Effects of Ivermectin with and without Doxycycline on Clinical Symptoms of Onchocerciasis

Hannan Masud,1 Tausif Qadir Qureshi and Meimei Dukley2

ABSTRACT
Objective: To compare and analyze the effects of ivermectin with combined therapy of doxycycline and ivermectin on clinical symptoms of onchocerciasis.
Study Design: Randomized, comparative trial without blinding, a quasi-experimental study.
Place and Duration of Study: Tubmenburg City (Bomy County) of Liberia, from March to December 2005.
Methodology: Two hundred and forty black local patients were included in clinical trial after recording their informed consent. Inclusion criteria was history of exposure to black fly in endemic area, symptoms of generalized and ocular itching, visual impairment associated with pannus and perlimbal pigmentation, punctate/sclerosing keratitis, iridocyclitis, chorioretinitis, optic atrophy, lesions suggestive of onchodermatitis and subcutaneous nodules. Patients suffering from allergic conjunctivitis, history of measles and rubella, pregnant / breast-feeding women and children under 16 years of age were excluded from the study. The patients were randomly placed into two groups. Group I (120 patients) was treated with ivermectin in a single dose of 150 µg/kg orally. Group II (120 patients) was treated with combined therapy of doxycycline 100 mg/day for 6 weeks followed by ivermectin in a single dose of 150 µg/kg orally. Topical steroid-antibiotic combination was given to patients of both groups where indicated. Follow-up was carried out for 6 months. Improvement or progression of clinical features was recorded on each visit. Results were compiled and analysed by SPSS 10.0 using Chi-square test.
Results: Eighty four patients (70%) of group I and 117 (98%) patients of group II responded to treatment, with improvement in onchocerciasis clinical symptoms (p <0.05). Pannus, punctuate keratitis and iridocyclitis healed in all patients, whereas irreversible eye lesions like sclerosing keratitis and optic atrophy did not respond to treatment in either group.
Conclusion: There was a significantly greater relief in patients of group II treated with a combination of doxycycline and ivermectin as compared to those patients who were treated with ivermectin alone.

Ivermectin is the drug of choice in the treatment of onchocerciasis.\textsuperscript{11-14} It has broader spectrum of activity and better tolerability compared with diethylcarbamazine and suramin, which were previously used to treat onchocerciasis.\textsuperscript{11} Diethylcarbamazine quickly eliminates microfilariae from the eye, but it is associated with reactive ocular changes and functional deficit.\textsuperscript{11} Sterility in adult female worms can be achieved by administration of doxycycline for 6 weeks followed by ivermectin, resulting in Wolbachia depletion, interruption of embryogenesis and reduction in microfilarial loads lasting up to 18 months.\textsuperscript{15,16} Use of albendazole has shown only a transient effect on early embryogenesis.\textsuperscript{17,18} Lymphatic filariasis and onchocerciasis-endemic villages are being targeted for mass albendazole/ivermectin therapy.\textsuperscript{13,18} Nodulectomy has been a traditional form of therapy in South America.\textsuperscript{13}

The objective of this study was to compare and analyze the effects of ivermectin with combined therapy of doxycycline and ivermectin on clinical symptoms of onchocerciasis.

**METHODOLOGY**

The study was conducted in Tubmenburg (Bomy County) of Liberia from March to December 2005. Study population included local black patients, attending eye outpatient department of UN Peacekeeping Mission Pakistan Field Hospital in Tubmenburg. Nine hundred and thirty five local black patients were registered in Eye Outpatient Department from January to March 2005. Out of them, 295 patients were diagnosed to be suffering from onchocerciasis. Two hundred and forty patients were included in this clinical trial after recording informed consent. It was a prospective, randomized, comparative trial without blinding, a quasi-experimental study.

Patients with history of exposure to black fly in endemic area, symptoms of generalized and ocular itching, visual impairment associated with pannus/perilimbal pigmentation, punctuate/sclerosing keratitis, iridocyclitis, chorioretinitis and optic atrophy were included in the study. Patients with lesions suggestive of onchodermatitis and subcutaneous nodules were also included. Patients suffering from allergic conjunctivitis, history of measles and rubella, pregnant/breast-feeding women and children under 16 years of age were excluded. Complete work-up was carried out in each patient. Best corrected visual acuity was recorded by illuminated Snellen's visual acuity chart. Slit lamp examination, biomicroscopy and digital photography with 7.1 mega pixel camera was done in all patients. Skin was examined for onchodermatitis and the number and location of nodules was recorded. Skin snips and nodulectomy was carried out in selected cases.

The patients were placed into two groups on random basis. Group I (120 patients) was treated with ivermectin in a single dose of 150 µg/kg orally. Group II (120 patients) was treated with combined therapy of doxycycline 100 mg/day for 6 weeks followed by ivermectin in a single dose of 150 µg/kg orally. Topical steroid-antibiotic combination was given to patients of both groups where indicated. Follow-up was carried out for 6 months. Improvement or progression of clinical features was recorded on each visit. Statistical analysis was performed by SPSS 10.0, using Chi-square test. The level of statistical significance was considered as $p <0.05$.

**RESULTS**

Two hundred and forty patients were included in the study. Mean age of the patients was 34 years. One hundred and fifty seven (65.42%) were males and 83 (34.58%) were females. There was a significantly greater relief in patients of group II treated with a combination of doxycycline and ivermectin as compared to those patients who were treated with ivermectin alone. Eighty four patients (70%) of group I and 117 (98%) patients of group II responded to treatment with improvement in clinical features. Visual improvement was seen in 57 (48%) patients of group II as compared to group I.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure1.png}
\caption{Sclerosing keratitis.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Figure2.png}
\caption{Blind patients with bilateral sclerosing keratitis.}
\end{figure}
to 54 (45%) patients of group I. Improvement in ocular features was also considered to be due to the adjunctive topical steroid/antibiotic treatment. Lesions like pannus, punctuate keratitis and iridocyclitis were completely healed in all patients of both groups. However, irreversible eye lesions like sclerosing keratitis and optic atrophy did not respond to treatment in both groups. Thirty four (28%) patients of group II showed improvement in skin lesions as compared to 22 (18%) patients of group I. Improvement in generalized itching and skin lesions was considered to be due to elimination of skin microfilariae and sterilization of the adult female filariae. Statistical analysis showed p-value of less than 0.05, which was considered significant. Results are summarized in Table I.

### DISCUSSION

Ivermectin is the drug of choice for treatment of onchocerciasis.\(^2,11-13\) It is given in a single dose of 150 µg/kg orally, yearly in Africa and semi-annually in South America.\(^12\) Ivermectin is a compound derived from the bacterium *Streptomyces avermitilis*. It causes a spastic paralysis of microfilariae. Repeated oral doses are required for up to several years, as this drug mainly targets mature microfilariae, and not the adult worms or early embryos.\(^12,13,19\) It depletes skin microfilariae for only a few months that reappear at 20% or more of pre-treatment levels within one year.\(^18\) This microfilariae density seems sufficient for transmission to continue and newly infected people continue to enter the transmission cycle.\(^16\) Ivermectin is contra-indicated in pregnant/breast-feeding women, children, severe liver or renal disease, documented hypersensitivity and in areas of Africa co-endemic for *Onchocerca volvulus* and Loa loa.\(^19-22\)

After studying the transmission cycle of onchocerciasis, it seems extremely difficult to eliminate onchocerciasis in endemic regions.\(^15,16\) River blindness control is complicated by the adult’s worm 10-15 years’ life span.\(^12\) The microfilariae live in the skin for about two years; their numbers are continually refreshed as long as adult females are alive in the body.\(^12\) Adult females remain fertile throughout most of their long lives. Therefore, the disease would not die out naturally for 15 years and the disease elimination attempts must last at least 20 years.\(^12-14\) African Programme for Onchocerciasis Control (APOC) is based on community distribution of one dose of ivermectin annually. It has successfully brought down microfilarial load in local population but it may not stop transmission before it ends in 2010.\(^11-14\)

The other possible strategy for control of onchocerciasis is to block embryogenesis at earlier stages, completely and for long-time. It is based on treatment with doxycycline 100 mg/day for 6 weeks to deplete Wolbachia endosymbionts, block early embryogenesis of microfilariae and produce permanent sterilization in adult female worms, followed by one or two doses of 150 µg/kg of ivermectin orally to target mature microfilariae, thereby completely eliminating microfilariae from the body of the patient.\(^15,16,23\) Antihelmintic drugs like Suramin and Praziquantel cause transient sterility at subcurative doses.

Hoerauf *et al.* proved in Ghana that doxycycline 100 mg/day orally for 6 weeks totally suppressed normal embryonic development of microfilariae during the early phase i.e. the oocyte/morula stages and lead to sterility of adult worms.\(^15\) In this study, immunohistological and PCR-based comparison of onchocercomata showed that none of the treated worms had usual bacterial loads or normal embryogenesis in doxycycline treated group and PCR showed an almost ten fold reduced index. Hoerauf *et al.* conducted another study with doxycycline 100 mg/day for 6 weeks followed by a single dose of ivermectin 150 µg/kg at 2.5 months and 6 months. This study showed that the period of sterility in worms after doxycycline treatment extended for at least 18 months.\(^16\)

Debrah *et al.* conducted an 18 months study in Ghana on 60 patients. Microfilariae reduction appeared to be

### Table I: Comparison of clinical features before and after treatment in group I and II.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Group I</th>
<th></th>
<th>Group II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients before treatment</td>
<td>Number of patients after treatment</td>
<td>Number of patients showing improvement</td>
<td>Number of patients before treatment</td>
</tr>
<tr>
<td>General and ocular itching</td>
<td>120 (100%)</td>
<td>36 (30%)</td>
<td>84 (70%)</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>88 (73%)</td>
<td>34 (28%)</td>
<td>54 (45%)</td>
<td>94 (78%)</td>
</tr>
<tr>
<td>Ocular signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perilimbal pigmentation</td>
<td>113 (94%)</td>
<td>67 (56%)</td>
<td>46 (38%)</td>
<td>117 (98%)</td>
</tr>
<tr>
<td>Pannus</td>
<td>109 (91%)</td>
<td>0 (0%)</td>
<td>109 (91%)</td>
<td>105 (88%)</td>
</tr>
<tr>
<td>Punctate keratitis</td>
<td>37 (31%)</td>
<td>0 (0%)</td>
<td>37 (31%)</td>
<td>53 (44%)</td>
</tr>
<tr>
<td>Sclerosing keratitis</td>
<td>26 (21%)</td>
<td>26 (21%)</td>
<td>0 (0%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Indocyclitis</td>
<td>17 (14%)</td>
<td>0 (0%)</td>
<td>17 (14%)</td>
<td>21 (18%)</td>
</tr>
<tr>
<td>Chorioretinitis</td>
<td>5 (4%)</td>
<td>5 (4%)</td>
<td>0 (0%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>23 (19%)</td>
<td>23 (19%)</td>
<td>0 (0%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Dermal signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>33 (27%)</td>
<td>11 (9%)</td>
<td>22 (18%)</td>
<td>47 (39%)</td>
</tr>
<tr>
<td>Nodules</td>
<td>21 (17%)</td>
<td>21 (17%)</td>
<td>0 (0%)</td>
<td>13 (11%)</td>
</tr>
</tbody>
</table>
greater in those patients who were given doxycycline 200 mg/day for 6 weeks followed by ivermectin 150 µg/kg orally 8 months after the start of doxycycline treatment.24

The study showed that there was a significantly greater relief in patients of group II treated with a combination of doxycycline and ivermectin as compared to those patients who were treated with ivermectin alone, thereby complementing the results of above-mentioned three studies. In this study, group II was given only a single dose of ivermectin 150 µg/kg orally 6 weeks after the start of doxycycline treatment. The duration of study was 9 months only, as the stay was limited to one year under United Nations Mission in Liberia. A significant number of patients remained symptom-free during this period and short-term results in local population were promising. To analyse long-term effects on local population, it would require a follow up for much longer period of time. It is considered that combined therapy would offer treatment and cure for United Nations Peacekeepers as they have transitory stay in endemic area.

Doxycycline is a broad-spectrum, synthetically derived bacteriostatic antibiotic of tetracycline group. It is unsafe in pregnancy and contra-indicated in children less than 8 years of age as it causes permanent discoloration of teeth. Both ivermectin and doxycycline are contra-indicated in pregnancy, breast-feeding women, children less than 8 years of age, patients with liver/renal disease and documented hypersensitivity. More than half of the population consist of these women and children who cannot receive treatment in the field clinics and APOC. They do not have protective clothing and insect repellents and they have to work along the river banks for their day-to-day living. They are the reservoir of infection in the endemic area that needs to be treated to control transmission cycle of the disease. There is a need to develop new safe drugs to treat this part of the population.

So far, vaccine and effective chemoprophylaxis are not available for this disease. There is no antihelmintic drug that kills adult *Onchocerca volvulus* and no prophylactic drug is effective against the infectious larvae.19,20 Protective measures include avoidance of black fly habitats and personal protection with appropriate clothing and insect repellents. Those who visit or live in endemic regions for more than 3 months are at greater risk of acquiring this disease. As military troops from Asian countries are being deployed as a part of United Nations Peacekeepers in endemic African countries, there is a possibility that some of them might have acquired this disease.25 Travellers and United Nations troops are advised to consult an ophthalmologist, dermatologist or specialist in tropical medicine when they leave endemic area. For ophthalmologists, it is essential to recognize the clinical features of this filarial disease at an early stage to avert permanent blindness. The prognosis is good, if treated, before irreversible eye lesions develop.

**CONCLUSION**

There was a significantly greater relief in patients treated with a combination of doxycycline and ivermectin, with marked improvement in onchocerciasis clinical symptoms, as compared to those patients who were treated with ivermectin alone. Ivermectin should be given twice a year to the whole population in Liberia to control transmission of onchocerciasis and combined therapy should be considered as an option in a National Onchocerciasis Programme.

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**REFERENCES**


