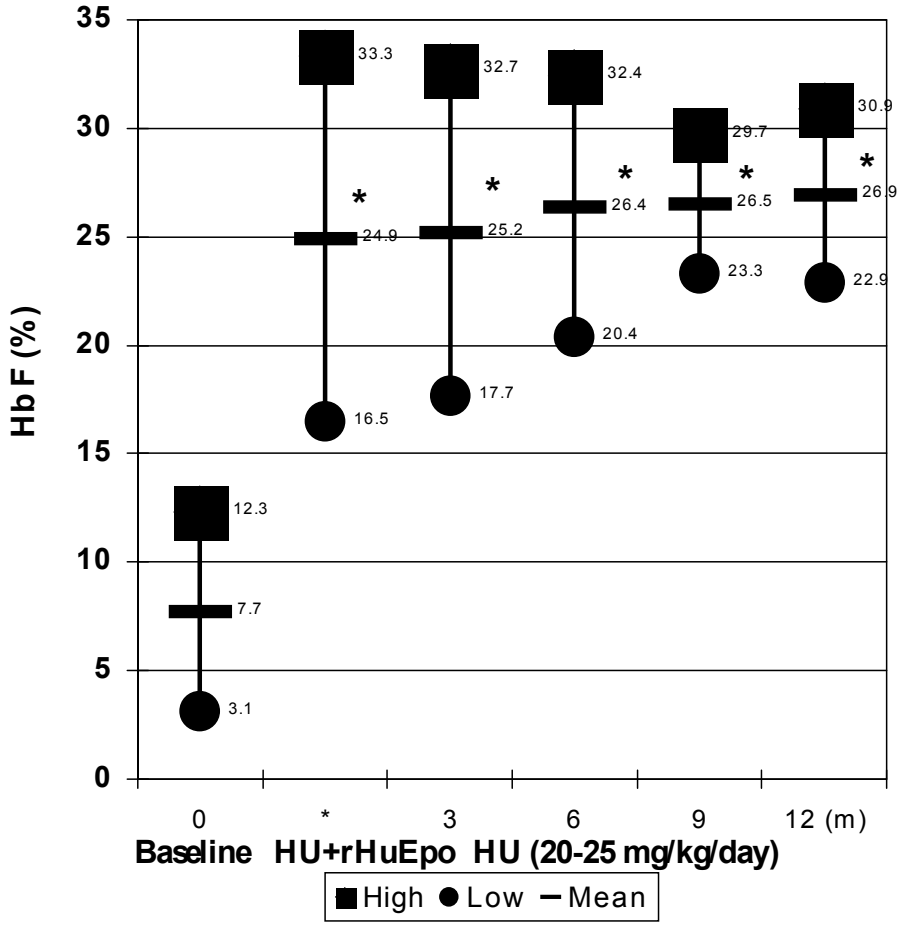


Figure 13.28: Effect of HU treatment:
Hb F Cells in patients treated with HU/HuEpo for 4 weeks

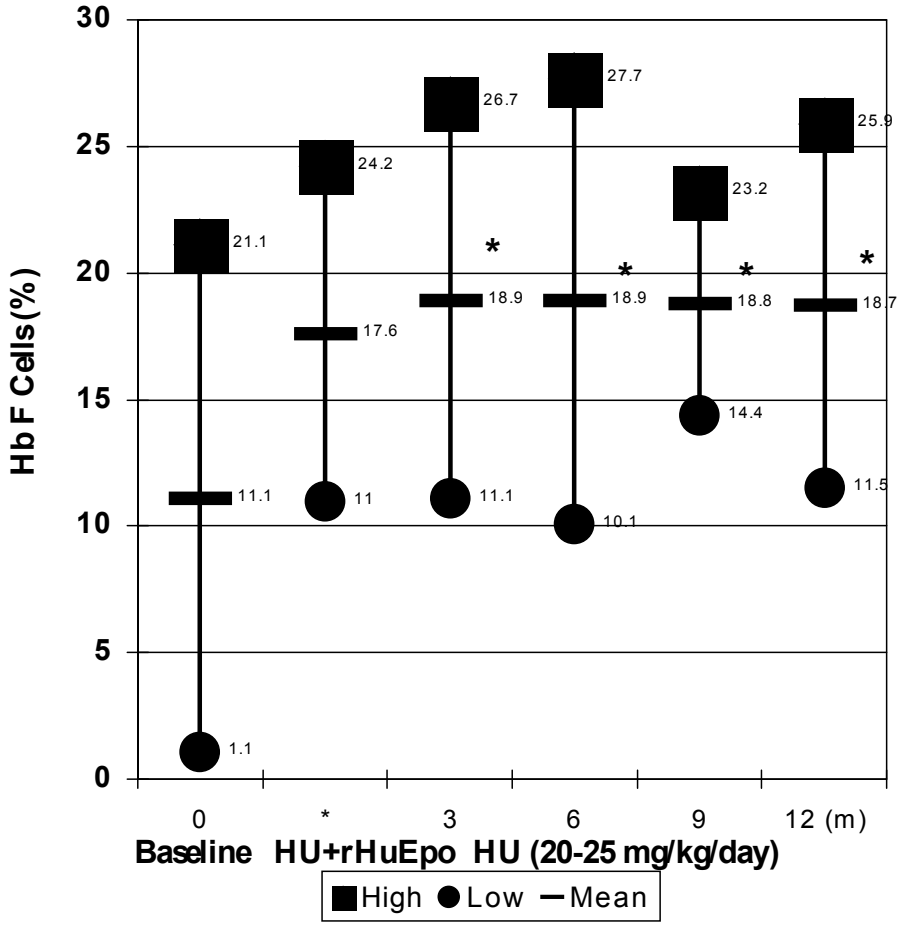


Figure 13.29: Effect of HU treatment:
WBC level in patients treated with HU/HuEpo for 4 weeks

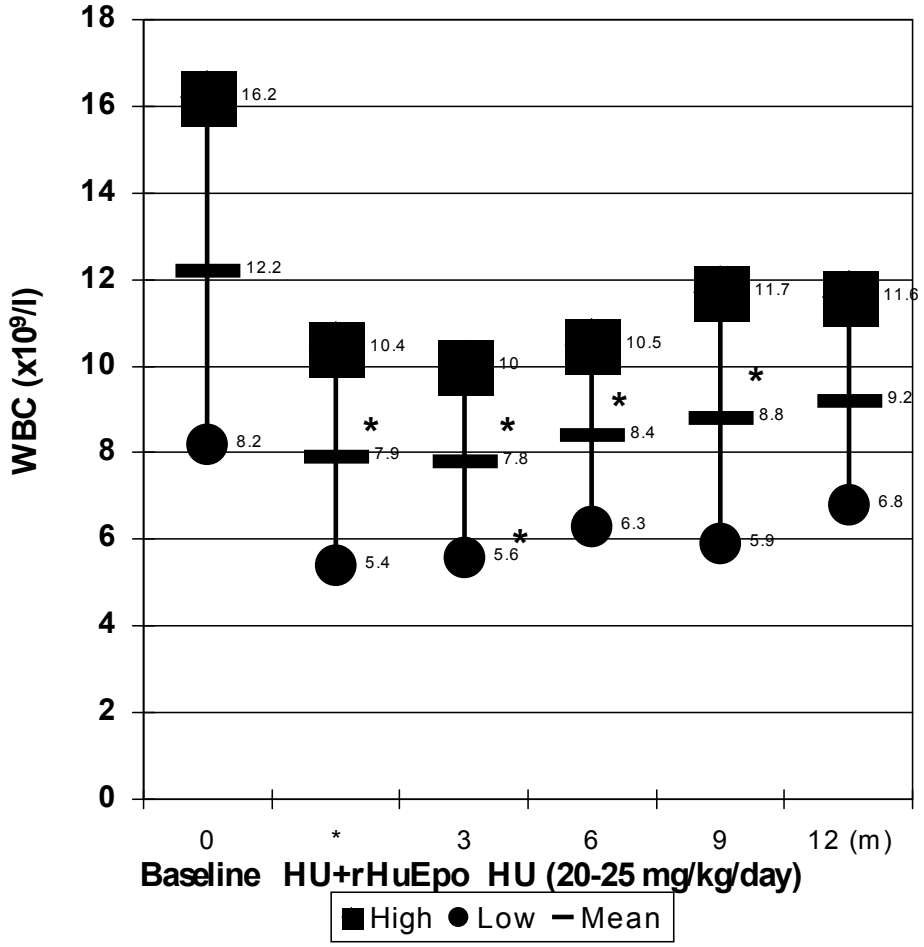


Figure 13.30: Effect of HU treatment:
Retic counts in patients treated with HU/HuEpo for 4 weeks

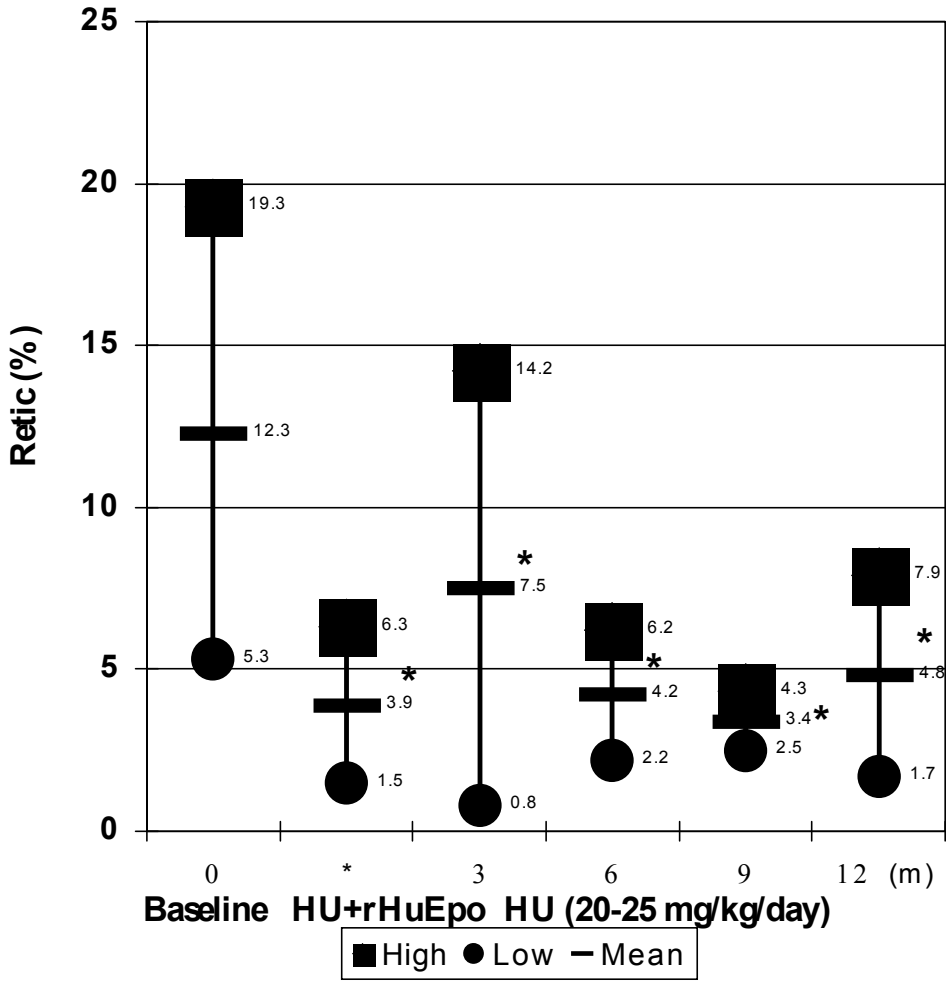


Figure 13.31: Effect of HU treatment:
MCV in patients treated with HU/HuEpo for 4 weeks

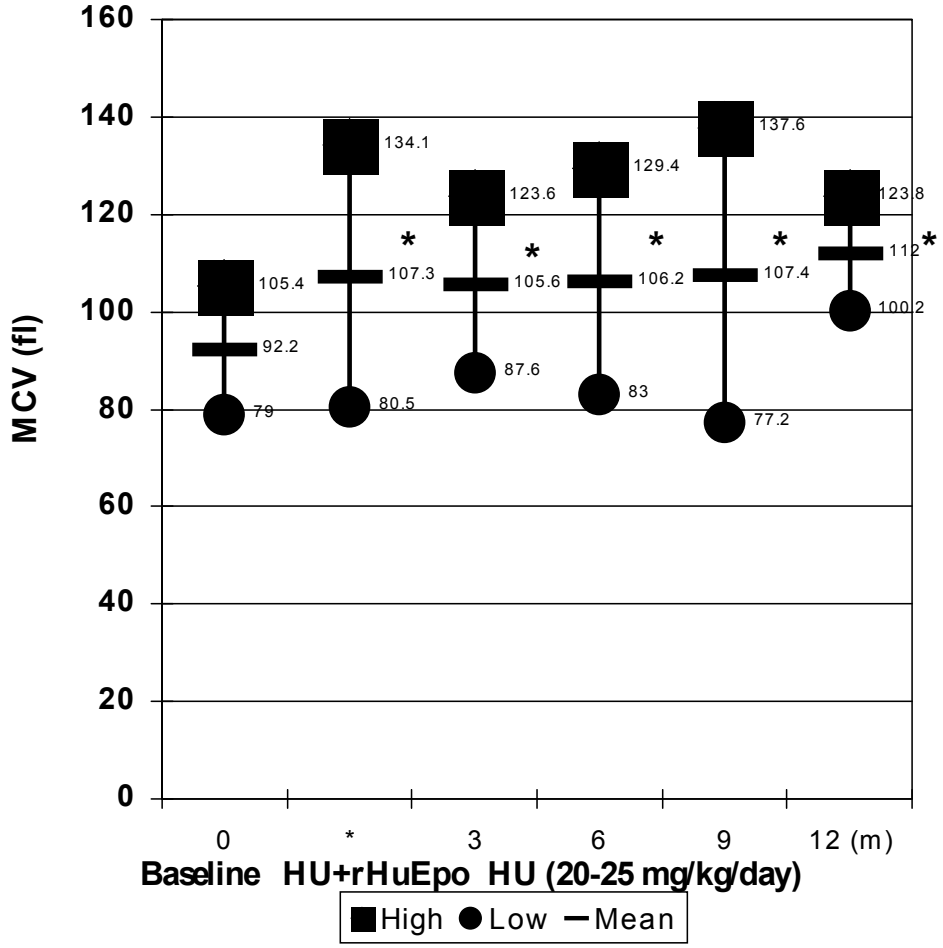


Figure 13.32

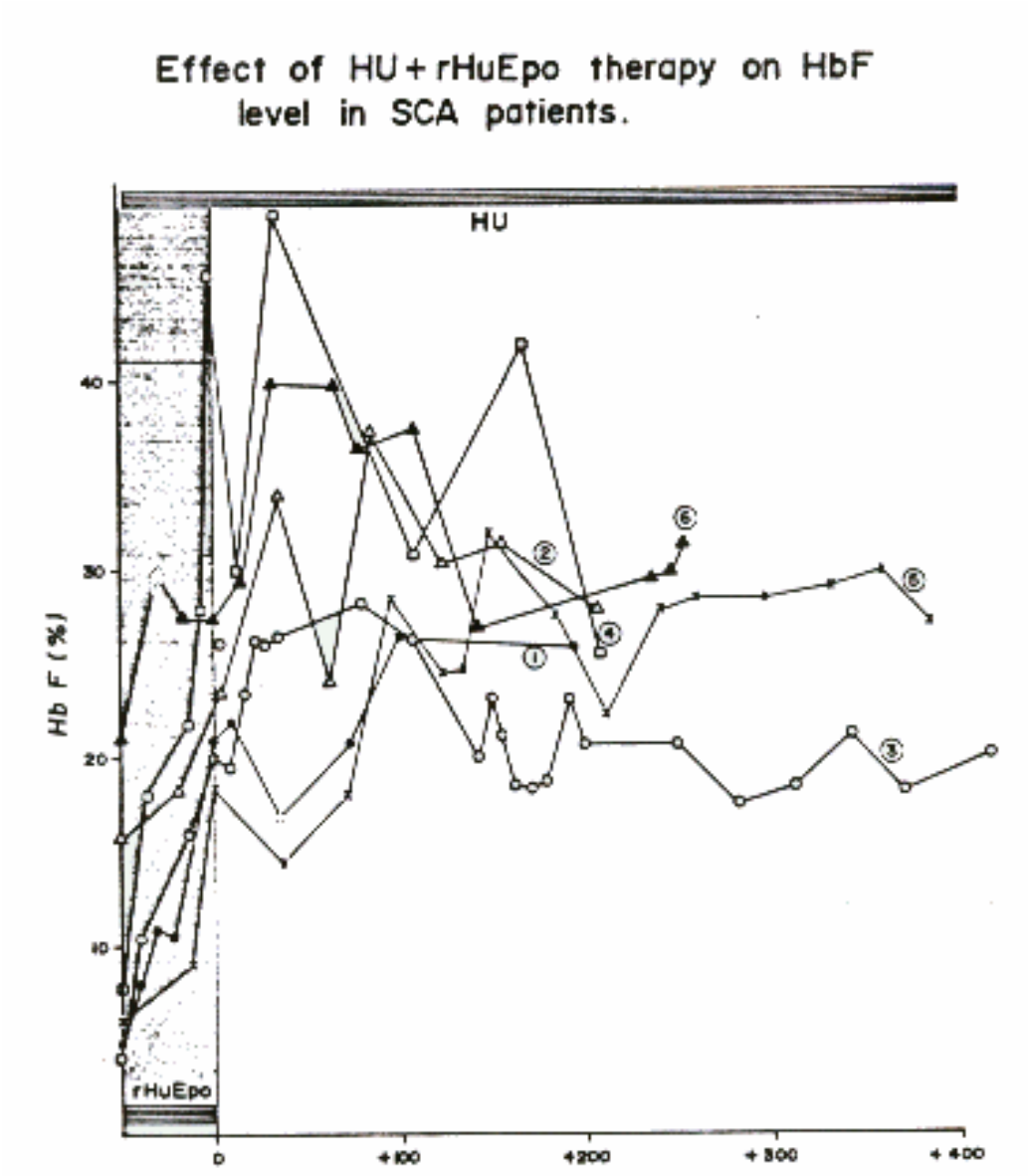

Effect of HU + rHuEpo therapy on HbF level in SCA patients.
HU
rHuEpo
Hb F (%)
40
30
20
10
0
+100
+200
+300
+400
①
②
③
④
⑤
⑥

Figure 13.33

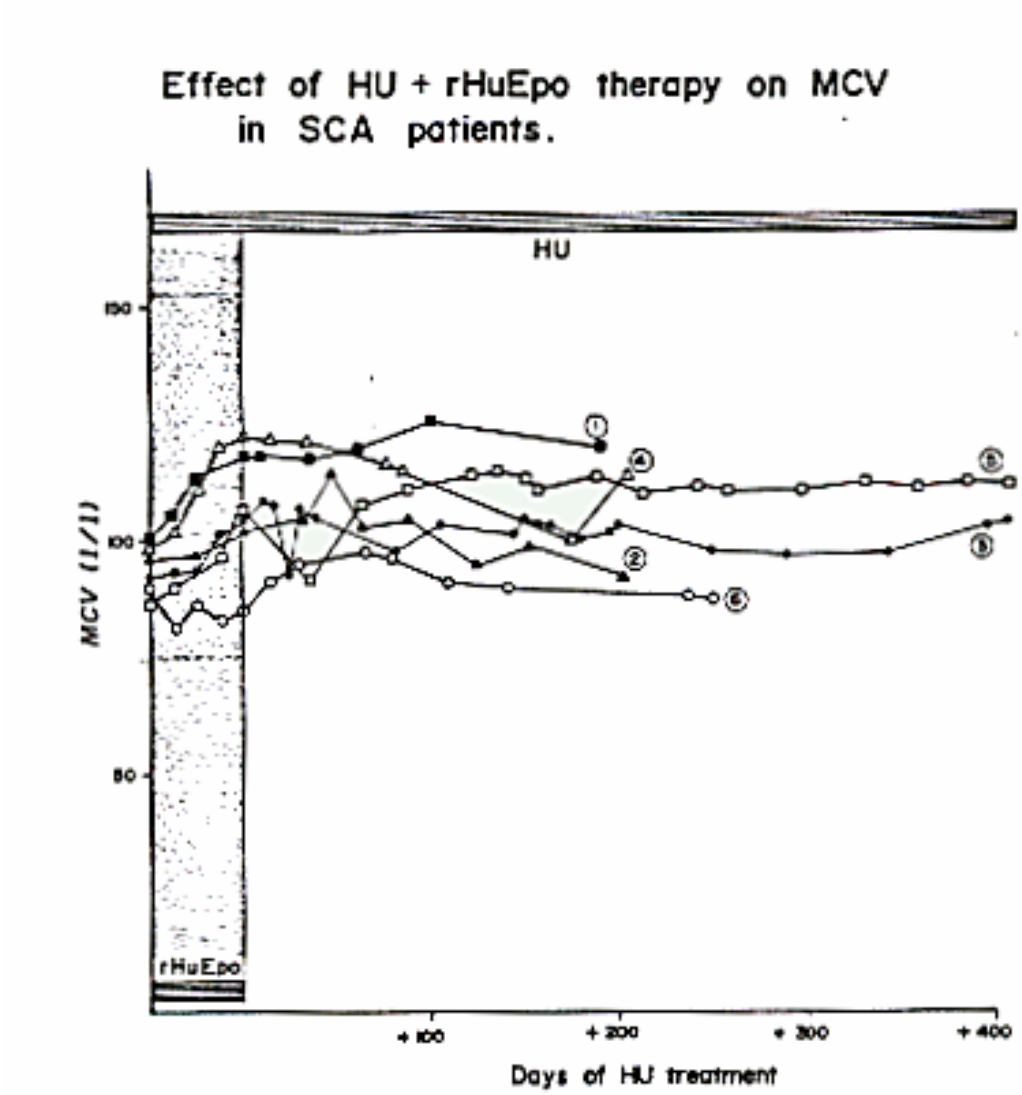
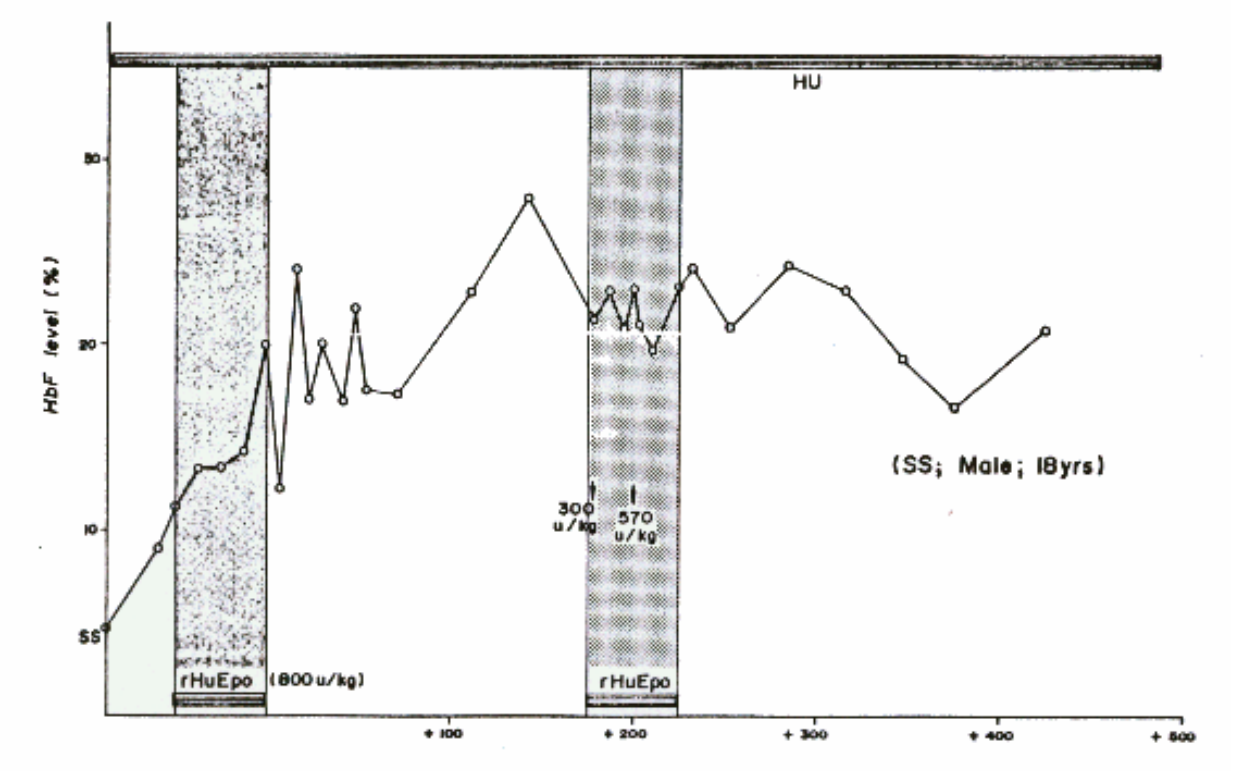

Effect of HU + rHuEpo therapy on MCV
in SCA patients.
HU
rHuEpo
MCV (1/1)
100
80
+ 100
+ 200
+ 300
+ 400
Days of HU treatment

Figure 13.34; Effect of HU and rHuEpo therapy on Hb F level



Day of the treatment

dose of HU and weekly rHuEpo for 4-8 weeks, there was a significant elevation in Hb F (more than when HU is given alone) and this effect continued when HU therapy alone was maintained. No toxic side effects were observed at doses used in our study. Of interest also is the finding that patients who were poor responders respond more effectively with the combination therapy. On the other hand, termination of HU therapy resulted in the reversal of all haematological and biochemical parameters to the baseline values.

The mode of action of HU has been evaluated considerably and remains more or less unclear. There are three major suggestions. Dover et al (1986) suggests that HU acts on late erythroid progenitors and reprograms these progenitor cells to produce Hb F. Stamatoyannopoulas's group (Umemura et al, 1988) suggest that HU is probably more cytotoxic to rapidly dividing late erythroid precursors, thus recruiting early erythroid precursors which produce more Hb F, while more recent observations suggests that HU has an effect similar to the transacting factors which bind to the promoter or enhancer regions and influence gene expression. The rHuEpo, on the other hand, is an haematopoietic growth factor and:thus:increases Hb F cell production.

Future studies should be directed towards alterations in the ratios of HU and rHuEpo and further evaluation of the effect of the sequence and the dose, and the elucidation of the mode and mechanism of action.

13.3 Treatment of Sickle Cell Anaemia Patients with Piracetam

A few drugs with few side effects, e.g. hydroxyurea, have been used successfully for treatment of adult patients but due to their myelosuppressive nature and unknown long term effects, their use has not been considered in children.

Piracetam (2-oxo-1-pyrrolidine acetamide; Nootropil), a cyclic derivative of γ-

aminobutyric acid has been used for the management of psychosenescent syndrome with no known toxic side effects, has been shown to have an antisickling effect both in vitro and in vivo and has an antiplatelet activity. The chemical nature of piracetam makes it a water soluble, readily absorbed and easily diffusable substance, which is not metabolised in the body and is ready excreted. Both oral and intravenous modes can be used for treatment. For over two decades piracetam has been used effectively for the treatment of psychosenscent syndromes where it exerts specific effect on nerve cells. Studies reported in the literature and those conducted in our laboratory, have shown that piracetam increases red cell deformability, and hence improves microcirculation, reverses and inhibits sickling in vitro and hence decreases vaso-occlusive crises. These effects are believed to be modulated through the spectrin-actin network in the red cell membrane, whereby the drug increases the membrane flexibility and the red cell deformability, reduce the viscosity of the deoxygenated Hb S within red cells and hence decreases and reverses sickling. But its effect, as an antisickling agent by inhibiting the interactions between Hb S molecules, is believed to occur only at a high concentration of piracetam. Pilot studies have shown a beneficial effect of piracetam treatment in patients with sickle cell disease. However, further detailed studies on a larger group of patients are necessary to confirm the long term beneficial effect of piracetam.

We initiated multicenter studies using piracetam for the treatment of children suffering from sickle cell anaemia with the aim to determine the effect of piracetam on clinical manifestations, haematological:and biochemical parameters.

The patients (62) included in this study were suffering from a severe form of sickle cell disease as judged from a Gini Score and Severity Index of 6 or more (Table 13.2). The

Patients were admitted during crises, where clinical assessment was carried out. Blood samples were drawn for the determination of the haematological parameters, red cell indices using a Coulter Counter and reticulocyte counts. The red cells, buffy coat and plasma were separated by centrifugation and the red cells were washed twice with cold physiological saline. The cells were haemolysed with cold distilled water and used for the separation of haemoglobin phenotypes on electrophoresis at alkaline and acid pH and for estimation of Hb A_2 and Hb F. The plasma was used for the estimation of liver function profiles on Autoanalyser American Monitor (Parallel).

The patients suffering from crises were immediately started on 300 mg Nootrophil/ kg/day (UCB) or placebo and on conventional supportive therapy to relieve pain and fever, if any. During the hospitalisation period daily clinical evaluation was carried out and the total quantity of liquid were recorded, until the day of discharge. The same protocol was followed for any subsequent vaso-occlusive crises.

On patient's discharge, prophylactic oral treatment of 160 mg Nootrophil/kg/day was initiated. The patients were given bottles full of the syrup (Nootrophil) for exchange of empty syrup bottles.

Figure 13.35: Study Flow Chart

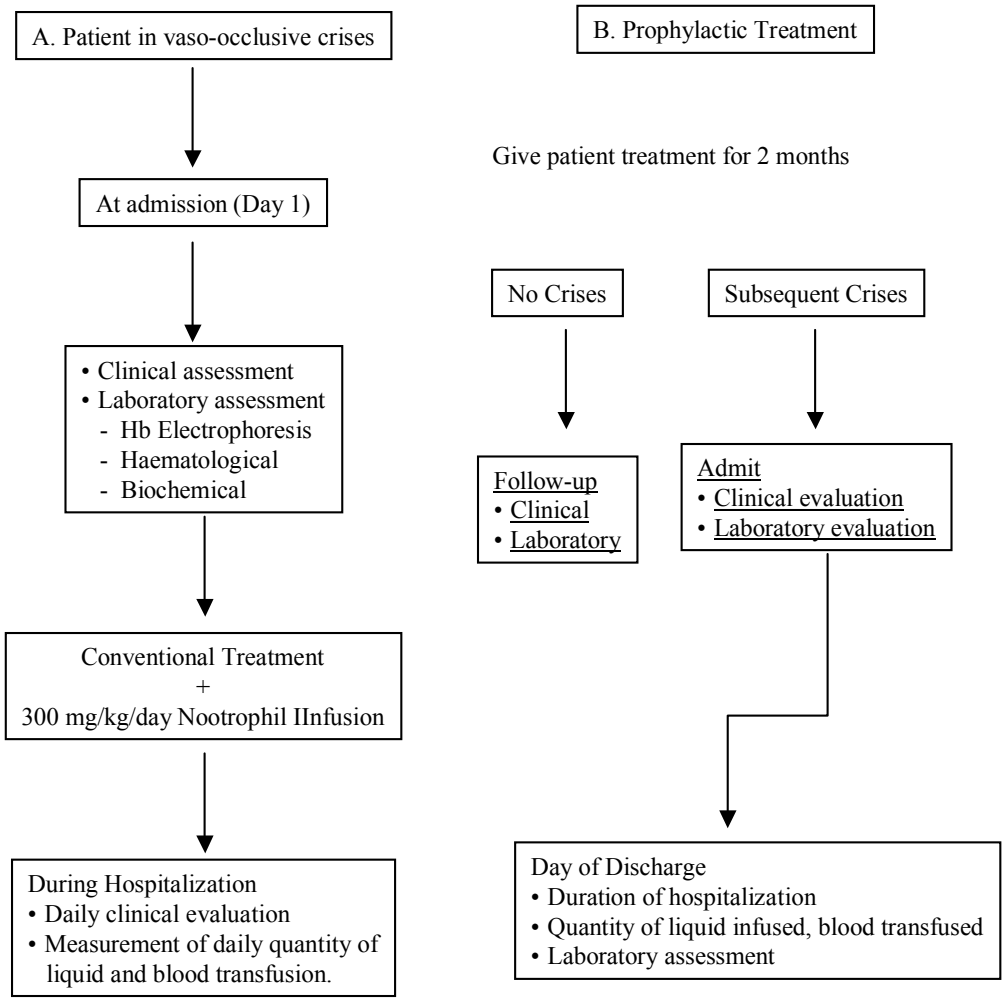


Figure 13.36

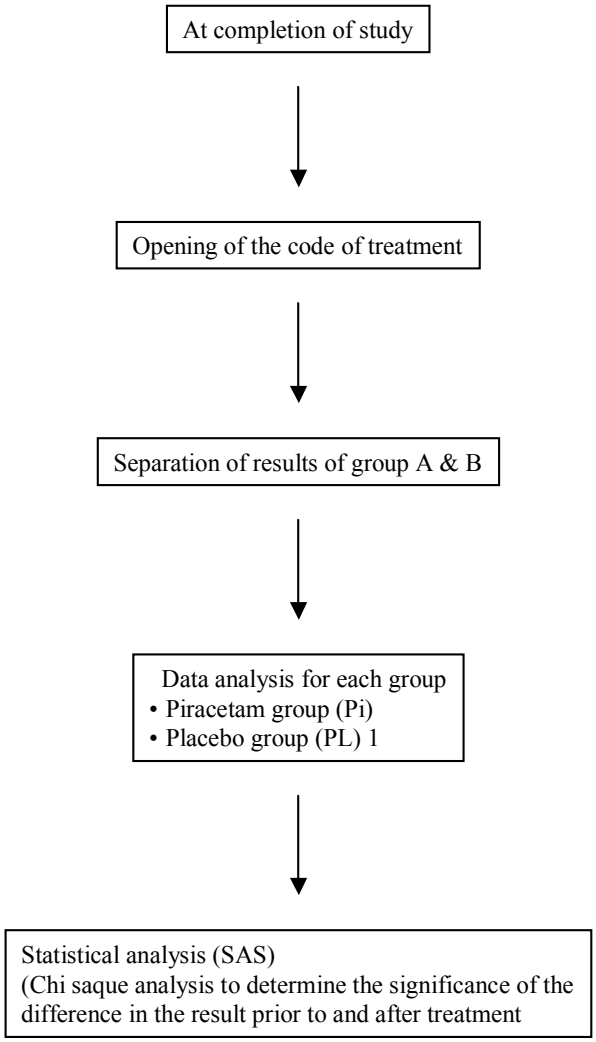

At completion of study
Opening of the code of treatment
Separation of results of group A & B
Data analysis for each group
• Piracetam group (Pi)
• Placebo group (PL) 1
Statistical analysis (SAS)
(Chi saque analysis to determine the significance of the difference in the result prior to and after treatment

Table 13.2: Study Design

- Double blind study
- Patients

  Group A: 3 - 6 years: 27

  Group B: 6 - 12 years: 35
- Inclusion Critera
  - Severe SCD (Gini score >6)
  - Informed consent of parents
  - Baseline results available
- Treatment Group
  - Piracetam
  - Placebo

The number of patients in this study maintained on piracetam and placebo protocol in different regions of Saudi Arabia is 62 and the maximum period of treatment so far is one year. The study was a double blind study and the code was opened after the completion of the study. The patients were grouped into the piracetam and placebo groups and the results were calculated separately for each group. The mean Gini Score prior to and after treatment were calculated for the patients recruited from different regions. The results showed that the severity (Figures 13.37 and 13.38) and vaso-occlusive crises (Figures. 13.39 and 13.40) decreased significantly after treatment with piracetam. However, no significant effect was observed on the value of haematological parameters i.e. total haemoglobin, RBC, WBC and MCV, before and following treatment (Figures 13.41 to 13.45). Similarly, no specific pattern of increase or decrease could be demonstrated for the biochemical parameters. The baseline values for liver function tests showed significant variation between the patients and were distributed over a wide range. After treatment, decrease was observed in some patients, while:an increase occurred in others. No clear pattern of the effect of piracetam could be observed during the treatment period covered in this report.

In our unit, the piracetam protocol was first designed in 1989 and its implementation was initiated in 1990. Preliminary studies on patients revealed its beneficial effect. The multicenter trial was started in the middle of 1992 and has been maintained for over one year. To date there are 8 centers, that have enrolled a total of 96 patients in the age groups of 3-6 years and 6-12 years.

Figure 13.37: Effect of Piracetam treatment:
on clinical presentation

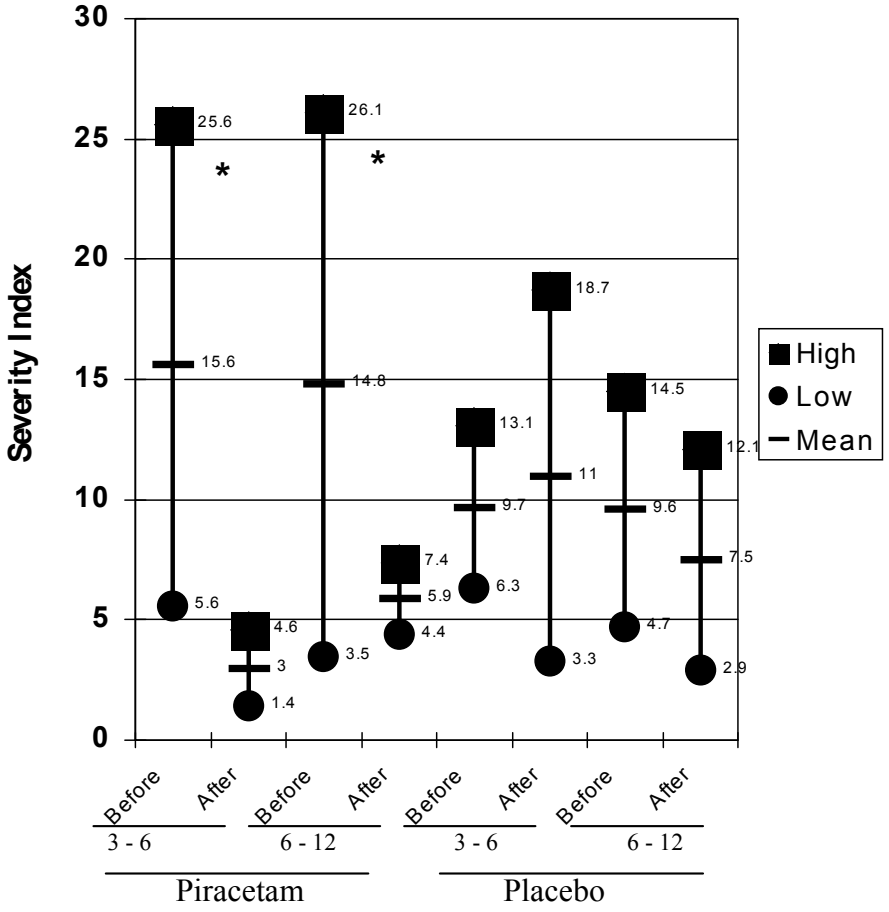


Figure 13.38: Effect of Piracetam on the Severity Index of SCD patients

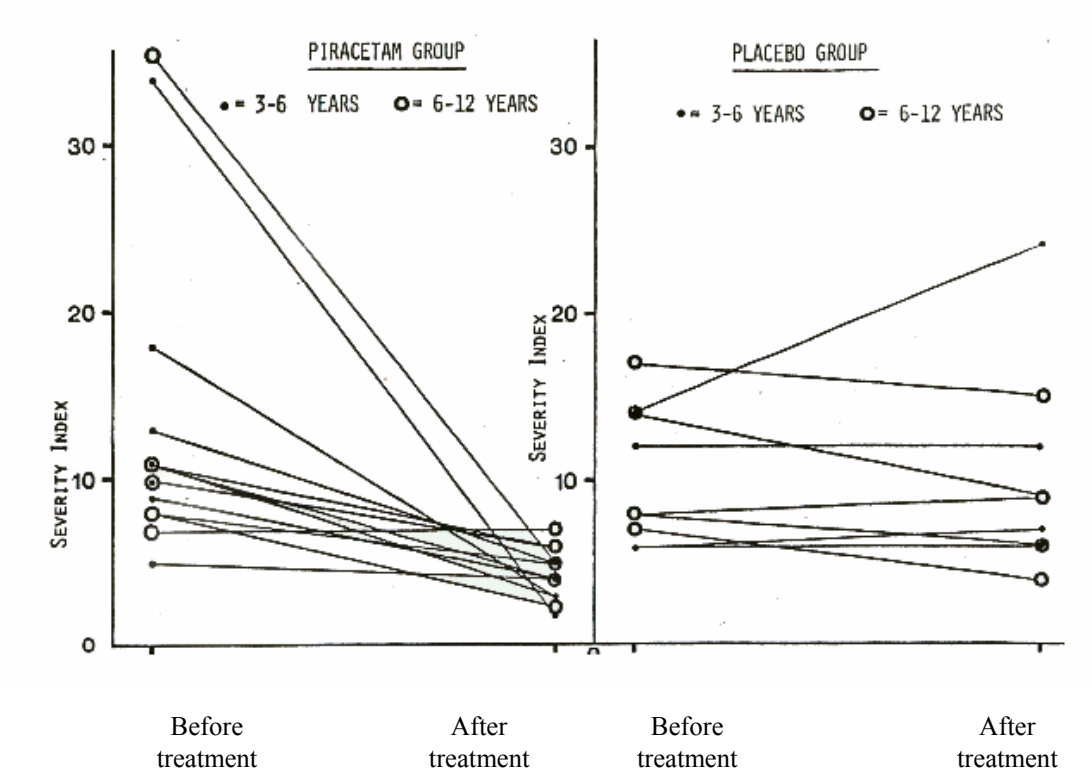


Figure 13.39: Effect of Piracetam treatment:
on clinical presentation

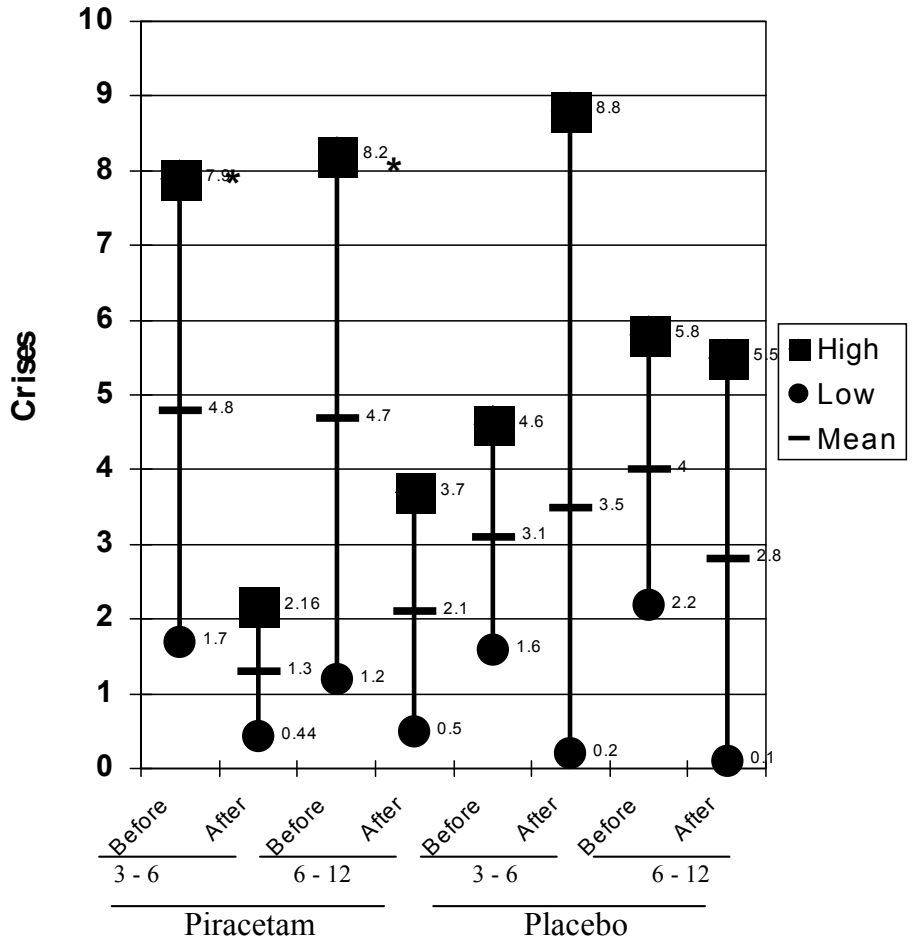


Figure 13.40: Effect of piracement on the number of crises per year in SCD patients

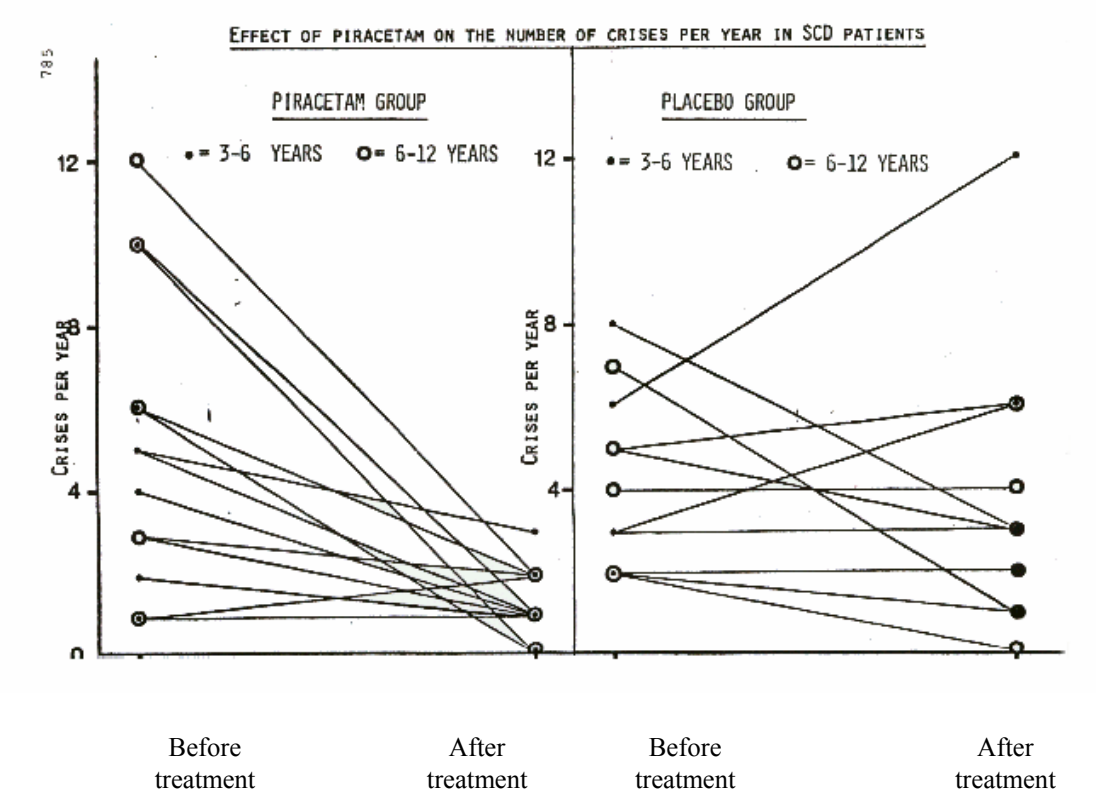


Figure 13.41: Effect of Piracetam treatment:
on haematological presentation

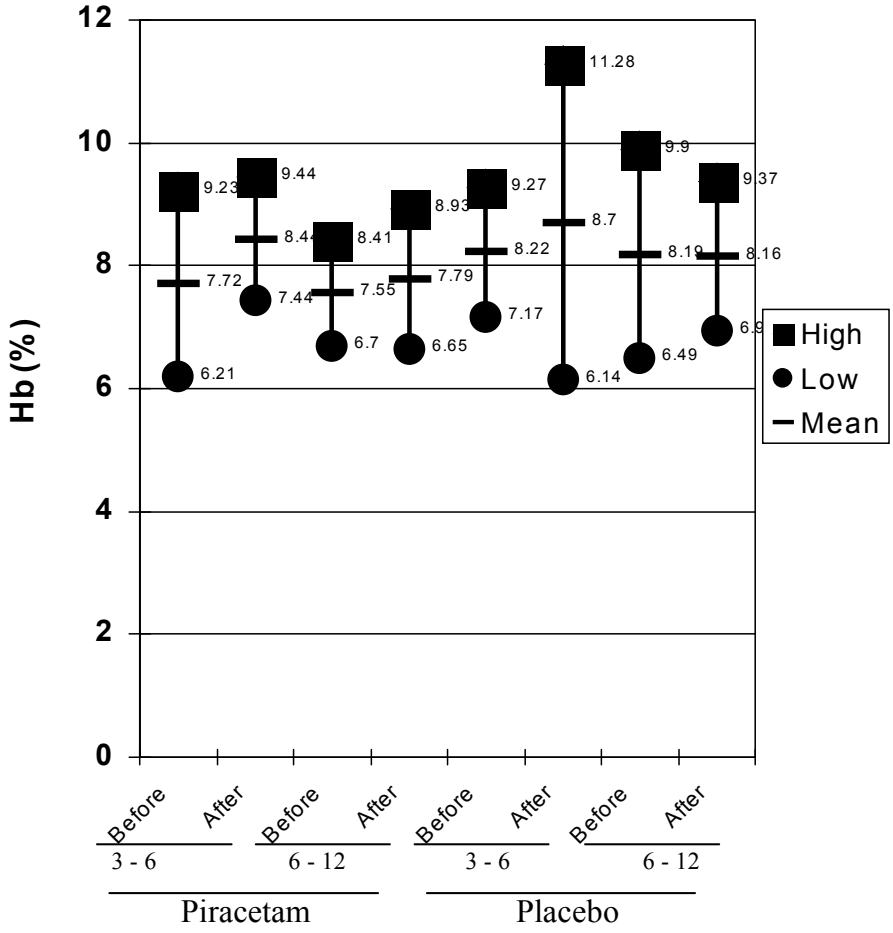


Figure 13.42: Effect of Piracetam treatment:
on haematological presentation

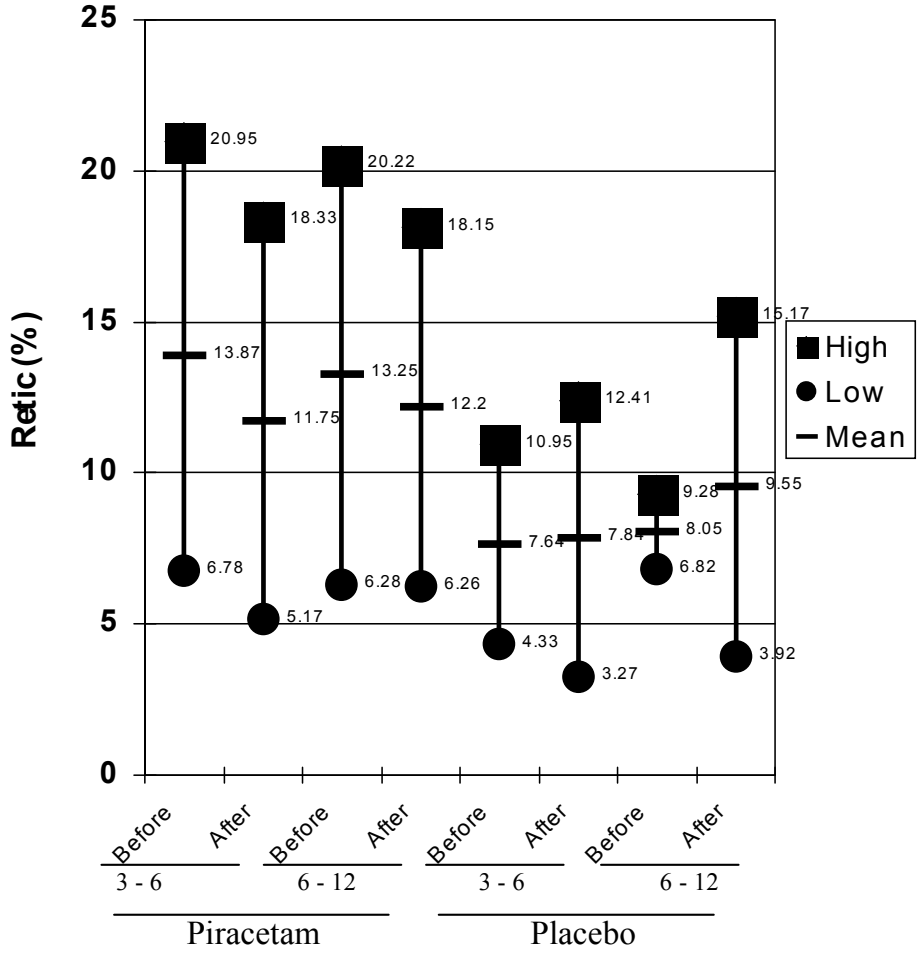


Figure 13.43: Effect of piracetam on the reticulocytes count in SCD patients

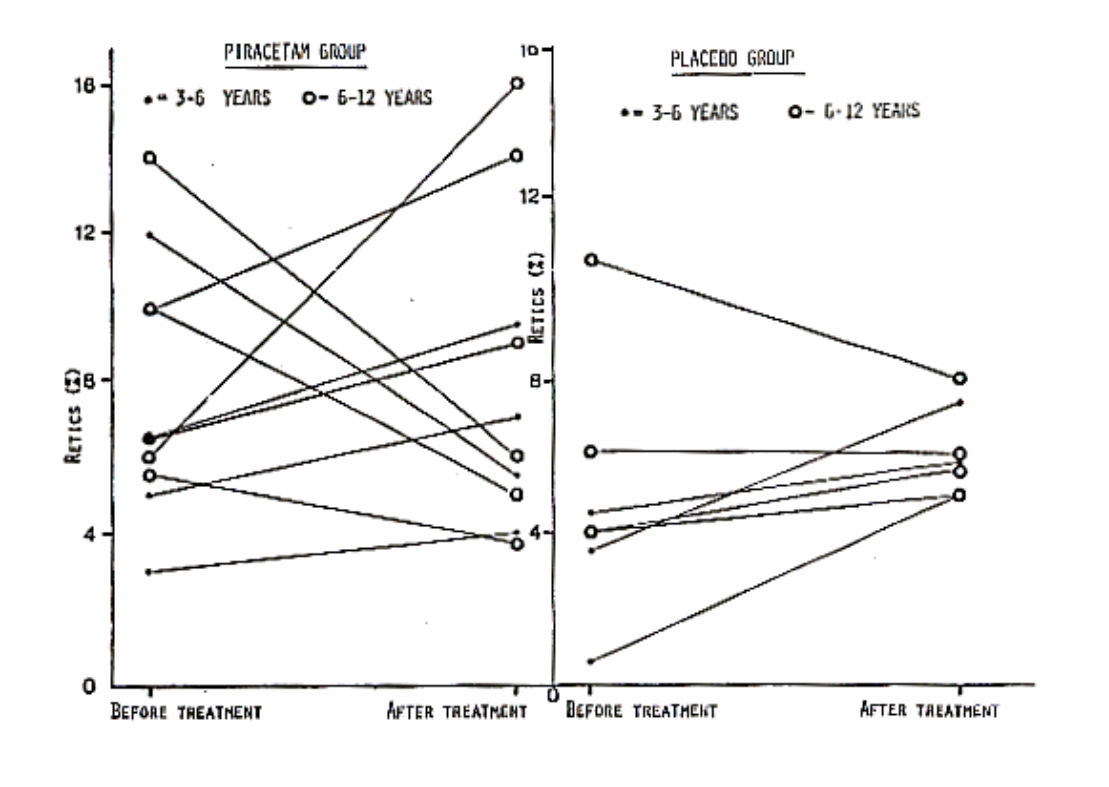
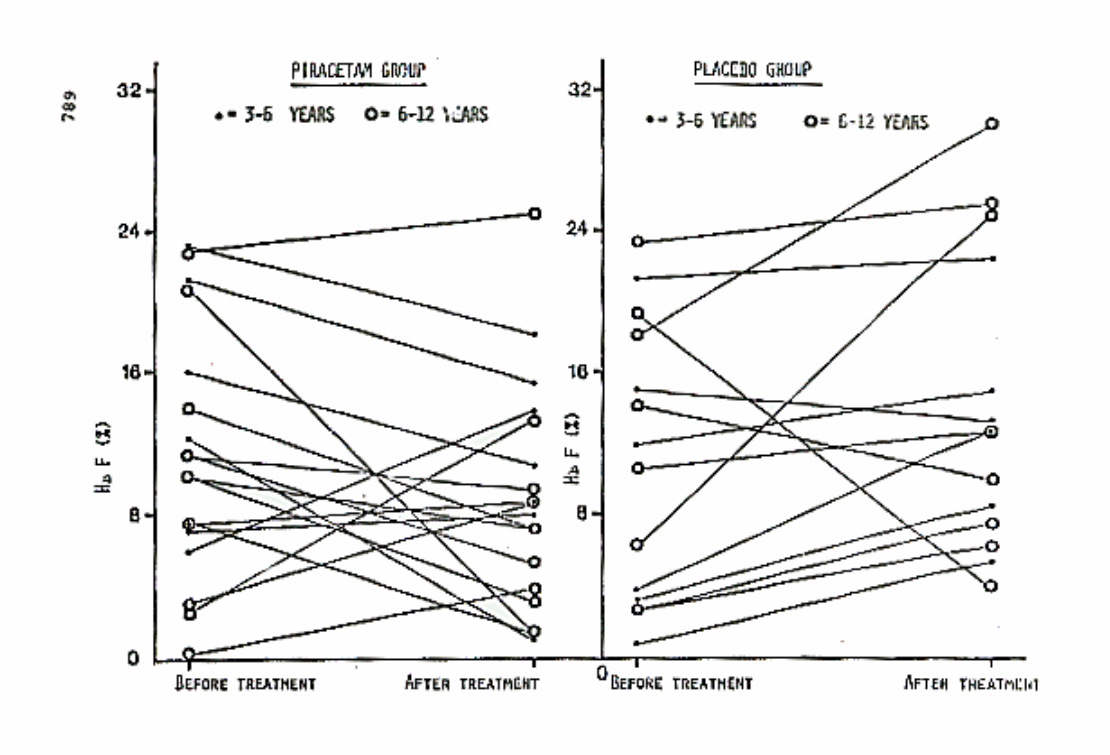


Figure 13.44: The Effect of piracetam on Hb F level in SCD patients



The preliminary data analysis shows that the frequency of vaso-occlusive crises is decreased during treatment of patients with piracetam. Whether this is a short term or lasting effect remains to be confirmed.On the other hand, no statistically:significant effects were seen on the haematological or biochemical parameters nor significant alteration of Hb F level was demonstrated. It is expected that long term treatment with piracetam in multicenter trials will confirm whether or not piracetam can be used sucessfully for treatment of Hb SS.

13.4. Conclusion

Several modalities have been suggested for the treatment of sickle cell disease and theoretically decreasing sickling and RBC entrapment in the narrow blood vessel is considered as an important factor in improving the clinical presentation in sickle cell disease (Figure 13.46). Bone marrow transplantation gene therapy are the ultimate goal for patients with a very severe disease. It is necessary that further clinical trials are conducted to decrease the clinical severity in these patients and in order that they may lead a normal life.

Figure 13.46.: Possibletherapeutic modalities for treatment of SCD