

ORIGINAL ARTICLE

# 알벤다졸 투여가 개회충증으로 인한 호산구성 간농양의 관해에 미치는 영향

장은영, 최문석, 광금연, 고광철, 백승운, 이준혁, 백용한, 유병철

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## Enhanced Resolution of Eosinophilic Liver Abscess Associated with Toxocariasis by Albendazole Treatment

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**Background/Aims:** Visceral larva migrans, caused by *Toxocara canis* and *Toxocara cati*, has emerged as a significant cause of eosinophilic liver abscess (ELA). Differentiation of ELA associated with toxocariasis (ELA-T) from metastasis or primary liver malignancy is sometimes difficult. However, the role of albendazole treatment remains uncertain in this condition. The aim of this study was to evaluate whether albendazole can enhance the radiologic resolution of ELA-T.

**Methods:** We retrospectively reviewed the medical records of the patients diagnosed with ELA-T at our institution between January 2008 and December 2011. ELA-T was diagnosed based on the imaging findings on computed tomography or magnetic resonance imaging and the presence of positive serum IgG antibody for *Toxocara canis*. Among a total of 163 patients, 32 patients received albendazole (albendazole group) and 131 did not (control group). Baseline characteristics and fate of liver nodules were compared between the two groups.

**Results:** Baseline characteristics (age, sex, number and maximal size of lesions, eosinophil count) were similar between the two groups. Median duration for achieving radiologic resolution in the albendazole group was significantly shorter than in the control group (207 days [range 186-228] vs. 302 days [range 224-380],  $p=0.023$ ). In Cox regression analysis of the cumulative rates of radiologic resolution, the hazard ratio for albendazole treatment was 1.99 (95% confidence interval, 1.22-3.23).

**Conclusions:** Radiologic resolution of ELA-T can be accelerated with albendazole treatment. Hence, inconvenience associated with long-term follow-up and unnecessary worries among patients can be eliminated with albendazole treatment. (Korean J Gastroenterol 2015;65:222-228)

**Key Words:** Toxocariasis; Larva migrans, visceral; Liver abscess; Liver diseases, parasitic; Albendazole

## INTRODUCTION

Eosinophilic liver abscess (ELA) is a focal eosinophilic infiltration and necrosis of the liver. It can be caused by para-

sitic infection, allergic diseases, drugs and hypereosinophilic syndrome involving liver. In addition, it might be rarely associated with malignancy, primary biliary cirrhosis, primary sclerosing cholangitis, and eosinophilic gastroenteritis.<sup>1</sup> ELA

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is more common in South Korea than in Western countries, and its characteristic clinical findings have been investigated by many authors.<sup>1-7</sup> In particular, toxocariasis, caused by *Toxocara canis*, has emerged as a significant cause of ELA in Korea.<sup>5,8</sup> Toxocariasis was originally known to be a disease affecting children. However, a habit of eating uncooked cow liver or meat has led to an increase in the prevalence of ELA associated with toxocariasis (ELA-T) among adults of this country.<sup>5-8</sup> Only a few cases of ELA-T have been reported in Western countries.<sup>9-12</sup>

ELA-T is usually asymptomatic.<sup>8</sup> However, abdominal pain, fever, and fatigue can be observed in patients with high disease burden.<sup>8</sup> Peripheral eosinophilia is a common laboratory finding. Due to its high specificity (90-95%) and sensitivity (80%), enzyme-linked immunosorbent assay (ELISA) for specific IgG antibodies against the antigen secreted by larva is widely used for making the serologic diagnosis of toxocariasis.<sup>13</sup>

Several studies have suggested that imaging findings of ELA-T usually consist of small (< 2 cm), multiple, and oval or trapezoid nodules with ill-defined and fuzzy margins.<sup>4,5,8</sup> However, differentiation of ELA-T from metastasis or primary liver malignancy is not always easy in actual clinical practice. Multiple ELA-T lesions can be confused with liver metastasis,<sup>14</sup> especially in patients with malignancy, while single ELA-T lesions can mimic primary liver cancer such as cholangiocarcinoma or hepatocellular carcinoma.<sup>7,15-17</sup> Although percutaneous biopsy or surgery can be performed to confirm the diagnosis of ELA-T in certain circumstances,<sup>14-19</sup> follow-up with or without treatment is another strategy in a considerable number of patients with suspected ELA-T.

A 5-day to 7-day course of albendazole 800 mg/day has

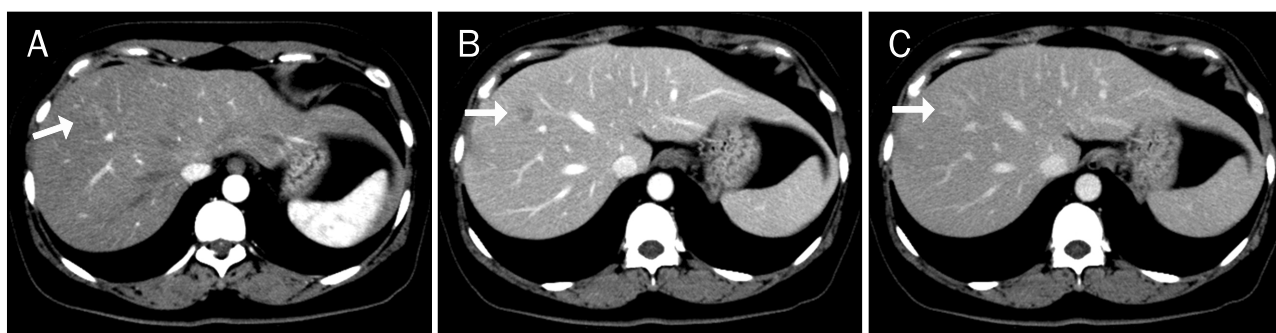
been recommended for toxocariasis in previous studies.<sup>13,20</sup> However, some studies have suggested that medication is not needed for patients without symptoms since toxocariasis is a self-limiting disease.<sup>21,22</sup> If albendazole treatment can promote radiologic resolution in patients with ELA-T, it can relieve unnecessary worries among patients and avoid the inconvenience of prolonged follow-up with imaging studies. However, the role of albendazole treatment remains uncertain in these patients.

Hence, we conducted this study to elucidate whether albendazole treatment can enhance the radiologic resolution of ELA-T lesions in patients.

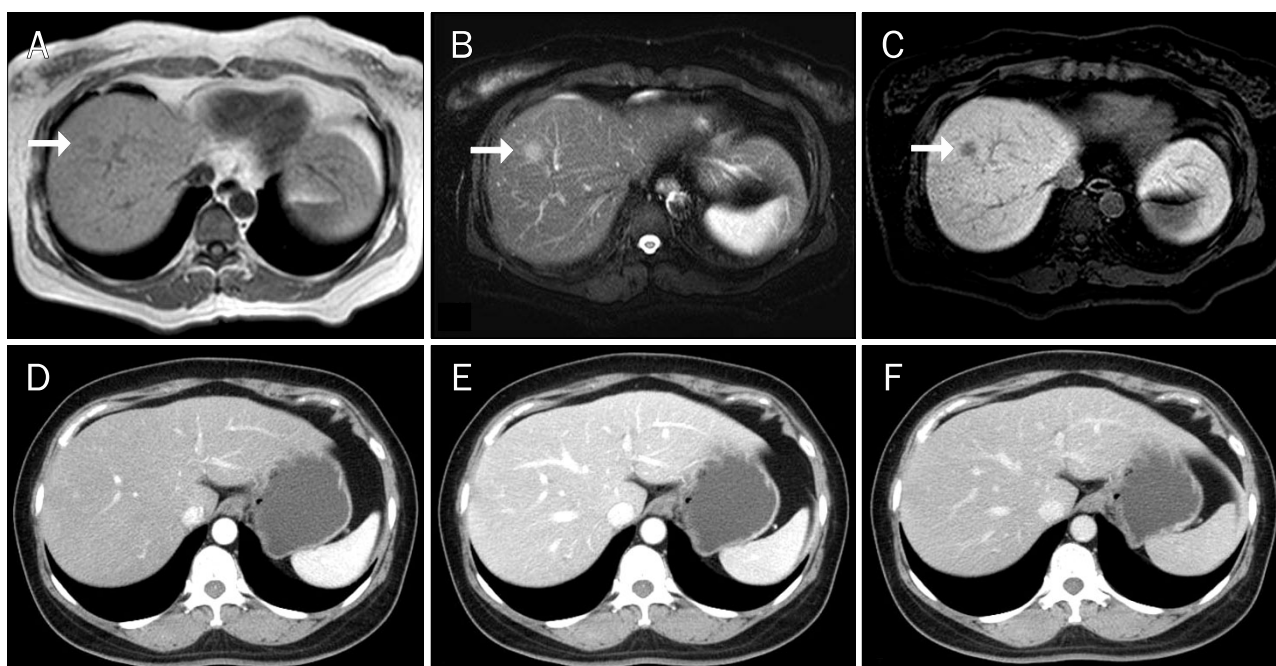
## SUBJECTS AND METHODS

### 1. Patients

We retrospectively reviewed the medical records of patients diagnosed with ELA-T at our hospital between January 2008 and December 2011. This study was approved by the Institutional Review Board of our institution. Diagnosis of ELA-T was based on the characteristic image findings with or without histology, and toxocariasis was diagnosed by the presence of positive serology for *Toxocara canis*. Typical features of ELA on imaging studies consist of oval or trapezoid shaped nodules with ill-defined margins and at least one of the following findings: (1) low-attenuation nodules on CT imaging, which are prominent or solely visible in the portal venous phase (Fig. 1); (2) a faint low-signal intensity on unenhanced T1-weighted images and a faint high-signal intensity on unenhanced T2-weighted images, or a low signal intensity in the portal phase images and isointensity in the arterial and equilibrium phase images of the gadoli-



**Fig. 1.** CT findings in a 51-year-old female patient with an eosinophilic liver abscess. (A) A 1.4-cm nodule (arrow) was poorly delineated in the arterial phase. (B) It presented as an ill-defined low-attenuation nodule (arrow) in the portal phase. (C) It was also invisible (arrow) in the equilibrium phase.

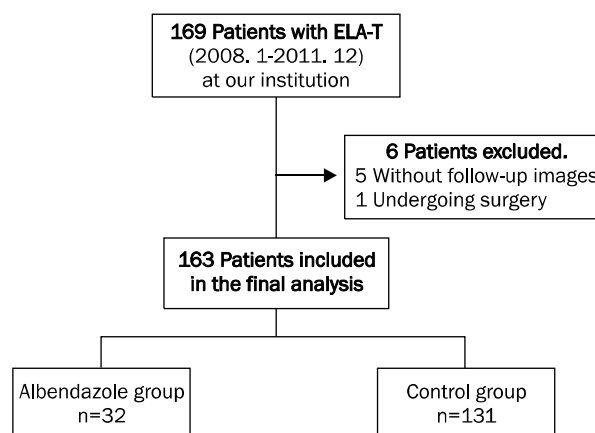


**Fig. 2.** Image findings in a 51-year-old female patient with an eosinophilic liver abscess before (A-C) and after (D-F) albendazole treatment. The gadolinium-enhanced dynamic MR findings showed (A) low-signal intensity on unenhanced T1-weighted images, (B) high-signal intensity on unenhanced T2-weighted images, and (C) low-signal intensity in the portal phase. The previously identified 1.4 cm nodule (arrows) had completely disappeared 1 year after initial diagnosis (D, arterial phase; E, portal phase; F, equilibrium phase).

nium-enhanced dynamic MRI (Fig. 2).<sup>8</sup> Serologic diagnosis was made by positive results using the *Toxocara* ELISA kit (Bordier Affinity Products, Crissier, Switzerland).

A total of 169 patients with ELA-T were initially enrolled. Among them, 5 patients with no follow-up images and one patient who underwent surgery were excluded (Fig. 3). Diagnosis of ELA was based on the characteristic image findings of ELA with histology (n=10) or without (n=153). Serology for toxocariasis was positive in all patients. While 32 patients received albendazole treatment (albendazole group), 131 patients were followed up without medication (control group). Dynamic CT or gadolinium-enhanced dynamic MRI was performed for evaluation of any change of ELA-T lesions at a median interval of 6 months (range 1-12).

Baseline demographic profiles and characteristics of nodules, including age, sex, initial number and maximum size of lesions, symptoms, underlying disease, and lung involvement were compared between the two groups by retrospective review of their medical records. Laboratory findings including eosinophil count, prothrombin time, albumin, total bilirubin, AST, ALT, ALP, and GGT were also evaluated. Radiologic resolution was defined as complete disappearance of lesions on imaging studies (Fig. 2).



**Fig. 3.** The enrolled patients in this study. A total of 169 patients with the eosinophilic liver abscesses with toxocariasis (ELA-T) were initially enrolled. Among them, six patients were excluded, and 163 patients were included in the final analysis. While 32 patients received albendazole treatment (albendazole group), 131 patients were followed up without medication (control group).

## 2. Statistical analyses

Differences in the baseline characteristics of the two groups were evaluated using Mann-Whitney test and Fisher's exact test as indicated. The Kaplan-Meier method was used for assessing the cumulative rates of radiologic resolution and the differences were calculated using the log-rank test.

Cox regression analysis was performed for determining the hazard ratio in the treatment group. If p-value was less than 0.05, the result was considered statistically significant. All statistical analyses were performed using SPSS for Window release ver. 20.0 (IBM Co., Armonk, NY, USA).

## RESULTS

### 1. Baseline characteristics

Baseline demographic profiles and characteristics of the 163 patients were evaluated. The median age of patients was 55 years (range, 28-82 years), and male sex was dominant (76.7%; male to female ratio=3.3). History of eating uncooked cow liver or meat was reported in 136 patients

(83.4%). A single lesion was noted in 57.1% of the patients. The size of the lesions was  $1.58 \pm 0.05$  cm (range, 0.6-5.3 cm), and lesions were smaller than 2 cm in 126 patients (77.3%). Most patients (87.1%) were asymptomatic, whereas 21 patients (12.9%) complained of various symptoms including abdominal pain (n=11), epigastric pain and chest discomfort (n=6) and cough (n=1). Twenty-four patients had chronic hepatitis B (14.7%). Underlying malignancy was reported in 50 patients (30.7%); malignancy of urologic system (n=14), hepatocellular carcinoma (n=13), stomach cancer (n=10), colorectal cancer (n=8), breast cancer (n=3), lung cancer (n=1), and thyroid cancer (n=1). Lung involvement was identified in 23 patients (14.1%). No significant difference in age, sex, history of eating uncooked cow liver or meat,

**Table 1.** Baseline Characteristics of Two Groups

Characteristic	Total (n=163)	Albendazole group (n=32)	Control group (n=131)	p-value
Age (yr)	55.57 $\pm$ 0.72	55.72 $\pm$ 1.53	55.53 $\pm$ 0.81	0.76
Sex				0.06
Male	125 (76.7)	20 (62.5)	105 (80.2)	
Female	38 (23.3)	12 (37.5)	26 (19.8)	
History of raw cover liver or meat	136 (83.4)	26 (81.3)	110 (83.9)	0.79
Lesion				0.69
Single	93 (57.1)	17 (53.1)	76 (58.0)	
Multiple	70 (42.9)	15 (46.9)	55 (42.0)	
Maximum size of lesions (cm)	1.58 $\pm$ 0.05	1.52 $\pm$ 0.10	1.59 $\pm$ 0.06	0.82
Symptom (yes)	21 (12.9)	7 (21.9)	14 (10.7)	0.14
Underlying disease				
Chronic hepatitis B	24 (14.7)	3 (9.4)	21 (16.0)	0.42
Chronic hepatitis C	1 (0.6)	0 (0)	1 (0.8)	1.00
Liver cirrhosis	9 (5.5)	1 (3.1)	8 (6.1)	1.00
Malignancy	50 (30.7)	10 (31.2)	40 (30.5)	1.00
Hepatocellular carcinoma	13 (8.0)	3 (9.4)	10 (7.6)	0.72
Other	37 (22.7)	7 (21.9)	30 (22.9)	1.00
Involvement of lung	23 (14.1)	7 (21.9)	16 (12.2)	0.17

Values are presented as mean $\pm$ SD or n (%).

**Table 2.** Laboratory Findings of Two Groups

Laboratory finding	Total	Albendazole group	Control group	p-value
Eosinophilia	121 (78.6)	24 (80)	97 (78.2)	1.00
Eosinophil count (/ $\mu$ L)	1,080.4 $\pm$ 87.3	1,345.8 $\pm$ 200.4	1,016.2 $\pm$ 96.5	0.07
PT > 1.10 (INR)	11 (8.3)	1 (3.7)	10 (9.4)	0.46
Liver function tests				
Albumin < 3.5 g/dL	2 (1.3)	0 (0.0)	2 (1.6)	1.00
Total bilirubin > 1.5 mg/dL	8 (5.1)	1 (3.1)	7 (5.6)	1.00
AST > 40 IU/L	11 (6.9)	0 (0.0)	11 (8.6)	0.12
ALT > 40 IU/L	22 (13.8)	3 (9.4)	19 (14.8)	0.57
ALP > 128 IU/L	3 (1.9)	1 (3.1)	2 (1.6)	0.49
GGT > 50 IU/L	38 (29.9)	8 (30.8)	30 (29.7)	1.00

Values are presented as n (%) or mean $\pm$ SD.

initial number and maximum size of lesions, symptoms, underlying disease, and lung involvement was noted between the albendazole group and control group (Table 1).

Initial laboratory findings of the 163 patients were examined. The eosinophil count was  $1,080.4 \pm 87.3/\mu\text{L}$  (mean $\pm$ SD) in 154 patients whose initial eosinophil count was available, and 121 patients (78.6%) showed eosinophilia. Elevation of GGT was the most common abnormal finding in liver function tests (29.9%). Presence of eosinophilia, eosinophil count, prothrombin time, albumin, total bilirubin, AST, ALT, ALP, and GGT were similar between the albendazole group and control group (Table 2).

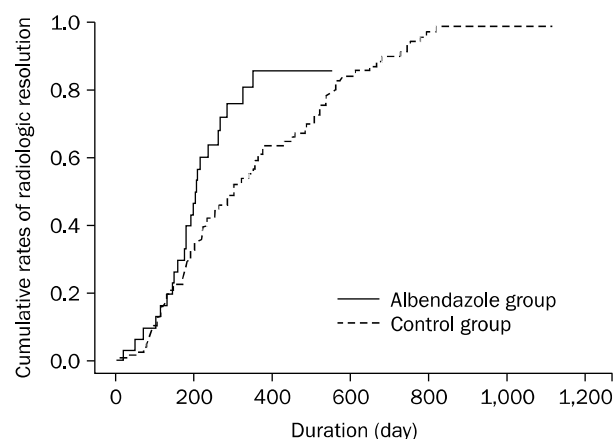
## 2. Clinical outcomes according to albendazole treatment

During the median follow-up period of 6.9 months (range, 1-37.3 months), 115 patients (70.6%) showed radiologic resolution. In Kaplan-Meier analysis, the median duration for achieving radiologic resolution was 207 days (range, 186-228 days) in the albendazole group, which was significantly shorter than 302 days in the control group (range, 224-380 days;  $p=0.023$ ) (Fig. 4). In Cox regression analysis of cumulative rates of radiologic resolution, the hazard ratio for albendazole treatment was 1.99 (95% CI, 1.22-3.23) compared to the control group.

## DISCUSSION

An increasing number of cases with ELA-T are being incidentally detected during routine imaging studies in our country, where people have a habit of eating raw cow liver or meat. While albendazole is recommended for symptomatic toxocariasis, its role remains uncertain in patients with ELA-T. We evaluated whether albendazole can enhance the radiologic resolution of lesions in 163 patients diagnosed with ELA-T. We showed that the median duration for achieving radiologic resolution in the albendazole group was significantly shorter than that in the control group (207 days [range, 186-228 days] vs. 302 days [range, 224-380 days],  $p=0.023$ , hazard ratio for albendazole treatment=1.99 [95% CI, 1.22-3.23]).

Baseline characteristics of the patients and ELA-T lesions in our study were similar to those reported in previous studies. Several authors reported that the median age of patients with ELA-T was between 50-60 years with male sex pre-



**Fig. 4.** Cumulative rates of radiologic resolution by Kaplan-Meier analysis. Kaplan-Meier analysis showed that the median duration for achieving radiologic resolution was 207 days (range, 186-228 days) in the albendazole group, which was significantly shorter than the median duration for achieving radiologic resolution of 302 days in the control group (range, 224-380 days,  $p=0.023$ )

dominance (male to female ratio=4.4-18),<sup>1,3-5,7</sup> which corresponds to the demographic profiles of our patients (male to female ratio=3.3). In previous studies of ELA, the mean size of lesion was 1.5-1.7 cm, and the majority of lesions were less than 2 cm,<sup>1,3-5,7</sup> comparable with the size of lesions in our study (size=1.58 $\pm$ 0.05 cm [mean $\pm$ SD]; 2 cm or smaller lesions in 77.3% of patients). A single lesion was more common in the study by Kim et al.<sup>7</sup> and in our study; however, multiple lesions were more frequently found in the studies by Yoo et al.<sup>3</sup> and Kim et al.<sup>4</sup>

In our study, 14.7% of patients were infected with hepatitis B, 9.0% had cirrhosis, and 30.7% had malignancy. We thought that there could be two possible explanations for the frequent association of underlying liver disease and malignancy in our patients. First, in patients with underlying liver disease (i.e., high risk group of hepatocellular carcinoma development), regular imaging studies are routinely performed; hence the likelihood of detecting liver nodules is relatively high compared to the general population. Second, there is a peculiar widespread belief among people in our country that eating raw cow liver is good for improving health, particularly in those with underlying liver disease and malignancy. These patients are prone to toxocariasis infection.

ELA-T is known to be asymptomatic in most cases. While a majority of our patients (87.1%) were asymptomatic, only 21 patients (12.9%) complained of symptoms such as abdominal pain or chest discomfort. Other previous studies

have reported that 40-68% of patients with ELA were asymptomatic according to the characteristics of the included patients.<sup>1,5,7</sup>

While biopsy through a percutaneous approach or surgery may be performed to confirm the diagnosis in cases of difficult characterization of the lesion, ELA-T is usually diagnosed based on a combination of characteristic imaging findings and positive toxocariasis ELISA results.<sup>5</sup> In this study, the diagnosis of ELA was made based on histological findings in only 10 patients, and without biopsy in 153 patients. Previous studies have reported a wide range of biopsy rates (13-80%), according to the study design.<sup>2,3,5,7</sup> In addition, the presence of eosinophilia supports the diagnosis of ELA. In our study, among 154 patients whose initial eosinophil count was available, 121 patients (78.6%) showed eosinophilia. Eosinophilia was reported in 57-100% of patients with ELA in previous studies.<sup>2-4,7</sup>

Because it is known to be a self-limiting disease, there are no established indications for treatment of human toxocariasis.<sup>23</sup> Treatment of ELA-T depends on the severity of the patient's symptoms and the clinician's decision. Some authors agree that treatment is needed when patients' symptoms are severe.<sup>13,23,24</sup> In cases of visceral larva migrans with no or mild symptoms, it remains uncertain whether treatment is necessary. Regular imaging follow-up until resolution without histologic confirmation is commonly performed in most patients with ELA-T. If treatment with anti-helminthic drugs reduces the duration for achieving radiologic resolution, unnecessary concern of the patients and medical costs for repeated tests can be alleviated. We showed that albendazole can significantly shorten the median duration to radiologic resolution (207 days [range, 186-228 days] in albendazole group vs. 302 days [range, 224-380 days] in control group,  $p=0.023$ ).

Among 50 patients with underlying malignancy, ELA-T was not detected at the time of initial diagnosis of the malignancy and developed later at a certain time point during follow up when residual or recurrent tumor was identified in 49 cases. ELA-T was simultaneously identified and pathologically confirmed in one case with renal cell carcinoma at the time of initial diagnosis; in this patient, effect of cancer or surgery on the development and outcome of ELA-T could not be ruled out.

Our study has a few limitations as a retrospective study. Although baseline characteristics were comparable between

the albendazole group and control group, possible bias related to physicians' preference for treatment and variable follow-up policy cannot be excluded. No consistent policy was noted with regard to deciding whether or not to treat in patients diagnosed as ELA-T without biopsy, although none of the biopsy-confirmed cases were treated. Follow-up imaging was performed at various intervals according to underlying disease, radiologic findings, or preference of physicians. Conduct of a prospective randomized study is warranted to confirm the role of albendazole treatment in patients with ELA-T. Nevertheless, this is the first study demonstrating the benefit of albendazole treatment in patients with ELA-T, suggesting that radiologic resolution can be facilitated and the duration of follow-up can be shortened with albendazole treatment.

In conclusion, radiologic resolution can be accelerated with albendazole treatment in patients with ELA-T. Hence, treatment with albendazole would be recommended to avoid the inconvenience and undue costs associated with long-term follow up and unnecessary worries among patients with ELA-T.

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