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Evaluation of modified short course chemotherapy in active pulmonary tuberculosis patients with human immunodeficiency virus infection in University College Hospital , Ibadan, Nigeria - a preliminary report

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Summary
Over the period, 1st October 1999 to 30th April2002 a clinical trial of the modified short-course chemotherapy (SCC) in newly diagnosed cases of pulmonary tuberculosis with human immunodeficiency virus (HIV) infection in Ibadan, Nigeria was carried out. The modified SCC used was adopted by World Health Organisation (WHO)/International Union against Tuberculosis and Lung Diseases (IUALTD) for developing countries and also by the Nigerian National Tuberculosis and Leprosy Control Programmed (NTLCP). The regimen used consisted of ethambutol (E), isoniazid (H), rifampicin (R) and pyrazinamide (Z) in the intensive phase of 2 months. The continuation phase was 6 months of ethambutol (E) and isoniazid(H), i.e. 2EHRZ/6EH. Sputum conversion was 90% at the second month of treatment and there was no bacteriological relapse after 18 months of follow-up. Side effects were few and consisted mainly of acne vulgaris in 20 (22.5%) of 89 patients during the continuation phase. It is concluded that this modified 8-month chemotherapy regimen adopted by NTLCP is efficacious in treatment of smear positive pulmonary tuberculosis (PTB) patients with background HIV infection.

Keywords: *Modified short course chemotherapy, active pulmonary tuberculosis, human immunodeficiency virus infection, Nigeria*

Résumé
D'octobre 1999 au 30 avril 2002 un essaie clinique de traitement des nouveaux cas diagnostiqués de tuberculose pulmonaire et l'infection du VIH étaient faite a Ibadan au Nigéria. Le SCC modifié adopté par l'organisation mondiale de la santé, l'Union Internationale de la contre la tuberculose et les maladies pulmonaires et le programme de contrôle de la lépre en pays sous –developés.Un dosage constitue d'ethanbutol, ionizide, rifampicine et pyrazinamide dans la phase intense de 2 mois.La phase polongée de 6 mois était faite d'éthanbutol et isoniazide(2 EHR +6EH).La conversion de sputum était de 90% dans la 2ième voie de traitement et n'avait pas de retourner de bactériologique aprés 18 mois de suivi. Les effects adverses étaient peu et consistaient principalement de la vulgarie chez 20(22.5%) des 89 patients suivi durant la phase prolongée. Il a été conclu que ce modéle modifié de 8 mois de traitement par NTLCP est éfficace pour le traitement des patients ayant les infections du VIH associées a la tuberculose.

Introduction

The enormous burden of human immunodeficiency virus (HIV) infection in sub-Sahara Africa is well documented, and is estimated that 70% of the world's HIV infected people (25.3 million) live in this region [1]. In most developing countries tuberculosis (TB) is clearly the most important opportunistic infection observed among HIV infected patients [2]. Pulmonary disease is the most common presentation of TB in persons with HIV infection and is seen with or without extra pulmonary involvement [3-5].

The efficacy of daily short-course chemotherapy (SCC) for pulmonary tuberculosis (PTB) using regimens containing rifampicin is no longer in doubt [6-8]. Several trials have shown that regimen consisting of isoniazid (H), rifampicin (R), pyrazinamide (Z) and streptomycin(S) or ethambutol (E) are highly effective in HIV-infected patients as in patients without HIV infection [8].

The two currently internationally accepted regimens for chemotherapy of tuberculosis for developed countries are 2SHR/7RH or 2EHR/7RH and 2SHRZ/4RH or 2EHRZ/4RH. These regimens especially the 4-drug intensive phase achieve complete bacteriological sterilization while the continuation phase of 4 months (or 7 months in the 3-drug regimen) ensures that the bacteriological relapse is acceptably low [7]. HIV related immunosuppresion does not interfere with the effectiveness of anti-TB therapy as the sputum conversion and resolution of chest radiograph abnormalities occur as rapidly in HIV-infected patients as patients without HIV infection [8,9]. The SCC of tuberculosis adopted from WHO/IUALTD for developing countries by the NTLCP is *2SHRZ/6TH* or *2EHRZ/6TH [10]*. These thiacetazone – containing regimens were used in Africa because of their low cost, however, thiacetazone has been associated with severe, often fatal cutaneous hypersensitivity reactions in persons with HIV infection [11-14]. Because of this, the WHO has warned against the use of thiacetazone in the treatment of TB in HIV-Infected patients [14-17]. Therefore, the modified SCC for tuberculosis now adopted for the developing countries is 2SHRZ/6EH or 2ERHZ/6EH [15]. However, in Nigeria, there is a dearth of studies on the bacteriological relapse

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following the use of the 8-month regimen (2SHRZ/6EH or 2EHRZ/6EH) in human immunodeficiency virus seropositive patients. Bacteriological relapse is an essential index of efficacy as a considerably relapse rate leading to re-treatment will not be cost effective and will also constitute public health problem.

Since 1995 the Damien Foundation has been supplying drugs for treatment of tuberculosis to the University College Hospital, Ibadan to enable the modified short course regimen to be incorporated into treatment. This study was carried out as a preliminary assessment of the efficacy of the modified SCC in the treatment of PTB in patients with human immunodeficiency virus seropositive adults in University College Hospital (UCH), Ibadan, a typical referral hospital in the south west geopolitical zone of Nigeria.

Methodology

The study was carried out in General Out-Patient, Medical Out-patient, Surgical Out-Patient Departments and Wards of UCH, Ibadan for two and half years (between 1st October 1999 and 30th April 2002). A total of 89 patients aged 15 years and above with pulmonary tuberculosis and HIV infections were studied.

Patients were eligible for inclusion into the study if they were newly diagnosed cases of PTB and their sputum contained tubercle bacilli on direct smear and/or culture. They were also confirmed by Western Blot Serology in UCH to be infected with HIV. Clinically suspected cases of PTB were confirmed by finding ≥ 2 out of 3 sputum smears staining positively for acid-fast bacilli by the Ziehl-Neelsen technique or sputum culture that is positive for M.tuberculosis (using lowenstien-Jensen culture medium). Patients and accompanying relations were carefully questioned regarding previous anti-tuberculous treatments and any patient with a history of previous treatment was excluded.

All the patients enrolled gave written informed consent. Details of clinical history, physical examination, and basic personal, social and demographic information were recorded. Patients were placed on an initial intensive phase of 2 months using: rifampicin,10mg/kg (maximum 600mg), pyrazinamide,30mg/kg (maximum 2g); ethambutol, 25mg/kg; (maximum 1.2g), and isoniazid, 5mg/kg (maximum 300mg). The continuation phase was 6 months of isoniazid, 5mg/kg (maximum 300mg); and ethambutol, 25mg/kg (maximum 1.2g). The intensive phase was directly observed therapy (DOT) while monthly pre-packed envelopes of EH were given to all the patients during the continuation phase.

For descriptive purpose the chest radiographs appearance was assessed according to a precoded format (6). Thus, minimal lesion, when lesion was confined to one zone; moderate if the lesion was confined to two zones of the same lung and severe, if lesion was found throughout the lung or three or more zones bilaterally. Attention was paid to the presence of pulmonary infiltrate, cavitation, nodular or streaky opacities, pleural effusion, lymphadenopathy and loss of lung volume due to fibrosis.

All the patients were started on anti-retroviral therapy (ARD) from time of recruitment into the study and throughout the clinical trial. These were Lamivudine, 150mg twice daily, Zidovudine, 200mg thrice daily and Nevirapine, 400mg daily in two divided doses.

Ethical clearance was obtained from the Joint Ethical Committee of the University College Hospital/ University of Ibadan.

Treatment Follow-up

The patients were enrolled in the tuberculosis unit under the TB treatment programme being sponsored by the Damien Foundation in UCH. They presented daily to MOP to obtain their anti-tuberculosis drugs in the presence of the nursing staff at MOP (DOTS); while subjects on admission in the wards were on a daily basis, being served and observed to take their anti tuberculous drugs by the nursing staff in the ward. Patients in the ward were reviewed weekly while those at MOP were reviewed on monthly basis.

Clini[illegible]t was assessed subjectively [illegible]e assessment of symptoms i[illegible]g, subsidence of cough and 1[illegible] included weight gain and def[illegible]s categorised as: (a) improved[illegible]d or (d) died.

Sputum examination by smear and culture was repeated monthly for the first 5 months, and at the end of therapy. Chest radiographs were done on enrollment and thereafter 3 monthly intervals during treatment, and repeated 3 months after treatment and at the end of follow-up. The radiographic findings were compared with the initial pre-treatment chest radiographs and were classified as (a) resolved (b) improved (c) worsened or (d) unchanged. In this study, the level of circulating CD_4 + T-lymphocytes was not estimated because it was not routinely done at the time.

Results

A total of 89 adult subjects confirmed to be HIV seropositive with smear or/and culture positive PTB were studied. Infection by HIV I was the commonest being the only HIV type found in 85 (96.5%) subjects. Two subjects had only HIV-2 infection while 2 other subjects had both HIV-1 and HIV-2 co-infection. Table 1 shows the age and sex distribution of the subjects.

Majority of the patients are within the age group 20 – 49 years accounting for 82 (93%) of the subjects. The largest number of subjects was in the age group 30-39 years i.e. 46(52%) subjects, this was followed by the age group 20 – 29 comprising 21 (24%) subjects.

All patients showed rapid clinical improvement during the first month of therapy and sputum cultures reverted to negative after 3 months of treatment in 85 (95.5%) subjects. All patients were sputum negative at the fourth month of treatment.

Table 1: Age and sex distribution of subjects

Age	Male	Female	Total (%)
15 – 19	0	2	2 (2)
20 – 29	9	12	21 (24)
30 – 39	31	15	46 (52)
40 – 49	9	6	15 (17)
50 – 59	0	3	3 (3)
60 – 69	2	0	2 (2)
Total	51	38	89 (100)

At 12 months, 82 patients were available for sputum examination and their sputa remained negative. At 18 months, 80 patients were available for examination but none could produce sputum for examination. Five patients were lost to follow-up while 4 patients died during the follow-up.

Table 2: Correlation of the months after starting therapy with the number of patients with smear and/or culture negative sputum

Month after starting treatment	Patients with Smear/culture negative sputum (n=89)
2	80 (90)*
3	85 (95.5)
4	89 (100)
5	89 (100)
8	89 (100)

* *Figures in parentheses are percentages*

Using the precoded format for assessing the chest radiographs appearance, there were 45 (50.56%) patients with minimal lesion while 8 (8.99%) of the 89 patients presented with extensive lesions including fibrosis and cavities. Maximal radiological clearance was noticed at the third month of treatment in 81 (92%) of the patients. The chest x-ray of the 80 patients available at the 18 months follow-up showed complete clearance than that observed at 3 months on medication.

Four patients died during the follow-up, one was due to Steven Johnson syndrome while the progression of the retroviral infection and PTB was likely responsible for the death of other 3 patients. Five (5.6%) patients complained of nausea in the first 2 months and were successfully treated with metoclopramide tablets. Joint pains were reported in 10 (11.2%) patients during the intensive phase of treatment and these responded to paracetamol tablets. There was no clinical evidence of gout in any of the patients. Twenty (22.5%) of the patients had acne vulgaris mostly on the face and the upper chest throughout the 8 months therapy which is most likely due to the isoniazid. The acne disappeared after the end of the treatment in all the patients.

Discussion

This trial has revealed that pyrazinamide, rifampicin, isoniazid and ethambutol are effective in sterilization of the sputum of the retroviral positive patients in the intensive phase of treatment of PTB without causing serious adverse effects. This is in agreement with the previous trial [8].

Despite using ethambutol and isoniazid (EH) during the continuation phase of therapy there was no bacteriological relapse to warrant the use of retreatment therapy during the follow-up. We are of the opinion that if all the patients remained sputum negative (92% of the patients available) at 12 months of stopping the regimen 2ERHZ/6EH, it could be concluded that the regimen would be effective in the management of PTB in HIV-infected adults in Nigeria. This modified 8 months SCC adopted by the NTLCP/WHO is less expensive compared with that of 2ERHZ/4RH and of comparative efficacy [7]. This makes it an acceptable regimen for economically depressed countries of the third world. In this study a case of Steven-Johnson syndrome was found which is in keeping with the earlier findings that adverse skin reactions may occur even when thiacetazone-free drugs are used [18].

Except the aforementioned case of cutaneous hypersensitivity other serious side effects were not observed and no clinical jaundice was noted. Acne vulgaris which was the commonest side effect disappeared during the follow-up.

In conclusion, in a developing country such as Nigeria where the prevalence of PTB and HIV infection is still high, an effective 4 drug regimen consisting of EHRZ during the intensive phase would achieve rapid sterilization of the smear positive sputum of patients PTB with background retroviral infection. The use of ethambutol and isoniazid for the last 6 months reduced the overall cost of treatment without loss of acceptable level of efficacy.

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