Frequency and clinical significance of localized adverse events following mass drug administration for lymphatic filariasis in an endemic area in South India

Vijesh Sreedhar Kuttiatt  
ICMR-Vector Control Research Centre

Roopali K Somani  
ICMR-Vector Control Research Centre

Subramanian Swaminathan  
ICMR-Vector Control Research Centre

Kaliannagounder Krishnamoorthy  
ICMR-Vector Control Research Centre

Gary J Weil  
Washington University School of Medicine in St. Louis

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

Recommended Citation
Kuttiatt, Vijesh Sreedhar; Somani, Roopali K; Swaminathan, Subramanian; Krishnamoorthy, Kaliannagounder; Weil, Gary J; and Purushothaman, Jambulingam, "Frequency and clinical significance of localized adverse events following mass drug administration for lymphatic filariasis in an endemic area in South India." The American Journal of Tropical Medicine and Hygiene. 102, 1. 96 - 99. (2020).  
https://digitalcommons.wustl.edu/open_access_pubs/8730

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.
Frequency and Clinical Significance of Localized Adverse Events following Mass Drug Administration for Lymphatic Filariasis in an Endemic Area in South India

Vijesh Sreedhar Kuttiatt,¹* Roopali K. Somani,¹ Subramanian Swaminathan,¹ Kaliannagounder Krishnamoorthy,¹ Gary J. Weil,² and Jambulingam Purushothaman¹

¹ICMR-Vector Control Research Centre, Puducherry, India; ²Division of Infectious Diseases, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri

Abstract. Fear of adverse events (AEs) negatively affects compliance to mass drug administration (MDA) for lymphatic filariasis (LF) elimination program. Systemic AEs are believed to occur because of killing of microfilariae, whereas localized soft tissue reactions might be due to the death of adult worms following therapy. Most AEs are mild and self-limited. However, localized AEs are sometimes more significant and of concern to participants. Here, we describe localized AEs that were noted during a large community study that evaluated the safety of a triple-drug regimen (ivermectin, diethylcarbamazine, and albendazole) for the treatment of LF in India. We have also discussed the importance of timely detection and careful management of AEs for preserving community confidence in MDA.

The WHO has adopted annual mass drug administration (MDA) with single-dose diethylcarbamazine (DEC) and albendazole as the principal strategy for lymphatic filariasis (LF) elimination program in areas where onchocerciasis is not coendemic.¹ Yearly MDA for 5 years with 65% compliance is recommended for successful elimination. Fear of adverse events (AEs) and rumors about such events can significantly decrease MDA compliance and efficacy.² Recently, a triple-drug regimen (ivermectin plus DEC and albendazole, IDA) has been reported to be more effective than DEC plus albendazole (DA) for clearing microfilariae (Mf).³,⁴ We conducted a study in an LF-endemic area in South India to evaluate the safety, efficacy, and effectiveness of IDA and DA when these medications were provided as MDA in communities.⁵,⁶ Here, we describe a series of localized AEs that occurred during this study and discuss their significance.

An open-label, block-controlled, randomized study was carried out in six villages in Yadgir district, Karnataka, India, as part of a five-country multicenter study. Details regarding that study have been recently published.⁶ The study villages were endemic for bancroftian filariasis. Although the area had received MDA for 13 years, compliance had been suboptimal. Enrolled participants were tested with Alere™ Filariasis Test Strip (FTS) for filarial antigenemia. Persons with positive antigen tests had right blood testing for Mf (60-μL-thick smear). Participants were administered (irrespective of infection status) either DA or IDA according to their village of residence. Participants were actively assessed for AEs by medical teams for 2 days, and passive follow-up was continued for another 5 days. Follow-up studies to assess the efficacy of these treatments in infected individuals and the impact of MDA on LF prevalence in the study villages will be reported separately. The study was approved by the Institute Human Ethics Committee of the ICMR-Vector Control Research Centre in Puducherry, India, and the trial was registered with the Clinical Trial Registry India-CTRI/2016/10/007399.⁵

Baseline antigenemia and Mf prevalence in the study area were 25.3% and 6.3%, respectively. A total of 9,060 participants were evaluated in their homes by medical teams during active follow-up on day 1 and 2 after treatment. The overall AE rate in the 7 days post-treatment was 7.1%, and the vast majority of these AEs were mild systemic events, such as headache, fever, and myalgia.⁶ Eight participants (0.08%) experienced localized AEs in the week following treatment.

CASE DESCRIPTIONS

Transient lymphedema. A 13-year-old girl (FTS positive, Mf negative) developed swelling and pain in her left inguinal region 4 days after treatment with DA. Two days later, she noticed swelling of her left ankle and the dorsal aspect of her left foot, and pitting edema was present (Figure 1). Tender left-sided inguinal lymphadenopathy was still present at that time. There was no history of trauma. She had no redness or pain over the leg and no other symptoms. She was reassured, advised to elevate her left leg at night, and instructed on exercises to improve lymphatic drainage. The child was also treated with diclofenac/ranitidine for 1 week. She was observed by our medical team periodically at home, and her

* Address correspondence to Vijesh Sreedhar Kuttiatt, ICMR-Vector Control Research Centre, Medical Complex, Indira Nagar, Puducherry 605006, India. E-mail: vijeshvrc.icmr@gmail.com or vijeshsreedhar@gmail.com

FIGURE 1. A 13-year-old girl developed edema of her left ankle and the dorsum of her left foot approximately 1 week after treatment with diethylcarbamazine plus albendazole. This figure appears in color at www.ajtmh.org.
family members were reassured. Her lymphadenitis subsided after one additional week and her edema resolved fully after 1 month (Figure 2). The girl was revaluated 1 year later. Her leg and inguinal area were normal; her filarial antigen test remained positive, but her Mf test was negative. She was retreated with IDA at that time and followed up for 1 month. No AEs were observed.

**Scrotal swelling.** Details for participants who developed testicular swelling are provided in Table 1.

**Skin nodules/subcutaneous swellings.** Case 1. A 25-year-old woman noticed a small nodule in the right arm above the elbow 7 days after DA treatment. Her FTS test was positive but her Mf test was negative. Swelling was nonprogressive but painful. She reported her problem to the field medical team 12 days after treatment. Two nodules measuring 1 cm in diameter were present on the outer aspect of the right arm. There was no axillary lymphadenopathy. She did not have other AEs. She was treated with diclofenac/ranitidine for 1 week. Swelling resolved after 2 weeks. One year later, her arm was normal; she was still FTS positive and Mf negative.

Case 2. A 30-year-old woman developed fever, nausea, vomiting, and abdominal pain the day after IDA treatment. Her FTS test was strongly positive, and she had 36 Mf per 60 μL. She had a tender subcutaneous nodule on the left arm, 2 cm below the deltoid tuberosity. She was treated with paracetamol, diclofenac, ranitidine, and ondansetron. She became afebrile the next day and vomiting also subsided. Diclofenac and ranitidine were continued for another 5 days. She was followed up by a medical team at her home regularly, and swelling disappeared after 2 weeks. She refused testing and re-treatment when she was visited 1 year later.

Case 3. A 14-year-old girl developed fever the night after IDA treatment. Her FTS test was strongly positive and she had 4 Mf per 60 μL. She noted tender swelling over her right forearm 2 days later. There was no lymphadenitis. She was treated with paracetamol, diclofenac, and ranitidine. Pain and fever resolved after 3 days. Diclofenac and ranitidine were continued for another 3 days. The swelling resolved over a period of 1 week. One year later, her FTS result was still positive but her Mf test was negative.

**Lymphadenitis.** Case 1. A 35-year-old woman developed pain and swelling in her left axilla with a tender 1-cm palpable lymph node 2 days after treatment with IDA. Her FTS test was positive, but her Mf test was negative. On day 4 after treatment, she noted tenderness and 3- by 2-cm area of induration over the medial aspect of her left forearm, 3 cm below the elbow. She was reassured and treated with diclofenac and ranitidine for 1 week, and both the swellings resolved. Her arm was normal and her FTS test was negative 1 year after IDA treatment.

Case 2. Inguinal lymphadenitis was present in the girl with leg edema, as aforementioned.

**DISCUSSION**

Systemic reactions (fever/headache/myalgia) and localized reactions (skin nodules/breast and scrotal swellings) have been reported following the treatment of filariasis with DEC or with other drugs.\(^7\)–\(^11\) Systemic AEs are believed to be caused by host responses to dying Mf and localized reactions, by host responses to dead/dying adult filarial worms.\(^7,12\)

Limb swelling following MDA similar to our case has been reported previously.\(^8\)–\(^10\) However, clinical details, treatment provided, and long-term outcome were not reported. Two

### Table 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Drug regimen</td>
<td>Double-drug therapy (DA)</td>
<td>Triple-drug therapy (IDA)</td>
<td>Triple-drug therapy (IDA)</td>
</tr>
<tr>
<td>FTS test</td>
<td>Strong positive</td>
<td>Strong positive</td>
<td>Strong positive</td>
</tr>
<tr>
<td>Mf test</td>
<td>4 per 60 μL</td>
<td>1 per 60 μL</td>
<td>7 per 60 μL</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Pain and swelling of the right testicle on day 2 after treatment. Participant was anxious and stressed</td>
<td>Pain and swelling of the right testicle 5 days after treatment</td>
<td>Fever, headache, body ache, pain, and swelling of the right testicle on day 2 after treatment</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>7</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Treatment</td>
<td>Reassurance and treatment with diclofenac and ranitidine</td>
<td>Reassurance and treatment with diclofenac and ranitidine</td>
<td>Reassurance and treatment with paracetamol, diclofenac, and ranitidine</td>
</tr>
<tr>
<td>Follow-up after 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTS test</td>
<td>Strong positive</td>
<td>Strong positive</td>
<td>Strong positive</td>
</tr>
<tr>
<td>Mf test</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

FTS = Filariasis Test Strips; Mf = microfilaria.
studies documented reversal of lymphatic pathology follow-
ing single-dose treatment with DEC plus albendazole in chil-
dren infected with filarial worms.13,14 None of the participants in those studies developed new onset lymphoedema or soft tissue reactions. Scrotal pain and swelling are well recognized but uncommon AEs following LF treatment. This appears to be es-
cially common after prolonged treatment with high doses of albendazole.15,16 Prior studies/reviews have also docu-
mented the occurrence of post-treatment subcutaneous
nODULES and lymphangiitis.12,17

Managing AEs in village communities poses unique chal-
 lenges. People often consider AEs to be the direct effect of
drugs, and it can be difficult to convince them that the AEs
result from death of filarial worms. Rumors can quickly spread
decrease compliance with MDA. Community trust was a
challenge for our study, as the region had already received
MDA for many years with poor compliance and villagers had
many misconceptions. Relatives of participants who experi-
enced AEs reacted harshly, and sometimes their neighbors
refused to participate. Often, illiterate villagers abused the
staff and threatened violence. There is no shortcut for estab-
lishing trust in a community. However, our close cooperation
with local health officials/village leaders and careful manage-
ment of AEs improved the situation over time.

Community preparation with various IEC (information/
education/communication) activities by our dedicated med-
ical social workers and formation of community advisory
boards comprising local leaders/village representatives/
health staff to oversee study activities were helpful in gaining
community trust. We provided a highly visible and well-
equipped rapid response medical team with a hotline mobile
telephone to respond to AE reports. Study staff were
acquainted with the local culture, and care was taken to avoid
panic and not to overreact to adversity. We preferred to
manage AEs in participants’ home whenever possible rather
than moving them to the local health center/hospital. Imme-
diate management of AEs, good counseling, repeated home
visits by our staff, and engagement of community leaders
were crucial for ensuring participants’ confidence. Frequent
and appropriate briefing of mass media (including social me-
dia) can help to curtail the spread of rumors regarding AEs.

The WHO has published guidelines addressing practical
aspects of prevention/detection/management of serious AEs
that occur following preventive chemotherapy programs (in-
cluding MDA).18 Tanzania has adopted a modified version of
these guidelines according to conditions specific to their
country.19 As India is considering the use of IDA for LF elimi-
nation in specific situations, this is the right time for develop-

ing a preventive chemotherapy safety surveillance component
in the program that will improve compliance and prevent mis-
conceptions regarding MDA.

Received July 18, 2019. Accepted for publication August 20, 2019.
Published online November 25, 2019.

Acknowledgments: We thank the Indian Council of Medical Research
(ICMR) for supporting this study. We thank the project staff involved in
participant enrollment, testing, and clinical care of the patients. We
gratefully acknowledge the support of the National Vector Borne
Disease Control Program (NVBDCP) in Delhi and in Karnataka state for
this study. We thank the district VBDCP officer Suryaprakash M for his
support in carrying out this work. We express our immense gratitude
to village/community leaders Sharanappa, Parvath Reddy, Gopal
Reddy, Sabanna, and Santosh for their enthusiasm in IEC activities
in their respective villages. We also gratefully acknowledge the co-
operation by primary health center (PHC) medical officers, other PHC
staff, anganwadi teachers, and ASHA (Accredited Social Health Ac-
vitist) workers.

Financial support: This study was part of a multicentric study of the
DOLF (Death to Onchocerciasis and Lymphatic Filariasis) project for
evaluation of the safety of IDA for treatment of LF that was supported by
grant OPP190749 from the Bill & Melinda Gates Foundation to Wash-
ington University in St. Louis, MO. We also acknowledge funding by the
Neglected Tropical Diseases Support Center, The Task Force for Global
Health, Decatur, GA. The funders had no role in the planning or perfor-
ance of this study, writing, or the decision to publish this paper.

Authors’ addresses: Vijeesh Sreedhar Kuttiatt, Roopali K. Somani,
Subramanian Swaminathan, Kallianagounder Krishnamoorthy, and
Jambulingam Purushothaman, ICMR-Vector Control Research Centre,
Medical Complex, Indira Nagar, Puducherry, India, E-mails: somani.,
roopali@yahoo.com, ssu bra@yahoo.com, drkgkmurthy@gmail.com,
and pcsaj@gmail.com. Gary J. Weil, Division of Infectious Diseases,
Department of Internal Medicine, Washington University School of
Medicine, St. Louis, MO, E-mail: gary.j.w eil @wustl.edu.

REFERENCES


3. Thomsen EK et al., 2016. Efficacy, safety, and pharmacokinetics of coadministered diethylcarbamazine, albendazole, and iver-


5. CTRI/2016/10/007399. Triple drug study for filariasis elimination. A community based study to compare the safety, efficacy and acceptability of a triple drug regimen (ivermectin, diethyl-
carbamazine and albendazole) with a two drug regimen (di-
ethylcarbamazine and albendazole) for lymphatic filariasis elimination program. Available at: http://ctrin ic.in/clinicaltrials/
ptmain /2.php?trialid=15852&EnChid=&userId=triple%20drug%20community%20study%20for%20filariasis.


8. WHO. 2003. Report on active surveillance for adverse events following the use of drug co-administrations in the global pro-


10. Lima AW, Medeiros Z, Santos ZC, Costa GM, Braga C, 2012. Adverse reactions following mass drug administration with di-


13. Shenoy RK, Suma TK, Kumaraswami V, Rahmah N, Dhananjayan
G, Padma S, 2009. Antifilarial drugs, in the doses employed in mass drug administrations by the global programme to


