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TREATMENT AND PROPHYLAXIS - ORIGINAL PAPER

Clinical tolerance and efficacy of anti-parasitic treatment with albendazole in patients with alveolar echinococcosis: long-term follow-up observation in 117 patients

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Abstract
Alveolar echinococcosis is the most severe worm disease primarily detected in the liver. This study aimed to determine the clinical tolerance and efficacy of albendazole in patients with alveolar echinococcosis, depending on the volume of previous surgical treatment or its absence and the duration of anti-parasitic therapy. We retrospectively (over the last 15 years) analyzed the data of 117 patients, who were divided into 4 groups according to curability: R_0 (radical resection), R_{1+2} (incomplete resection), N_r (unresectable), and R_r (recurrence). All of them received albendazole from 3 months to 11 years, depending on the volume of resection. We evaluated patients' tolerability of albendazole according to the level of hepatic transaminases and blood cell count. The effectiveness of anti-parasitic treatment was evaluated by imaging studies and the absence of serum antibodies. There was no direct relationship between the frequency of adverse reactions and the duration of taking albendazole ($r - 0.20229$). Adverse reactions were significantly more often observed in unresectable patients ($p < 0.01$), which is most likely associated with the general serious condition of the patients and with individual drug intolerance. The effectiveness of the anti-parasitic treatment was manifested in the inhibition of tumor development in 88% of patients in group R_{1+2} and 60% in group N_r. Follow-up of group R_0 patients from 3 to 14 years did not reveal new lesions of the liver and other organs. The chance of a complete cure depends on the early detection of a parasitic tumor and can reach 50%.

Keywords Alveolar echinococcosis · Albendazole · Anti-parasitic treatment · Clinical tolerance · Adverse reaction · Parasitic lesion · Tumor

Introduction

Human alveolar echinococcosis (AE) is a zoonosis caused by the metacestode stage of *Echinococcus multilocularis*. This disease is characterized by a long asymptomatic course, infiltrative growth of a parasitic tumor and the potential for metastasis. The main method for treatment of AE is the surgical removal of the parasitic lesion — liver resection within healthy tissues. However, AE can be only cured with radical resection if it is detected early, which usually occurs in 20–35% of patients (Bresson-Hadni et al. 2011; Kadry et al. 2005). In some European cohorts, the resectability rate has reached 50–53.8% (Grüner et al. 2017; Kern et al. 2017). Unfortunately, in most cases, the diagnosis is made at a late stage of the disease, when only palliative operations are possible to eliminate complications. If the resection is carried out nevertheless, then it is always accompanied by anti-parasitic treatment for at least 2 years thereafter (Reuter et al. 2000; Brunetti et al. 2010). Treatment with benzimidazoles (albendazole, mebendazole) was introduced into clinical practice in 1975 (Schantz et al. 1982; Davis et al. 1986). Currently, benzimidazoles are the only drugs approved for the treatment of human echinococcosis. Albendazole (ABZ) is the drug of choice to treat AE (Horton 2003; Crouzet et al. 2010). Long-term or lifelong anti-parasitic treatment is indicated in cases of unresectable AE, after liver transplantation (LT), and after incomplete lesion resection. The evaluation of the tolerance and effectiveness of long-term administration of ABZ in AE is ambiguous since it is extremely difficult to form equivalent groups of patients by age, volume

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and lesion topography, nature of complications, and previous surgical and/or conservative treatment. The most common side effects are elevation of transaminases, proteinuria, transient hair loss, gastrointestinal disturbances, leukopenia up to agranulocytosis, and neurologic symptoms, including sleeplessness and vertigo (Kern et al. 2017).

This study aimed to determine the clinical tolerance and efficacy of ABZ in patients with AE, depending on the stage of the disease, the volume of previous surgical treatment or its absence, and the duration of anti-parasitic treatment.

Patients and methods

From 2006 to 2020, 192 patients with AE turned to the Clinical Department of Medical Parasitology and Tropical Medicine of Sechenov University. Of these patients, 117 (47 men and 70 women) were observed from 3 to 14 years. Some of the patients had concomitant diseases: 5 people had acute calculous cholecystitis in their anamnesis, 1 gastric ulcer, 1 duodenal ulcer, and 3 chronic gastritis, and 4 people were infected with hepatitis C virus and 3 hepatitis B virus. There were no immunosuppressive conditions in the patients treated in our department. A decision as to whether there was the possibility of surgical treatment or only anti-parasitic therapy (if there were contraindications for surgery) was taken based on the results of clinical and instrumental research methods for each specific patient. Surgeries were carried out in the Sklifosovsky Clinical and Research Institute for Emergency Medicine, Vishnevsky Institute of Surgery, Petrovsky Russian Research Center of Surgery, Sechenov University Moscow, as well as in other surgical centers of the Russian Federation.

The diagnosis of AE was based on physical examination: ultrasound scans (USs), magnetic resonance imaging (MRI), or multispiral computed tomography (MSCT), as well as data from morphological studies of biopsy material in previously operated patients, as determined by the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) criteria (Brunetti et al. 2010). Serum antibodies (Ab) against Echinococcus antigens (Ag) were determined using an enzyme-linked immunosorbent assay (ELISA) (Echinococcus-IgG, kit, Vector-best, Russia), which is the only test system licensed in our country. The results were considered positive or negative according to the manufacturer's recommendations and the proven effectiveness of the test system for AE (Poletaeva et al. 2011). All *E. multilocularis* lesions at diagnosis were classified according to the PNM (P, parasitic mass in the liver; N, involvement of neighboring organs; and M, metastasis) system (Kern et al. 2006). The PNM stage at the time of diagnosis or resection was assigned retrospectively, based on radiological and operative findings and the histological report of the resected specimen.

The time interval between diagnosis and ABZ initiation varied significantly from patient to patient. ABZ treatment began 4–6 weeks after any surgical treatment or immediately after establishing the impossibility of resection, at a dose of 10–15 (rarely 20) mg/kg body weight per day. The drug was prescribed with normal hepatic enzymes and leukocytosis of at least 3.0×10^9. These indicators after surgery often deviated from the reference values and returned to normal after 4–6 weeks. Increase in alanine transaminase (ALT) values up to 542 and aspartate transaminase (AST) 668 IU/L after resection was recorded. All patients received continuous ABZ therapy. The exceptions were persons (mainly from group R_r) who had been operated on for AE earlier not in Moscow but remote regions. For several of them, therapy was carried out in courses immediately after surgery (two or three courses of 28 days with 14-day breaks). After going to our department, therapy was uninterrupted.

The duration of therapy depended on the results of the resection. Inoperable patients and patients with incomplete resection received treatment for a long time, often for life. Pregnant women and women planning pregnancy were not prescribed anti-parasitic treatment, since ABZ is potentially teratogenic. Throughout the observation period, we evaluated our patients' tolerability of ABZ according to the level of hepatic enzymes (AST, ALT, alkaline phosphatase, gamma-glutamyltransferase) and blood cell count. In cases where such levels went 3–4 times beyond the reference values and/or there was a decrease in the number of leukocytes below 2.5×10^9, drug treatment with ABZ was adjusted, and symptomatic treatment was prescribed, with ABZ being resumed after normalization. These indicators were monitored at 2-week intervals (during the first 3 months) and then, if tolerated, monthly (Vuitton 2009). Patients carried out these studies at their place of residence, sent the results of tests and studies to our clinic, and received online consultations on further medication intake. Local capabilities and the availability of a license to use the test systems in Russia were taken into account as part of these research methods. ABZ was discontinued in cases of increased symptoms of toxic liver damage, persistent leukopenia, and agranulocytosis, as well as in cases of severe allergic reaction that could not be stopped with antihistamines.

We classified the patients into 4 groups, according to curability. Group R_0 was defined as patients who underwent hepatectomy with complete resection of the lesion. Group R_{1+2} included 3 patients with R_1 (microscopic residue), 18 patients who underwent hepatectomy consisting of reduction surgery based on anatomical resection, with the greatest possible portion of the tumor removed (macroscopic residue, R_2), and 5 patients with radical resection of the liver but with the presence of foci in the lungs. Group N_r was defined as

patients in whom the tumor was recognized as not resectable (24 patients). All these patients were prescribed long-term (lifelong) therapy with ABZ. From the moment of diagnosis, 99 patients from the above 3 groups were under observation.

A further 18 patients (group R_r), previously operated on in other cities of the country, applied for consultation regarding the possibility of anti-parasitic treatment in connection with a recurrence/reactivation of the disease.

Follow-up of patients is complicated by the large distances between the places of residence of patients and our department. Anti-parasitic treatment is carried out at home, on an outpatient basis. The attending physician indicates his phone number and email address in the list of appointments, and the patient sends the results of biological tests and imaging studies (USs, MSCT). Radiological follow-up of patients was carried out at the place at the residence and with available local possibilities (USs or MSCT) every 6 months for the first 2 years and then once per year. As a rule, the examination was performed by the same radiologist. The patient sends the conclusion of the radiologist and the patient's image itself to our department, where it was also evaluated. The criteria for assessing the effect of ABZ were the absence of new lesions foci, no changes in the size of the lesion, and an increase in calcifications (for groups R_1, N_r and R_r). Monitoring of the course of treatment is mainly carried out remotely. Patients from the central regions of the European part of Russia come to our department once a year for examination (less often in 2 to 3 years).

Ethical approval was not required for this retrospective study. All patients were informed and give their consent to this study.

All continuous variables were expressed as the mean ± SE and were compared using one-way analysis of variance and one-way analysis of independent measures. Categorical variables were analyzed using Fisher's exact test. The point-biserial correlation coefficient was used to calculate the correlation between the duration of ABZ intake and the presence of adverse reactions.

Results

Description of the patient population

A total of 63 (53.8%) patients who applied to our clinical department were residents of the central regions of the European part of Russia, while 24 (20.5%) lived in Moscow and the Moscow region. All of these patients claimed that they had not visited the regions that were endemic for AE. A total of 77 (65.8%) patients lived in rural areas, 30 (25.6%) patients had dogs, and 9 (7.7%) were linked to hunting and/or the animal fur dressing. The patient characteristics are summarized in Table 1. The gender distribution showed the predominance of women in the general population of patients, but men predominated in group R_r ($p < 0.05$). Comparison of the age of the patients showed significantly higher rates in the N_r group.

Circumstances of diagnosis

The diagnosis of AE was unexpected for 54 asymptomatic patients: the tumor was found during a dispensary and prophylactic examination, with USs in 26 patients and X-ray in 4 patients; as a result of blood tests that went beyond the reference values in 4 patients; by USs and MSCT performed for other diseases in 13 patients; and directly during operations (cholecystectomy, ovarian resection, etc.) in 5 patients.

The remaining patients had some form of symptom. Most noted pain in the epigastric or right hypochondrium, heaviness, and discomfort in the upper abdomen, with two patients discovering a tumor themselves by paying attention to the indurations in the right hypochondria. Patients at stages IIIa, IIIb, and IV of the disease had jaundice, fever > 38 °C, and weight loss of 5–10 kg.

Surgical data and PNM stages

For 75 patients, the surgeons considered a possible surgical intervention in the form of atypical resection (AR), left hemihepatectomies (LHHE), right hemihepatectomies (RHHE), or extended LHHE/RHHE. Fifty patients (group R_0) underwent radical resection of the parasitic lesion. Unfortunately, in 25 operated patients (group R_{1+2}), it was not possible to completely remove the parasitic lesion because of the close adherence or invasion of the hepatic hilum, inferior vena cava, or other great vessels of the liver (8 patients), additional metastases in the lungs (5 patients), and it not being possible to carry out a radical resection of the parasitic tumor with multifocal lesions of various parts of the liver (7 cases).

The primary focus of AE was detected in the liver in all patients, mainly in the right lobe (75.2%). Most patients (76.9%) had one parasitic lesion, but there was also a multifocal lesion of the liver (from 2 to 7 formations). One-third of all patients (29.9%) had parasitic lesions in neighboring organs (N_1) of the liver, 17.1% had distant metastases (M_1).

For 24 patients (group N_r), radical liver resection was not performed due to the extent of the lesion (up to 23.8 × 14.4 × 12.8 cm), including multiple lesions (4 patients), the presence of metastases (6 patients), or concomitant diseases (3 patients).

Out of the 18 patients (group R_r) who applied for consultation in connection with a recurrence/reactivation of the disease, 5 did not take ABZ after the first resection due to adverse reactions, 8 took ABZ for a short time (3–6 months), 2 took ABZ in an insufficient dose (3.5–7 mg/kg), and 3 did

Table 1 Patient's characteristics before the start of albendazole treatment

Characteristic	Group R_0 ($n = 50$)	Group R_1 ($n = 25$)	Group N_r ($n = 24$)	Group R_r ($n = 18$)	Total ($n = 117$)	p value
Gender (M/F)	17/33	13/12	5/19	12/6	47/70	Total: R_r – 0.0428
Age at diagnosis (median years ± SE, range)	38.7 ± 2.4(10–71)	41.6 ± 3.0(16–73)	50.8 ± 3.0(22–74)	35.3 ± 3.7(16–66)	42.2 ± 1.5(10–74)	R_0: N_r – 0.04164N_r: R_r – 0.00436
Symptoms +/-	20/30	12/13	16/8	15/3	63/54	R_0: N_r – 0.0466R_0: R_r – 0.0022
Pain in the epigastria or right hypochondrium	17	7	8	10	42	R_0: N_r – 0.0122
Jaundice	1	4	5	1	11	R_0: R_1 – 0.0397R_0: N_r – 0.0122
Fever > 38 °	2	–	3	2	7	–
Weight loss of 5–10 kg	–	1	–	2	3	–
Size of tumor (cm), mean ±SE	9.5 ± 0.8	14.0 ± 1.2	16.4 ± 1.5	–	12.5 ± 0.7	R_0: R_1 – 0.02702R_0: N_r – 0.00039
PNM stage [†]						
I ($P_1N_0M_0$)	23	1	–	–	24	R_0: R_1, N_r, R_r < 0.001
II ($P_2N_0M_0$)	8	1	–	–	9	R_0: R_1, N_r< 0.05
IIIa ($P_3N_0M_0$)	8	6	4	1	19	R_0: R_r < 0.10
IIIb ($P_{1\text{-}3}N_1M_0$)	4	4	–	1	9	–
IIIb ($P_4N_0M_0$)	5	3	11	3	22	R_0: N_r – 0.0016R_1: N_r – 0.0121N_r: R_r – 0.0574
IV ($P_4N_1M_0$)	2	5	1	6	14	R_0: R_1 – 0.0375R_0: R_r – 0.0033
IV ($P_{1\text{-}4}N_0M_1$)	–	3	2	3	8	R_0: R_1 – 0.0341R_0: R_r – 0.0163
IV ($P_{1\text{-}4}N_1M_1$)	–	2	6	4	12	R_0: N_r – 0.0007R_0: N_r – 0.0038
Surgical intervention						
AR[‡]	24	7	–	7	38	–
LHHE [§]	3	3	–	2	8	–
RHHE [¶]	10	2	–	4	16	–
Extended LHHE	1	2	–	1	4	–
Extended RHHE	12	11	–	4	27	–

[†]*PNM* (*P*, parasitic mass in the liver; *N*, involvement of neighboring organs; and *M*, metastasis) — international staging system for alveolar echinococcosis lesions from Kern et al., 2006; [‡]*AR*, atypical resection; [§]*LHHE*, left hemihepatectomies; [¶]*-RHHE*, right hemihepatectomies

not receive anti-parasitic treatment. On average, reactivation of growth of the parasitic tumor was observed after 4.2 years (from 1 to 14 years) and occurred mainly in the area of surgical intervention. The tumor invaded the hepatic hilum (5 patients) and neighboring organs, such as the diaphragm (2 patients), retroperitoneal space (2 patients), parietal peritoneum, and spleen (1 patient), right adrenal gland, and kidney (2 patients). Metastases were detected 3–4 years after liver resection, in the lungs of 5 patients and the brain of 1 patient.

Comparison of the size of the tumors and the presence of any symptoms showed an increase in these indicators from group R_0 to N_r. On the contrary, the proportion of patients with stages I and II of the disease decreased from the R_0 group (62.0%) to the R_{1+2} (8.0%), N_r (0%), and R_r (0%) groups ($p < 0.001$).

ABZ therapy

All 50 patients from group R_0 received anti-parasitic treatment with ABZ from 3 months to 3 years until negative ELISA values with Echinococcus Ag were obtained (Table 2). A decrease in anti-echinococcal Ab titers to negative values was observed within 3–12 months in patients who underwent AR, LHHE, and RHHE. Only 2 of 13 patients who underwent extended LHHE/RHHE had anti-echinococcal Ab titers become negative after 3 months; in

Table 2 Clinical tolerance and efficacy of albendazole in patients with alveolar echinococcosis

Characteristic	Group R_0 (n = 50)	Group R_{1+2} (n = 25)	Group N_r (n = 24)	Group R_r (n = 18)	Total (n = 117)	p value
Duration of taking ABZ †						
3 months	3	–	–	–	3	
6 months	12	–	–	–	12	
1 year	15	7	–	2	24	
2 years	17	5	5	4	31	
3–5 years	3	12	5	8	28	
6–10 years	–	1	14	4	19	
Adverse reaction +/-	17/33	9/16	17/7	9/9	52/65	$R_0 + R_{1+2}$: $N_r < 0.01$
Elevation of transaminases	10	4	10	7	31	$R_0 + R_{1+2}$: $N_r < 0.01$
Dyspeptic syndrome	5	1	4	2	12	–
Allergic manifestations	1	2	–	–	3	–
Neurologic symptoms	1	1	–	–	2	–
Other symptoms	–	1	3	–	4	–
Ab were not detected through						
3 months	9	–	–	–	9	R_0: R_{1+2}, $N_r < 0.05$
6 months	12	2	–	–	14	R_0: N_r, $R_r < 0.05$
1 year	15	4	–	–	19	R_0: N_r, $R_r < 0.01$
2 years	4	5	–	–	9	–
3–5 years	3	7	–	–	10	R_0: $R_{1+2} < 0.05$
Ab titers are retained	–	7	22	18	47	R_0: R_{1+2}, N_r, $R_r < 0.01$
Ab titers were negative	7	–	2		9	–
Observation time						
3–5 years	27	14	12	12	65	
6–14 years	23	11	12	6	52	

† *ABZ*, albendazole; ‡*Ab*, antibody

the remaining patients, they persisted from 1.5 to 3 years. In 7 patients, all at stage I of the disease ($P_1N_0M_0$), ELISA with Echinococcus Ag was negative both before and after surgery. In the medical history sheets of these patients, no immunosuppressive conditions were noted.

The group of patients in R_{1+2} has been taking ABZ continuously for 3 to 7 years. Eighteen patients (including 3 patients with R_1) showed no serum antibodies to Echinococcus Ag after 1–5 years of ABZ intake.

To restrain tumor growth and metastasis, patients from groups N_r and R_r were treated with ABZ continuously, for life. Abs against Echinococcus Ag were not detected in two patients from groups N_r with large tumors (18–20 cm in diameter). In the rest of the patients, these indicators were high — up to 123 antibody units. A tendency towards a decrease in indicators during the treatment was only observed in 2 patients.

Adverse reaction

A third of patients in groups R_0 and R_{1+2} (34% and 36%, respectively) experienced adverse reactions while taking ABZ, mainly manifested in an increase in the level of hepatic transaminases (ALT up to 247 IU / L). The remaining patients noted mild allergies, headache, fatigue, and nausea. In the R_r group, such adverse reactions were observed in half of the patients.

Almost all patients from group N_r showed a temporary rise in hepatic transaminases during treatment (ALT up to 305 IU/L and AST up to 139 IU/L in a male patient). While taking ABZ, 2 patients had transient hair loss. One patient with initially low hemoglobin had to reduce the dose of ABZ to 10 mg/kg.

In general, adverse reactions were significantly more common in the N_r patient group compared to the resectable ($R_0 + R_{1+2}$) groups (70.8 % of cases versus 34.7 %, respectively, $p < 0.01$). Most likely, the high incidence of adverse reactions related to the severity of the disease with cholestasis and/or hepatic insufficiency.

The effect of concomitant diseases on the clinical tolerance of albendazole is difficult to assess due to the small number of observations. It can be noted that all persons infected with the hepatitis C virus (3 from the N_r group and 1 from the R_1 group) noted adverse reactions in the form of

a four- to fivefold increase in liver enzymes. Patients infected with the hepatitis B virus (all of them were in the R_0 group) took albendazole for 2 years without side effects.

On average, 44.4% of patients experienced adverse reactions when taking ABZ, 26.5% suffered from elevated liver transaminases, but only 7.7 % had severe liver toxicity requiring pause or discontinuation of the drug.

Follow-up management

Follow-up of the group R_0 patients after discontinuation of ABZ from 3 to 14 years did not reveal new lesions in the liver and other organs, and there was no increase in serological parameters. Currently, patients are under dynamic supervision.

In 2 patients from group R_{1+2}, a negative dynamic was noted in the form of recurrent tumor growth. In the remaining 22 patients, according to USs, MRI, and MSCT data, no new focal lesions were found.

Abdominal MRI revealed a recurrence of AE lesions in 1 unresectable patient due to a long interruption in treatment or discontinuation of ABZ. According to USs, MSCT, and MRI data, no significant dynamic was observed in the size of tumors in 18 unresectable patients over a long period (up to 11 years). Signs of calcification of the lesion were noted in 8 patients while taking ABZ, and 2 patients showed a 20–60% decrease in the size of all previously identified foci in the lungs. Unfortunately, 3 patients died, all of whom had AE detected at a late stage, and communication was lost with 5 patients.

At the end of the follow-up period, 82.0% of patients were either surgically healed or the remaining lesions were judged to be stable or regressive with ABZ treatment.

Discussion

AE is widespread in Russia, mainly in Siberia and the north of the Far East. In the European part of the country, AE foci are found in the Republics of Bashkiria and Tatarstan. In the two last decades, sporadic cases of AE have been increasingly recorded in the central regions of the European part of Russia, with 5–17 new cases of the disease registered here every year (unpublished data of state surveillance). The overwhelming majority of patients — residents of Moscow, Bryansk, Smolensk, and other neighboring regions — did not travel to regions that are endemic for this disease, i.e., the infection occurred in the territory of their residence (Tumol'skaia et al. 2013). Meanwhile, only one-tenth of patients had a risk of infection in connection with their professional activities (hunting, dressing of animal skins). There is an explanation for this situation: a study of the intermediate hosts of *E. multilocularis* (murine rodents) and the final hosts (carnivorous mammals) in the central regions of the European part of Russia showed the presence of natural foci of AE. *E. multilocularis* infestations of foxes have reached 23.8% (with a 1.2-fold increase in the number of foxes in 6 years), while infestations of raccoon dogs have reached 18.7% and domestic dogs 3.6% (Andreyanov 2020). The same trend is observed in Western Europe. *E. multilocularis* tapeworms are increasingly common and are being detected in more countries due to the spread of infected wild (foxes, wolves) and domestic (dogs) animals (Davidson et al. 2012). Unfortunately, in recent reviews, a worsening AE situation in Eastern Europe was noted only for the Baltic countries but not for Russia (Vuitton & Bresson-Hadni 2014; Gottstein et al. 2015; Wen et al. 2019).

There are few means to combat this disease. As before, the main method of treatment that leads to complete recovery is radical liver resection, with complete removal of the parasitic lesion (R_0). The remaining patients are prescribed anti-parasitic treatment. Due to the widespread introduction of instrumental methods (USs) during dispensary examinations of the population, it has been possible to identify AE in patients who did not have any symptoms to indicate this disease and to carry out a radical resection of the tumor in the early stages. Group R_0 accounted for half of all the patients we observed (50.5 ± 5.0%), which is slightly higher than the data published at the beginning of the twenty-first century and comparable to those published by the Ulm group in Germany (Kadry et al. 2005; Bresson-Hadni et al. 2000; Grüner et al. 2017). Other results obtained by our group and the Ulm group (Grüner et al. 2017) are also comparable: the proportion of persons with stage I of the disease was 20.5 and 12.8% and with stage IV 29.0 and 25.0%; 55.5% and 45.5% did not experience any side effects of long-term BMZ treatment; 26.5% and 28.5% suffered from elevated liver transaminases; and 7.7 and 6.9% had severe liver toxicity requiring drug switching or pause, respectively. At the end of the follow-up period, 82.0 and 88.8%, respectively, of the patients had a favorable outcome and were either cured by surgery or the remaining lesions were rated as stable or regressive with BMZ treatment. Similar data were obtained in Swiss and French patient cohorts (Torgerson et al. 2008; Piarroux et al. 2011).

The most common side effect is elevated serum ALT. In different patient populations, this indicator varies from 5 to 66%; abdominal pain, abdominal distension, dyspepsia, nausea, and vomiting occur in up to 4–11% of cases (Vuitton & Bresson-Hadni 2014). The higher frequency of adverse reactions observed in our study in unresectable patients was manifested mainly in elevated hepatic transaminases (41.7%) and dyspeptic syndrome (16.7%). Thus, our results do not differ significantly from the data of other researchers.

Even though the frequency of adverse reactions was higher in the group of unresectable patients than in the other groups, there was no direct relationship between the frequency of adverse reactions and the duration of taking ABZ ($r - 0.20229$). An adverse reaction to the drug in the form of multiple increases in the level of hepatic transaminases, nausea, and weakness was noted in all patient groups. A total of 15 out of 50 patients who underwent radical resection (group R_0) were unable to take the drug for more than 3–6 months due to side effects. This is acceptable for patients with AE stage I and II (Brunetti et al. 2010). Other patients (including unresectable patients) took ABZ for many consecutive years without adverse reactions.

The problem of reducing the frequency of side reactions can be solved by pharmacological monitoring ABZ sulfoxide plasma levels, which should be determined at the beginning of treatment (after 4 weeks of continuous treatment or earlier if there is a side effect) and every 3 or 6 months with long-term treatment (Brunetti et al. 2010). Unfortunately, such measurements are only available in very specialized reference centers; this prevents their use in most settings in the endemic areas.

According to the WHO-IWGE recommendations, surgical treatment is not prescribed if radical removal of the parasitic lesion is not possible, and treatment can be limited to percutaneous bile or abscess drainages or stent placement for vascular complications (Vuitton & Bresson-Hadni 2014). Nevertheless, the results of our observations show that patients who underwent incomplete resection (group R_{1+2}) tolerated anti-parasitic treatment better than those who were not operated on, and 88.0% of patients showed no tumor growth. It is believed that ABZ has only parasitostatic effects and not parasiticidal effects (Reuter et al. 2004). Despite that no controlled studies have proven the efficacy of treatment with ABZ in cases of AE, open clinical studies have suggested that this compound can slow down the growth of the parasitic mass and lead to a regression of AE lesions, with no evidence of recurrence (Ammann et al. 1994; Crouzet et al. 2010). Our observation also showed that taking ABZ inhibits or stops the growth of the parasitic tumor. A mild positive dynamic (a slight decrease in the size of the parasitic focus, its pronounced focal calcification) was observed in 4 out of 25 patients with non-radical tumor resection and in 3 out of 16 patients in whom the lesion was recognized as not resectable. The most noticeable effect of ABZ was observed in patients with AE lung metastases. For group R_{1+2}, there was no tumor growth or appearance of metastases in most patients (18) for several years (up to 8) while taking ABZ, which can also be assessed as a positive effect.

Long-term (lifelong) observation of patients, as well as anti-parasitic treatment for unresectable patients or those who have undergone LT, is necessary even when AE is not detected in other organs and tissues at the time of surgery. Recurrence/reactivation of the disease was observed in patients (with incomplete resection (R_1, R_2), unresectable (N_r), and LT) who either did not take ABZ after surgery or did not take it regularly due to side effects or the increasing economic impact from needing treatment throughout his/her life (Reuter et al. 2004; Zavoikin et al. 2020).

According to expert recommendations, long-term follow-up of the AE patient includes pharmacological monitoring, tracking of the disappearance and permanent absence of highly specific antibodies such as antibodies against Em18, and imaging studies (USs, MRI) at intervals of 2–3 years. In recent years, positron emission tomography (18F-FDG-PET-CT) and contrast-enhanced ultrasound (CEUS) have been considered as possible tools to assess parasite viability (Brunetti et al. 2010; Crouzet et al. 2010; Tappe et al. 2010; Vuitton & Bresson-Hadni 2014).

Unfortunately, the implementation of all these recommendations is not possible for both doctors and patients. We could not use Em18 ELISA for analysis since this test system is not licensed for use in our country. In addition, the treatment of this disease represents a considerable financial burden. The government takes upon itself only part of the treatment cost without paying for complex examinations such as MSCT and PET. In some regions of the Russian Federation, the government also does not pay for drugs (ABZ) that are prescribed for vital indications.

Conclusion

The prolonged asymptomatic course of AE, often accompanied by the absence of Ab to Echinococcus Ag, complicates the detection of the disease in the early stages and makes radical resection of the tumor impossible. Our study has shown that dispensary examination of the population of the Russian Federation using USs significantly increases the likelihood of cure (up to 50%). Adverse reactions when taking ABZ were more often observed in unresectable patients, which was more likely associated with the general serious condition of the patients than with the duration of drug intake. There was no direct relationship between the frequency of adverse reactions and the duration of taking ABZ. The effectiveness of anti-parasitic treatment was demonstrated by the inhibition of tumor development in 88% of patients with incomplete resection (R_{1+2}) and 60% of unresectable patients (N_r). The absence of highly qualified parasitologists in the places of residence of patients with AE is compensated by the possibility of online monitoring by specialists of our department.

Declarations

Ethical approval Ethical approval was not required for this retrospective study.

Conflict of interest The authors declare no competing interests.

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