Thiabendazole for the prophylaxis of strongyloidiasis in immunosuppressed patients with hematologic diseases: a randomized, double-blind placebo-controlled study

To evaluate the efficacy of thiabendazole for prophylaxis of strongyloidiasis in patients with hematologic diseases, we performed a randomized, placebo-controlled trial. The incidence of strongyloidiasis was similar in both groups (p=0.36), but the compliance was better in the placebo group (p=0.04). This study does not support the use of thiabendazole prophylaxis in patients with hematologic diseases.

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Strongyloidiasis has a worldwide distribution, and usually causes mild or asymptomatic infection.[1] In immunosuppressed individuals, it may cause a frequently fatal disseminated syndrome.[2] In a former study, we observed a high prevalence of strongyloidiasis (21%) in a population of 253 patients with hematologic malignancies, with only one case of the disseminated syndrome.[3] Despite this apparently low incidence of dissemination, some experts recommend that immunocompromised patients receive some sort of prophylaxis.[4] However, no controlled trials have ever tested this strategy. In this study we evaluated the efficacy of thiabendazole for the prophylaxis of strongyloidiasis in patients with hematologic diseases in a randomized double-blind, placebo-controlled trial.

Appropriate informed consent was obtained and clinical research was conducted in accordance with Good Clinical Practices, and approved by the authors' institutional review board.

Patients with hematologic malignancies or those with a benign condition receiving corticosteroids who had three negative stool specimens for Strongyloides stercoralis (Baermann-Moraes method)[5] and signed an informed consent were eligible. Pregnant or nursing women and those with a previous history of severe side effects to thiabendazole were excluded. The patients were randomly assigned to receive placebo or thiabendazole (25 mg/kg PO daily, maximum of 3 g, given b.i.d. for two consecutive days, and repeated monthly) in a 1:1 ratio. Patients with strongyloidiasis at baseline were treated with thiabendazole 25mg/kg PO b.i.d. for two days, and could be subsequently admitted to the study if the strongyloidiasis had been eradicated.[6] Monthly stool examinations were performed.

The presence of diarrhea, abdominal pain, itching, nausea, dyspnea and fever were recorded at baseline and at each follow-up. The regimen was discontinued in the case of severe side effects attributable to thiabendazole, if a diagnosis of strongyloidiasis was made, or at the discretion of the patient. The compliance was assessed as excellent (the patient took all doses of the study drug), good (80% of the prescribed doses) or poor (less than 80% of the prescribed doses).

Based on the 21% prevalence of strongyloidiasis of our previous study,[3] we estimated that 53 patients in each arm would be needed, considering clinically significant a reduction in the incidence of strongyloidiasis to 2% (α error of 0.05 and β error of 0.20).

Between May 1995 and April 1997, 49 patients were randomized to receive thiabendazole, and 54 received placebo. Both groups were balanced for pretreatment characteristics, except for autoimmune disease (4 patients in the thiabendazole group and none in the placebo group, p=0.05) (Table 1). The median number of stool specimens examined per patient during follow-up was three in both groups (p=0.16). Five patients had strongyloidiasis during the study period (all asymptomatic): one patient from the thiabendazole group (2%) and four patients (7%) from the placebo group (relative risk 3.63, 95% confidence interval [CI] 0.42 – 31.38). No cases of disseminated strongyloidiasis were diagnosed. Six patients from the thiabendazole group and three from the placebo group died (p=0.3; 95% CI 4% – 18%). No death was attributed to strongyloidiasis. Abdominal pain was more frequent in the thiabendazole group (53% versus 31%, p=0.03). The frequency of other side effects was similar in both groups. The compliance was excellent or good in 55% of patients in the thiabendazole group and in 74% in the placebo group (p=0.04).

Table 1. Characteristics of patients.

Characteristic	*Thiabendazole n=49 (%)*	*Placebo n=54 (%)*	*p*
Gender (female)	27 (55)	25 (46)	0.37
Age (years), median	38	48	0.17
Underlying disease			
Acute lymphoid leukemia	5 (10)	6 (11)	0.88
Acute myeloid leukemia	3 (6)	2 (4)	0.67
Non-Hodgkin's lymphoma	18 (37)	20 (37)	0.97
Hodgkin's disease	11 (22)	14 (26)	0.68
Multiple myeloma	4 (8)	3 (6)	0.70
Chronic myeloid leukemia	2 (4)	5 (9)	0.44
ITP or IHA	4 (8)	–	0.05
Other diseases	2 (4)	4 (7)	0.68
Use of steroids	32 (65)	40 (74)	0.33
Underlying cancer in relapse	7 (14)	9 (17)	0.74
Parasitic diseases			
Strongyloidiasis (treated)	4 (8)	4 (7)	1.0
Ascariasis	3 (6)	2 (4)	0.67
Trichuriais	3 (6)	1 (2)	0.34
Schistosomiais	1 (2)	–	0.47
Hookworm disease	1 (2)	2 (4)	1.0
Amebiasis	1 (2)	–	0.47
Giardiasis	3 (6)	3 (6)	1.0

ITP: idiopathic thrombocytopenic purpura; IHA: immunohemolytic anemia.

In this first randomized placebo-controlled trial of prophylaxis of strongyloidiasis in immunocompromised patients, we observed that thiabendazole seems not to be superior to placebo. A comparison of incidence rates (2% versus 7%, p=0.36) revealed no significant differences between the two groups. On the other hand, side effects were more frequent in patients receiving thiabendazole, which resulted in a lower compliance. Therefore, considering these results, giving monthly prophylaxis with thiabendazole seems not justified. An alternative to this strategy would be to screen patients before starting immunosuppressive therapy.[7,8] We have recently reported that an immunoenzymatic test (ELISA) was a good screening method to rule out strongyloidiasis in patients with hematologic malignancies.[9]

A major shortcoming of our study is that the actual statisti-

cal power was lower than the projected 80%, because the incidence of strongyloidiasis observed was far lower than expected based on our previous study. With the 7% incidence observed, at least 600 patients would be needed to show a significant difference between the two arms. Despite these limitations, and given the low incidence of dissemination, strategies other than prophylaxis should be explored. Regarding other drugs, ivermectin has been show to be active in patients with strongyloidiasis,[10] but its efficacy has not been evaluated in patients with hematologic diseases. Prospective studies evaluating this drug as well as different strategies for managing strongyloidiasis in immunocompromised patients are warranted.

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Chronic graft-versus-host disease following allogeneic peripheral blood and bone marrow stem cell transplants: a single center experience

We examined the influence of graft-versus-host disease (GVHD) on outcome in patients with hematologic malignancies undergoing allogeneic bone marrow transplantation (allo-BMT) and peripheral blood stem cell transplantation (allo-PBSCT). Our data confirm that allo-PBSCT patients experience more chronic GVHD than allo-BMT patients, translating into a more potent graft-versus-leukemia (GVL) effect.

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Previous studies have shown that the development of a GVL effect is closely associated with development of GVHD.[1-3] We examined the influence of GVHD on outcome in 121 consecutive patients with hematologic malignancies undergoing allo-BMT or allo-PBSCT for the first time from HLA-identical siblings at our institute between January 1987 and June 2001. Six patients in whom engraftment failed or who did not survive long enough to be evaluated (≥21 days), were excluded from analysis (Table 1). Data from only those patients who had GVHD prior to leukocyte infusion were used to analyze the incidence of GVHD in this study. p values are two-tailed.

Ten (11%) of 89 patients with allo-BMT and 9 (35%) of 26 patients with allo-PBSCT developed grade II-IV acute GVHD (Fisher's exact probability, p=0.01). As to chronic GVHD, 78 recipients of allo-BMT and 24 recipients of allo-PBSCT who survived at least 100 days after transplantation were subjected to analysis including a multivariate study. Thirty-two (41%) of the 78 patients and 21 (88%) of the 24 patients developed chronic GVHD (p=0.0002). Concerning quality of life in patients with chronic GVHD, the Karnofsky prognostic score of 80% or less was seen in 6 (19%) of the 32 allo-BMT patients with chronic GVHD, and in 5 (24%) of the 21 allo-PBSCT patients with chronic GVHD, suggesting that the chronic GVHD was tolerated in this study. However, it is uncertain whether this would hold true when allo-PBSCT is performed in older patients.[4]

Twenty-nine (31%) of 89 patients who received allo-BMT, and 6 (23%) of 26 patients who received allo-PBSCT, relapsed (p=0.35). Of the 89 patients who received allo-BMT, 13 died of treatment-related causes, which were not related to relapse, after the transplantation. In contrast, no deaths, other than those from relapse, were observed among the 26 patients who received allo-PBSCT. Chronic GVHD was the cause of death in 2 of 13 patients who were receiving long-term immunosuppressive therapy to control the GVHD, one of whom died from bacterial meningitis and the other of systemic aspergillosis.

To detect the possible influence of allo-BMT and allo-PBSCT on relapse in patients with or without GVHD, patients were categorized into 4 groups. The 4 groups were as follows: patients without acute or chronic GVHD; patients with acute but not chronic GVHD; patients with chronic but not acute GVHD; and patients with both acute and chronic GVHD. As a reference, results from the group of patients without acute or chronic GVHD were compared to those from each of the other 3 groups. The relative risk of relapse for each of the comparison groups, compared to the reference group, was calculated using a Cox proportional hazards regression model. Table 2 shows the risk of relapse according to the development of GVHD in patients who received allo-BMT and allo-PBSCT, based on the results of mul-