



**REPORT ON A MEETING OF THE PRODUCT DEVELOPMENT TEAM FOR
AFRICAN TRYPANOSOMIASIS CHEMOTHERAPY TO REVIEW THE
COMPARATIVE STUDY OF 14-DAY VERSUS
7-DAY TREATMENT OF LATE STAGE T.B. GAMBIENSE AFRICAN
TRYPANOSOMIASIS WITH EFLORNITHINE**

WHO, GENEVA, 14 JULY 1998

CONCLUSIONS AND RECOMMENDATIONS

RELAPSING PATIENTS

The 14-day regimen is highly effective.

In addition, considering the findings of the multicentre study, as well as those of a previous open trial at Nioki, Democratic Republic of Congo (DRC) with the 7-day regimen in relapsing cases (*Khonde et al, Transactions of the Royal Society and Tropical medicine and Hygiene (1997) 91, 212-213*), and in view costs of the 14-day regimen, the group felt that the 7-day regimen could be considered an acceptable alternative, and that it could be used by national control programmes and hospitals in endemic countries.

However, considering that only a limited number of relapsing cases has been treated with the 7 day regimen in this study, it is recommended that relapsing cases treated with the 7-day regimen are closely followed up and that national control programmes should collect and maintain data on the efficacy of the 7-day regimen.

NEW CASES

In Côte d'Ivoire, DRC and Congo, the 14-day regimen was highly effective for new cases and continues to be recommended. In Uganda, the 14-day regimen was considerably less effective than in the other three countries. The reasons for this were not clear (see discussions, page 4).

When the results in Côte d'Ivoire, Congo and DRC are combined, the 7-day regimen was significantly less effective than the 14-day regimen. In Uganda, there was no statistically significant difference between the 7-day and 14-day regimens and the drug cannot be recommended.

DRUG COMBINATIONS (new and relapsing cases)

Consideration should be given to studies of drug combinations, either sequentially or simultaneously. As melarsoprol and eflornithine are already in use in humans for late stage *T. b. gambiense* African trypanosomiasis and there is experimental evidence of synergism in a murine model, priority consideration should be given to clinical studies on combinations of melarsoprol and eflornithine.

CONCOMITANT INFECTIONS

Eflornithine is a trypanostatic drug. In view of the implications of immuno-suppression in HIV patients, the HIV status of patients recruited into future clinical trials should be determined.

RESEARCH

Collection and characterization of trypanosome strains from NW Uganda should be continued and trypanosomes should be examined for susceptibility/resistance to eflornithine.

INTRODUCTION

The US FDA registered eflornithine for the first time in 1990 as a drug for *T. b. gambiense* African trypanosomiasis. However, the cost of the drug, among other limitations, is a major factor preventing its use by endemic countries.

The standard treatment regimen of eflornithine for *T. b. gambiense* African trypanosomiasis is 100mg/kg intravenously every 6 hours for 14 days. In 1992, TDR in collaboration with Marion Merrell Dow, (now Hoechst Marion Rousel -HMRI), initiated a multicentre, randomized, comparative study of a 14-day versus 7-day regimen to assess the efficacy of the 7-day regimen. The ultimate goal was to reduce the duration of treatment and thereby reduce costs.

A total of 320 patients from four countries (Côte d'Ivoire, Congo, Democratic Republic of Congo [formerly Zaire] and Uganda) were recruited from July 1993 – February 1996. Originally each centre was to enrol 80 patients, but due to inadequate numbers of patients in Côte d'Ivoire and Congo, the other two centres enrolled more to make up the total intake. The normal 2-year follow-up of patients was hampered by civil disturbances. There was a civil war in the Congo in 1997, and in Zaire from 1996-1997. Ongoing guerrilla warfare in Northern Uganda disrupted patient recruitment and follow-up. The overall follow-up period at the four centres ended in April 1998.

HIGHLIGHTS OF RESULTS

Patients were classified into two categories: Relapsing Cases - those who had previously been treated with another drug, usually melarsoprol and had relapsed; and New Cases - patients who had not previously been treated.

As the number of patients recruited in Côte d'Ivoire and Congo was less than anticipated and in view of the proximity of Congo and the DRC, data from Côte d'Ivoire, Congo and DRC were pooled together for analysis, while the data from Uganda were considered separately.

Adverse Events

Five deaths occurred during treatment, of which 2 were in Uganda and 3 in Côte d'Ivoire. Overall, 4 of 17 (24%) patients who had convulsions died compared with 1 out of 303 (0.3%) among those who did not experience convulsions ($p < 0.0001$). In Uganda convulsions were significantly more common with the 14-day regimen than the 7-day regimen ($p = 0.006$, χ^2 -test).

Overall, diarrhoea, vomiting and abdominal pain were all more common on the 14-day than on the 7-day regimen. Convulsions were more common among relapsing cases than among new cases (6/49, 12.2% vs. 11/271, 4.15% respectively; $p = 0.05$).

Treatment Failures

In Côte d'Ivoire, Congo and Zaire combined, the number of treatment failures was significantly higher in the 7-day treatment group than in the 14-day treatment group (12/101 vs 2/104; $p = 0.01$, χ^2 -test). In Uganda the number of treatment failures was almost the same in the 7-day as in the 14-day treatment group (15/57 vs 12/59, $p = 0.6$, χ^2 test).

Identification of risk factors associated with treatment failure with eflornithine (multivariate analysis)

The primary objective of the study was to compare 7-day and 14-day treatment. However, further analyses were carried out to identify factors, other than treatment regimen, which may be associated with treatment failure. These factors were age, presence of stupor on admission and lymph node aspirate. Overall, the risk of failure **decreased** with age, and was **higher** among new cases than relapsing cases, among patients whose lymph node aspirate was positive, and among patients who were not in stupor on admission to hospital ($p < 0.05$ in each case).

For Côte d'Ivoire, Congo and Zaire combined, the **Adjusted Hazard Ratio (AHR)** for treatment failure of the 7-day relative to the 14-day regimen was 7.6, which was highly significant. When only new cases were considered, the AHR of treatment failure was 6.43. This means that, in the three countries mentioned above, the 7-day treatment is 8 times more likely to fail than the 14-day treatment.

Among all cases in Uganda, the AHR for treatment failure on the 7-day relative to the 14-day regimen was 1.33, which is not statistically significant. When only new cases are considered the AHR was 1.37. This means that, in Uganda, the two regimens have almost equal chances of failure.

DISCUSSION

The reported frequency of treatment failure with eflornithine in new cases of *T. b. gambiense* sleeping sickness from NW Uganda is much higher compared to other countries, and also much higher than has been hitherto reported from any previous study; this is an important finding. Uganda is the only country where both *T. b. gambiense* and *T. b. rhodesiense* occur. The latter species is refractory to eflornithine, but there is no evidence of geographic overlap of the two species. Recent investigation by Enyaru et al. confirmed that only *T.b. gambiense* was endemic in the study area. However according to Brun (personal communication, 1998), 3 out of 5 strains of *T. b. gambiense* examined from NW Uganda were resistant *in vitro* to eflornithine. As this drug has not been previously used in NW Uganda before this study, the underlying mechanisms of the resistance needs to be elucidated.

The prevalence of HIV infection in Adjumani area in NW Uganda is not known, but it is unlikely to be high enough to explain the high treatment failure rate in Adjumani.

In Côte d'Ivoire, Congo and Zaire, treatment failure was less frequent than in NW Uganda, but the 7-day regimen was clearly inferior to the standard 14-day regimen. The cure rate of 88% after 2 years follow-up precludes further consideration of the 7-day regimen for new cases. However, it may be argued that, in view of costs, the 12% who may fail on an eflornithine 7-day regimen could be subsequently treated with melarsoprol.

For relapsing patients, there was difference in cure rate between the 7-day and the 14-day regimen, probably due to better penetration of the central nervous system as a result of blood brain barrier damage. The numbers of relapsing patients recruited in Uganda were small and no conclusions can be made about geographic variation. Overall, the total number of relapsing patients was too small to detect any differences in efficacy between the treatment regimens and

between the centres. However, the current observations are in line with those reported from an open trial in Nioki where 3 (6.5%) treatment failures were reported among 47 relapsing cases treated with the 7-day regimen (Khonde et al, 1997).

A pilot trial is in progress in Nioki, of a combination of 4 days intravenous eflornithine (at a dosage of 100mg/kg every 6 hours) and melarsoprol (at a dosage of 3.6mg/kg per day for 3 days). Twenty relapsing cases were enrolled between March 1996 and February 1998. In 12 months follow-up, 2 patients were lost, but no treatment failure was recorded. PRCT, Daloa, Cote d'Ivoire, also reported the treatment of five patients who simultaneously received eflornithine and melarsoprol with no failure. It thus appears that a combination of eflornithine and melarsoprol holds promise for treatment of late stage *T. b. gambiense* African trypanosomiasis.

THE FUTURE

HMRI has offered to WHO, free of charge, the last 2400 vials of eflornithine in its possession since 1993. WHO (CTD) has identified certain donors who are interested in paying for the production of additional stocks of eflornithine by ILEX Oncology Inc. However, certain conditions have been laid down, including a site visit to the production plant, and a certificate of quality control to the effect that the product is of the same quality as the originally produced by HMRI. TDR will continue its efforts relentlessly to make eflornithine available at an affordable cost, including efforts in developing a new synthetic route and evaluating an oral formulation. With regard to improved use of existing drugs, an improved regimen of melarsoprol, the only available drug for late-stage *T. b. gambiense* and *T. b. rhodesiense*, apart from eflornithine, is under study in Angola under the auspices of the Swiss Tropical Institute, Basel, in collaboration with CTD and other institutions. The search for lead compounds that have activity against trypanosomes and other parasites will continue.

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ANNEX 1

| Comparative study of eflornithine 14-day versus 7-day treatment of late-stage <i>T. b. gambiense</i> African trypanosomiasis Probability of Cure over a 2-year period | | | | |
|--|------------------|-------|------------------------|--------|
| Patients | New Cases | | Relapsing Cases | |
| Treatment duration (days) | 7 | 14 | 7 | 14 |
| Uganda | 62% | 73% | } 94% | } 100% |
| DRC (Zaire) Congo Côte d'Ivoire | } 88% | } 97% | | |

ANNEX 2

PDT Meeting to review the Comparative Study of 14 day versus treatment of late stage *T.b.gambiense* African trypanosomiasis with Eflornithine

List of Participants

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ANNEX 3

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