Long-Term Albendazole Effectiveness for Hepatic Cystic Echinococcosis

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Abstract. Little is known about the long-term effectiveness of albendazole in the medical therapy of non-complicated hepatic cystic echinococcosis (HCE) in resource-constrained settings. We performed a retrospective review of patients starting albendazole for HCE in Lima, Peru from January 1997 to December 2007. Patients successfully recontacted underwent chart abstraction and clinical and ultrasonographic reevaluation. Descriptive statistics were used to delineate patient characteristics and treatment effectiveness at the conclusion of albendazole and after reevaluation. Patients ($N = 27$) were primarily female, mean age was 51. Initial treatment success at albendazole conclusion was 26% ($N = 7$) per patient and 37.5% ($N = 24$) per cyst. After 3.8 ± 2.5 years, albendazole success was 34% ($N = 9$) per patient and 40% ($N = 24$) per cyst. We found a gap in the effectiveness of albendazole HCE therapy compared with the efficacy reported in clinical trials. This underscores the need for further investigation into alternate therapeutic strategies for this neglected disease.

INTRODUCTION

Cystic echinococcosis (CE) is a zoonotic parasitosis caused by the larval stage (metacestode) of *Echinococcus granulosus*. It involves a definitive host (dog) and an intermediate herbivorous animal (sheep, cattle) and may accidentally infect humans through fecal-oral contact leading to slowly growing hepatic (70%) and/or pulmonary (20%) cystic lesions. These cystic lesions may be complicated by bacterial superinfection, cyst rupture, and anaphylactic shock.¹ Despite a global burden calculated at over 1 million disability-adjusted life years, funding and research into CE remains limited and it is considered a neglected disease.² In Peru, where there are no national control programs, CE prevalence has been reported to be up to 9.1% in certain rural areas with an annual cost estimated to be 1.5 million dollars mainly burdening impoverished populations of the Andean highlands.^{3,4}

The past three decades have seen an expansion of the therapeutic options available for hepatic cystic echinococcosis (HCE) beyond the former mainstay of surgical intervention. Increasing experience with other treatment modalities including laparoscopy, PAIR (Punction, Aspiration, Injection of scolical agent, and Reaspiration), and oral antiparasitic therapy, are now alternatives to open surgery in selected cases.^{5,6} Albendazole is currently recommended for the medical management of selected HCE in patients including those with inoperable cysts, multiple cysts in ≥ 2 organs, small cysts, peritoneal cysts, after prior non-curative surgical resection/recurrence, and for the prevention of CE dissemination after spontaneous rupture or cyst aspiration.^{7–9}

The vast majority of studies assessing the efficacy of albendazole in HCE were performed in Europe and Asia,¹⁰ and little is known about the effectiveness of albendazole, particularly in Latin America where the correct use of this therapeutic modality is challenging because of limited resources.¹¹ This study sought to ascertain the rates and factors associated with the success of albendazole in the treatment of non-

complicated HCE, and to establish the frequency of long-term worsening and recurrence of disease after treatment completion in Peru.

METHODS

The Instituto de Medicina Tropical Daniel A. Carrion (IMT-DAC) is located in the Universidad Nacional Mayor de San Marcos (UNMSM), Lima, Peru and is a subspecialty referral center with outpatient clinics providing care for individuals with HCE and other tropical diseases. Detailed socio-demographic, clinical, and laboratory information on patients receiving HCE care is captured and stored at the IMT-DAC. Patients receiving standard medical therapy for HCE between 1997 and 2007 were considered for inclusion. Standard medical therapy for HCE is albendazole at 10–15 mg/kg/day orally given in cycles of 28 days interrupted by a 15-day period with monthly clinical and ultrasonographic follow-up while on albendazole and every 6–12 months thereafter. The length of therapy (usually ≥ 3 cycles) is a consequence of patient and cystic response; adverse reactions, medication, and clinic visit compliance. Informed consent was obtained from all participants. The Ethics Committee of the UNMSM and the University of Alabama at Birmingham Institutional Review Board approved this study protocol.

Study design. After retrospective chart review, attempts were made to contact all patients who had received albendazole as HCE therapy at the IMT-DAC between January 1997 and December 2007. Eligible patients had to have the following: 1) ultrasonographic evidence of HCE meeting criteria for medical management with albendazole, (active or transitional liver cysts = World Health Organization [WHO] classification CE1, CE2, CE3),¹² and either a positive serologic test or epidemiologic exposure (past residence in endemic area, dog ownership); and 2) been contacted successfully at ≥ 1 year after completion of albendazole therapy and completed follow-up ultrasonographic evaluation.

Attempts (phone and home visit if recorded address in Lima) to contact all subjects with HCE were made during 2008. Individuals in whom successful contact was made and informed consent was obtained; detailed socio-demographic and clinical data was abstracted by a team of four reviewers

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(J.A., D.C., Y.A.V., and L.T.) during the period of albendazole therapy (Treatment phase). Any discrepancies in chart abstraction were resolved by a team of two clinical providers (J.L.S. and H.V.G.). Patients meeting study inclusion criteria were then scheduled for follow-up ultrasound (Reevaluation phase), where they underwent a cross-sectional evaluation of HCE status after albendazole therapy (a new clinical assessment, abdominal ultrasound, plain posterior-anterior chest radiography, and enzyme-linked immunotransfer blot [EITB]).

Patients with initial ultrasonographic evidence of inactive cysts (WHO CE4, CE5); pulmonary involvement (determined by chest x-ray); or unavailable baseline clinical data were excluded from the study.

Study variables. Independent variables included: age, sex, history of residence in an endemic area, dog ownership, clinical signs and symptoms, serology for HCE (EITB: positive, negative, absent), cyst size (major diameter in cm), ultrasonographic WHO classification (active cysts: CE1, CE2; transitional cysts: CE3),¹² number of cysts per patient, and individual cyst location (left or right hepatic lobe). Treatment characteristics considered were number of treatment cycles, adverse reactions, post-treatment length of follow-up, and compliance to follow-up (average of ≥ 1 clinical visit/year).

Dependent variables included: treatment effectiveness defined as resolution versus non-resolution on ultrasound evaluation at the conclusion of initial albendazole therapy (Treatment phase) at both per patient and per cyst levels was completed. Repeat abdominal ultrasonographic after recontacting was performed and determination of long-term resolution was completed (per patient and per cyst). Criteria to determine albendazole effectiveness were constructed from the available literature and existing WHO ultrasonographic classification of cyst status.^{7,12,13} According to our classification, individual cysts and patients were classified as achieving success (cure or marked improvement) or no success (mild improvement, no change, worsening and/or recurrence), wherein cure was defined as disappearance of the cyst(s) in follow-up ultrasonography and marked improvement was defined as either cyst size reduction of $\geq 25\%$ and/or transition to inactive phase (CE4, CE5), further details are outlined in Table 1. For cyst level analyses, two observers determined suitability for longitudinal analysis based on cysts having distinctive anatomical localization within the liver. Cysts without distinctive localization were excluded from cyst level analyses.

Statistical analysis. Descriptive statistics were used to evaluate overall patient, cyst, and treatment characteristics and

to ensure distributional assumptions for statistical tests were met. The χ^2 and Fisher's exact test were used to compare patient and treatment characteristics between the successful and unsuccessful treatment groups (patient and cyst level outcomes) at the conclusion of initial therapy (2–6 cycles) or Treatment phase. These analyses were not performed at the time of Reevaluation (2008), because the variability from time of initial treatment to time of reevaluation was different in each individual; this lack of uniformity precluded the construction of comparison groups. All analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL).

RESULTS

From 1997 to 2007, 41 cases of HCE were treated with albendazole at the IMT-DAC. Among them, five lacked baseline data and were excluded. The remaining 36 patients met inclusion criteria and were selected for subsequent contact. Of these in calendar year 2008, we were unable to contact six patients, two refused participation, and one had previously expired (not caused by HCE). In total, 27 patients underwent retrospective chart review and reevaluation.

Treatment phase. Pretreatment characteristics.

1. Demographics: Among the 27 patients included in the Treatment and Reevaluation phases of the study, the majority was female (74%, $N = 20$), with a mean age at diagnosis of 51 ± 14 years. The most common preceding epidemiologic exposures were dog (85%, $N = 23$) or livestock (30%, $N = 8$) ownership and having lived in a known endemic area (78%, $N = 21$). A total of six patients (22%) reported prior treatment (prior albendazole $N = 2$, prior surgical therapy $N = 2$, prior albendazole and surgery $N = 1$) (Table 2).
2. Clinical features: The majority of patients reported clinical manifestations at the time of initial diagnosis ($N = 21$). The most commonly reported manifestations were: abdominal pain (56%, $N = 15$), hepatomegaly (15%, $N = 4$), pruritus (11%, $N = 3$), "abdominal heaviness" (11%, $N = 3$), and fever (4%, $N = 1$). Eosinophilia was found in 22% ($N = 6$) of subjects. Lung involvement was ruled out by chest radiography in all patients.
3. Baseline ultrasonographic findings: Among detected cysts ($N = 97$), a total of 64 were suitable for subsequent analysis as described in the Methods ($N = 57$ active or CE1, CE2; $N = 7$ transitional or CE3 all with distinctive ultrasonographic localization permitting follow-up) (Table 2). Median cyst burden was 2 (interquartile range [IQR] 1–4).

TABLE 1
Definition of treatment effectiveness

Effectiveness		Per cyst	Per patient
Success*	Cure	Cyst disappeared after treatment	Complete disappearance of all cysts
	Marked improvement	Reduction of cyst size $\geq 25\%$ and/or transition to inactive phase (CE4, CE5)	Size reduction $\geq 25\%$ or degenerative changes in all cysts
No success	Mild improvement	Cyst size reduction $< 25\%$ or partial consolidation	Size reduction $\geq 25\%$ in some, not all cysts
	No change	Cyst size variation $< 10\%$, with no change in echogenic structure	Variation of $< 10\%$ and no change in echogenic structure of all cysts
	Worsening	Continued growth of cyst	Continued growth of all cysts
	Recurrence	Reappearance of a cyst in the location of a previously cured cyst	

* Success was a composite of cure and marked improvement at the patient and cyst levels.

TABLE 2

Association between independent variables and study-defined success at the end of the treatment phase among 27 patients who received albendazole therapy for HCE at The Tropical Medicine Institute: Daniel A. Carrion 1997–2007*

Variables	Per cyst (N = 64)			Per patient (N = 27)		
	Success† N = 24 (%)	No success‡ N = 40 (%)	P value	Success† N = 7 (%)	No success‡ N = 20 (%)	P value
Sex						
Male	10 (41.7)	11 (27.5)	0.24	1 (14.3)	6 (30)	0.63
Female	14 (58.3)	29 (72.5)		6 (85.7)	14 (70)	
Age§						
< 50	5 (20.8)	10 (25)	0.70	4 (57.3)	7 (35)	0.39
> 50	19 (79.2)	30 (75.2)		3 (42.9)	13 (65)	
Dog ownership						
Yes	20 (83.3)	31 (77.5)	0.75	5 (71.4)	18 (90)	0.27
No	4 (16.7)	9 (22.5)		2 (28.6)	2 (10)	
Residence in endemic area						
Yes	21 (87.5)	39 (92.5)	0.66	6 (85.7)	15 (75)	1.0
No	3 (12.5)	3 (7.5)		1 (14.3)	5 (25)	
Number of cysts per patient						
< 3	7 (29.2)	10 (25)	0.72	6 (85.7)	9 (45)	0.09
3 or more	17 (70.8)	32 (75)		1 (14.3)	11 (55)	
EITB (initial)						
Positive	16 (72.7)	20 (51.3)	0.10	5 (83.3)	11 (57.9)	0.36
Negative	6 (27.3)	19 (48.7)		1 (16.7)	8 (42.1)	
Previous treatment						
Yes	3 (12.5)	8 (20)	0.51	0 (0)	6 (30)	0.15
No	21 (87.5)	32 (80)		7 (100)	14 (70)	
Length of treatment¶						
< 3 cycles	2 (8.3)	0 (0)	0.14	1 (14.3)	1 (5)	0.46
3 or more cycles	22 (91.7)	40 (100)		6 (85.7)	19 (95)	
Compliance to follow-up						
Yes	19 (79.2)	26 (65)	0.23	5 (71.4)	12 (60)	0.68
No	5 (20.8)	14 (35)		2 (28.6)	8 (40)	
Adverse reactions						
Yes	7 (29.2)	28 (70)	< 0.01	1 (14.3)	12 (60)	0.07
No	17 (70.8)	12 (30)		6 (85.7)	8 (40)	
Cyst size						
< 5 cm	18 (75)	28 (70)	0.66	NA	NA	NA
5 cm or more	6 (25)	12 (30)				
Cyst activity						
Active (CE1, CE2)	21 (87.5)	36 (90)	1.0	NA	NA	NA
Transitional (CE3)	3 (12.5)	4 (10)				
Cyst location						
Left lobe	8 (33.3)	19 (47.5)	0.26	NA	NA	NA
Right lobe	16 (66.7)	21 (52.5)				

*HCE = hepatic cystic echinococcosis; EITB = enzyme-linked immunotransfer blot; NA = not available.

†The Success group includes patients with cure and marked improvement as detailed in Table 1.

‡“No success” includes those with mild improvement, no change, worsening, or recurrence as detailed in Table 1.

§Mean age at diagnosis was 51 ± 14 years; median age was 54 years (interquartile range [IQR]: 42–62).

¶Length of therapy was based on the number of albendazole cycles per patient: (1 cycle = 2 patients; 3 cycles = 19 patients; 4 cycles = 4 patients; and 6 cycles = 2 patients).

Treatment characteristics. Patients underwent a mean of 3 ± 1 cycles of albendazole. Nearly half reported side effects to albendazole therapy (48%, $N = 13$). The most commonly reported side effects were liver enzyme elevation (15%, $N = 4$), vertigo (11%, $N = 3$), and abdominal pain (7%, $N = 2$). No cystopenias or alopecia was documented.

Effectiveness at the end of albendazole treatment phase.

1. Per patient: Among patients evaluated at the end of treatment ($N = 27$), none achieved ultrasonographic cure (complete resolution of all cysts) and 44.5% ($N = 12$) exhibited mild improvement. Treatment success (cure and marked improvement) was seen in 26% ($N = 7$) on repeat ultrasound. A total of 22% ($N = 6$) had no change and 7.5% ($N = 2$) had worsened (Table 2).
2. Per cyst: A total of 64 cysts localized at baseline were included in cyst level analyses. At the end of therapy 9.5% ($N = 6$) were cured, 28% ($N = 18$) had experienced marked improvement, 14% ($N = 9$) moderate improvement, 37.5% cysts ($N = 24$) were successfully treated (cure and marked

improvement). A total of 37.5% ($N = 24$) did not change, whereas 11%, ($N = 7$) worsened. Two new cysts were detected (Table 2).

Factors associated with treatment success at the end of treatment. Bivariate comparison of characteristics of those patients achieving and not achieving success at the conclusion of therapy were determined at the patient and individual cyst level. Only those with an absence of adverse reactions to albendazole achieved a statistically significant difference in treatment success per cyst ($P = 0.001$) but not per patient analyses ($P = 0.07$). No other patient, cyst, or treatment level variables were associated with a statistically significant difference in the likelihood of achieving cure (Table 2).

Reevaluation phase. *Treatment effectiveness of albendazole at reevaluation in 2008.* At the time of reevaluation, 3.8 ± 2.5 years after albendazole therapy had transpired and the median number of clinic visits after concluding treatment was 3 (IQR 2–5). Long-term albendazole effectiveness was evaluated by comparing baseline and repeat ultrasounds.

1. Per patient: Reevaluation of the 27 study participants showed: 4% ($N = 1$) were cured, 30% ($N = 8$) had a marked improvement, 18% ($N = 5$) had a mild improvement, 15% ($N = 4$) did not change, and 33% ($N = 9$) worsened. Reevaluation (long-term) success per patient was 34%. No new lung involvement was seen in Reevaluation chest x-rays.
2. Per cyst: At the time of reevaluation, the 64 initially localized cysts showed: 7% ($N = 4$) cure, 33% ($N = 20$) marked improvement, 10% ($N = 6$) moderate improvement, 15% ($N = 9$) no change, 35% ($N = 21$) worsened, $N = 10$ were a new growth, and $N = 1$ cyst recurred after initially documented clearance. Long-term success per cyst was 40%.

DISCUSSION

In our series, success rates improved over time, from end of treatment to reevaluation at the patient (26–34%) and cyst (37.5–40%) levels. These findings confirm that CE is slow to resolve with lesions lasting several years. Existing evidence supporting decision making for the treatment of HCE is scarce and primarily based on case series.^{7,13–15} The initial trials on the efficacy of albendazole were primarily performed outside of Latin America, and to this day a relative lack of effectiveness data persists.¹¹ In previous studies on long-term resolution of hepatic cysts after albendazole therapy both the interval to re-evaluation (1, 3, or more years) and the reported efficacy rates (50–75%) have varied. In this study, the mean time until reevaluation was 3.8 ± 2.5 years and the albendazole per cyst effectiveness was 40%, a value lower than previously reported findings.^{7,16,17} We suspect, several potential factors contribute to this disparity including: methodologic differences (i.e., inclusion criteria, treatment success definitions, and lengths of follow-up), biologic singularities (potentially dissimilar drug kinetics/dynamics in the Peruvian population), and socioeconomic disparities (i.e., potentially leading to barriers for close monitoring evidenced by one-third of patients being unable to maintain adequate follow-up). In addition, efficacy (trial outcomes) versus effectiveness (outcomes in routine clinical settings) gaps have been reported in the treatment of multiple conditions potentially caused by differences in the populations selected and the receipt of care in a clinical trial versus a routine outpatient treatment setting and the current investigation may be indicative of such a gap in albendazole therapy.^{18,19}

Although cyst size (< 6 cm) has been associated with better treatment outcomes in the past,²⁰ this was not the case in our study. This may reflect a sample size issue secondary to our limited number of participants. In a systematic review, treatment failure (expressed as return to cyst activity or relapse) increased over time and was ~40% at 2 years, a trend mirrored in our findings were rates of worsening from end of treatment to reevaluation per patient (from 7% to 33%) and per cyst (from 11% to 35%) increased. Such data may point to a need for longer post-treatment observation periods and further research into HCE medical therapy. Length of albendazole therapy was not associated with treatment success in our study, possibly because of a small number of patients or insufficient therapy duration. It is now accepted that albendazole therapy for < 3 cycles (< 3 months) is associated with suboptimal outcomes; although a widely accepted “standard” duration is not available, most experts recommend albendazole for

3–6 months¹¹ and some authorities propose even longer therapies²¹ (> 6 months), although this approach requires further validation.¹¹

In our series of 27 Peruvian patients, the absence of adverse reactions to albendazole was associated with higher rates of successful initial therapy. Adverse reactions have been associated with non-adherence and discontinuation of therapy and have been found to affect adherence to visits in conditions requiring prolonged therapy.²² Overall decreased cyst exposure to albendazole would have disrupted the continuity of therapy and may have contributed to the lower rates of cure in those with side effects compared with patients with an uneventful treatment course. In regards to serologic testing (EITB), despite consensus on its value in the diagnosis of HCE, no well-defined role in the follow-up of HCE therapy exists.^{23,24} In our study 5 of 6 patients with an initially negative EITB seroconverted after albendazole initiation, becoming negative shortly after treatment completion without correlation with treatment outcomes.

Our findings should be interpreted with respect to the limitations of our study. We report the experience of one center located in the vicinity of an endemic area with a limited sample of patients. Additional limitations include the absence of data regarding compliance to albendazole therapy, and the impossibility of differentiating disease recurrence from reinfection. As in all HCE studies, we were not able to assess the impact of spontaneous decay on treatment success rates. As with all observational studies, we are able to identify associations but could not attribute causality, and unmeasured confounding such as the impact of incomplete adherence to care may have affected our findings. However, our findings are reflective of the realities of ambulatory HCE care in developing countries and contribute to the gap in knowledge regarding albendazole effectiveness for HCE treatment in a routine care setting.

These limitations notwithstanding, our results advance the understanding of HCE in several ways. First, we present the largest series of patients treated with albendazole in Peru adding effectiveness data in the medical treatment of HCE in developing countries empirically treated on the basis of ultrasonographic and epidemiologic criteria for HCE. Our study also shows that regardless of ultrasonographic evidence of progression of liver involvement, subsequent pulmonary involvement is rare in patients meeting criteria for albendazole therapy of HCE.

In conclusion, long-term HCE treatment outcomes and the success rate of albendazole were modest. We found a gap in the effectiveness of albendazole HCE therapy compared with the efficacy reported in clinical trials. This underscores the need for further investigation into alternate therapeutic strategies for this neglected disease.

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