ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2009, p. 4167–4171 Vol. 53, No. 10
0066-4804/09/$08.00+0 doi:10.1128/AAC.00874-09

Prospective Randomized Trial of Six-Month versus Nine-Month Therapy for Intestinal Tuberculosis[▽]

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Received 28 June 2009/Returned for modification 20 July 2009/Accepted 3 August 2009

Intestinal tuberculosis (TB) continues to be a common disease worldwide. However, the optimal duration of anti-TB medication has not been well established. We therefore compared the efficacy of 6-month and 9-month therapy in the treatment of intestinal TB. Ninety patients definitely diagnosed with intestinal TB were randomized into 6-month ($n = 45$) or 9-month ($n = 45$) treatment groups, prospectively. The primary end point was complete response, defined as endoscopic healing of active lesions. Patients were followed up monthly for 3 months after therapy initiation, then every 3 months until the end of therapy, and finally 1 year later. Relapse was assessed 1 year after the end of therapy by patient interview and colonoscopy. Baseline characteristics were similar in the 6-month and 9-month groups. Intention-to-treat analysis revealed no significant differences between the two groups in complete response (6-month group, 93.3%; 9-month group, 91.1%; $P = 1.00$) or recurrence rate (6-month group, 2.4%; 9-month group, 0.0%; $P = 1.00$). Median follow-up duration was 39 months in the 6-month group and 32 months in the 9-month group. No surgery was performed on any patient in either group. In conclusion, the 6-month therapy was as effective as 9-month therapy in patients with intestinal TB and may have the additional benefits of reduced treatment cost and increased compliance.

Tuberculosis (TB) can affect virtually any organ or tissue of the body, and a broad range of clinical illnesses is seen. After introduction of effective antimicrobial therapy and improvements in living standards, the disease became controlled. However, a worldwide TB resurgence has occurred in recent decades, with an estimated global infection prevalence of 32% (in 1997, via tuberculin surveys), mainly because of the human immunodeficiency virus (HIV) infection epidemic in several developing and developed countries. In addition, the emergence of multidrug-resistant *Mycobacterium tuberculosis* has been a growing challenge to successful TB control in certain regions of the globe (10, 13, 14, 18). In Africa and Asia, TB continues to be a major problem and is responsible for considerable morbidity and mortality (35). Extrapulmonary TB has become more common, and the frequency of extrapulmonary organ involvement is 15 to 20% in patients not infected with HIV but about 50 to 70% in patients with concurrent HIV infections and TB (18, 26, 31).

Intestinal TB is one of the most common forms of extrapulmonary disease, primarily involving the distal ileum and cecum, followed by the jejunum-ileum, colon, and rectum (15, 17, 20, 22, 26). Intestinal TB remains prevalent in developing countries where TB is a common health problem. A commonly used, effective regimen for treating pulmonary TB is combination chemotherapy with isoniazid, rifampin (rifampicin), ethambutol, and pyrazinamide for 6 months. The addition of pyrazinamide to a regimen containing isoniazid and rifampin enabled shortening of therapy duration from 9 months to 6 months (5). Although few studies have examined treatment of extrapulmonary TB, the basic principles that underlie pulmonary TB treatment have also been applied to extrapulmonary disease forms (9, 23, 26, 33). However, many physicians, especially in developing countries, have been reluctant to use 6-month therapy to treat extrapulmonary TB (such as intestinal TB) because of difficulties in bacteriological diagnoses and assessment of therapy responses (12).

There are few controlled studies exploring the optimal duration of intestinal TB treatment, apart from some retrospective reviews (3, 11). We therefore performed a randomized clinical trial comparing the efficacy of 6-month therapy with that of 9-month therapy in patients with intestinal TB.

MATERIALS AND METHODS

Study design. This prospective, randomized, single-center open trial was conducted between October 1995 and October 2005 at the Asan Medical Center, a university hospital in Seoul, South Korea. Patients definitely diagnosed with intestinal TB were eligible for the study. A definite diagnosis of intestinal TB was made if at least one of the following criteria was met: (i) demonstration of caseating granuloma upon endoscopic biopsy; (ii) identification of acid-fast bacilli (AFB) in a histological specimen; (iii) positive culture of *M. tuberculosis* from a biopsy specimen; (iv) typical colonoscopic findings strongly suggestive of intestinal TB associated with active pulmonary TB, regardless of the result of AFB smear or mycobacterial culture in sputum. We excluded patients aged under 18 years or over 75 years; those with extrapulmonary TB other than intestinal TB, histories of anti-TB chemotherapy within the past 5 years, immunosuppressive disorders, or chronic liver disease; and those who were pregnant. Those from whom poor compliance was anticipated, who refused to participate in the study, or who were not referred to investigators were also excluded. The Institutional Review Board of the Asan Medical Center approved the study design, and all patients gave their informed consent before enrollment.

Pretreatment assessment and follow-up. At study entry, each patient gave a medical and family history and received a complete physical examination, blood counts, routine biochemical tests, and a chest X-ray. Colonoscopy was performed on every patient before trial entry and at the end of anti-TB treatment. Patients

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▽ Published ahead of print on 10 August 2009.

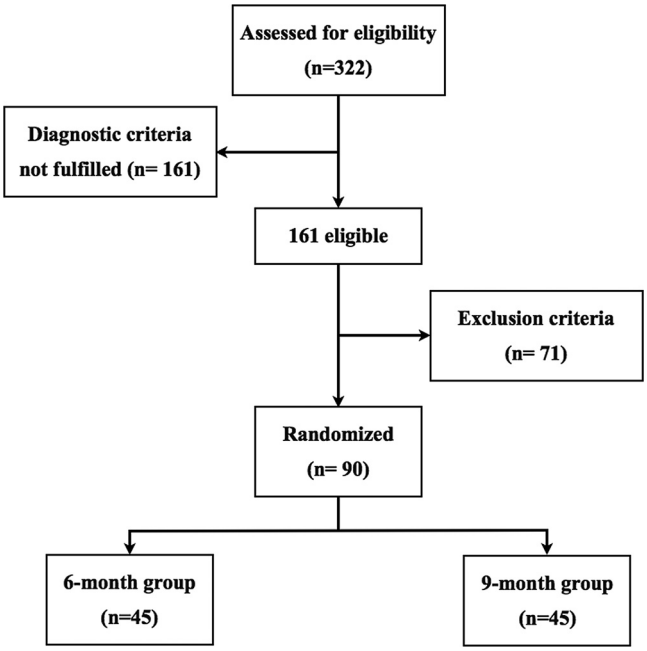

FIG. 1. Trial profile.

were scheduled for follow-up visits every month until 3 months after therapy initiation, then every 3 months until the end of therapy, and 1 year later.

Study protocol. Intestinal TB patients who fulfilled inclusion criteria were randomized into two groups receiving either 6-month or 9-month therapy. Randomization was performed using a computer-generated list. The 6-month group received the Z2H6R6E6 combination, consisting of isoniazid, rifampin, and ethambutol for 6 months, supplemented with pyrazinamide during the first 2 months. Patients allocated to the 9-month group received the Z2H9R9E9 cocktail, with isoniazid, rifampin, and ethambutol for 9 months, again supplemented with pyrazinamide during the initial 2 months. The decision to retain ethambutol in the continuation phase was based on high rates of primary drug resistance in South Korea (32). The isoniazid dose was 300 mg/day for those under 50 kg in body weight and 400 mg/day for those 50 kg and over. The rifampin dose was 450 mg/day for patients under 50 kg and 600 mg/day for those 50 kg and above. The ethambutol (15 to 20 mg/kg of body weight) and pyrazinamide doses (20 to 30 mg/kg) were 1,000 mg/day and 1,250 mg/day, respectively, for those under 50 kg and 1,200 mg/day and 1,500 mg/day for those 50 kg and over. After the first 2 months, ethambutol was reduced to 800 mg/day for all patients. From March 2004, enrolled patients received 300 mg/day of isoniazid regardless of body weight and 1,000 mg/day of ethambutol if they weighed 50 kg or above, according to new pulmonary TB treatment guidelines adopted by our study center. Other drug doses and durations were as described above. No corticosteroids were given to any patient, and surgery was reserved primarily for complications such as intestinal obstruction, perforation, and fistula (1).

Outcome measures. Data obtained at diagnosis, treatment end, and 1 year after the end of therapy were compared between the two groups to assess improvements in abdominal symptoms and to achieve endoscopic documentation of complete healing of active lesions. Complete response was defined as endoscopically demonstrated healing of active lesions at the end of treatment. Relapse was defined as endoscopic documentation of recurrent lesions after complete response had been achieved. Because most relapses occur within the first 6 to 12 months after treatment cessation (21, 29), we evaluated disease status 1 year after the end of treatment.

Sample size and statistical analysis. We assumed that the true success rate of 9-month therapy was more than 95% (12) and estimated that at least 40 subjects were needed in each group to afford the statistical power necessary to exclude, with 80% probability, the possibility that the success rate of 6-month therapy was at least 5% less than that of 9-month therapy (the noninferiority of 6-month therapy hypothesis; one-sided P value, <0.05). All outcomes were analyzed on an intention-to-treat basis. Between-group comparisons were made using the Wilcoxon rank sum test for continuous variables, and the chi-squared test or Fisher's exact test, as appropriate, for binary variables. A P value of less than 0.05 was considered statistically significant. All evaluations were performed using the statistical software package SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Study population. During the study period, 322 patients with intestinal TB were assessed for eligibility. After screening, 161 patients were definitively diagnosed with intestinal TB, thus meeting the inclusion criteria described above. Finally, 90 patients were included in the study because 71 patients met exclusion criteria. Of these 71 patients, 21 (30%) had TB in other body sites, 25 (35%) were not referred to investigators, 11 (15%) had concurrent illnesses such as malignancy and/or liver diseases, 7 (10%) took immunosuppressants including corticosteroids, 4 (6%) were older than 75 years, and 3 (4%) refused to participate. Forty-five patients received 6-month therapy, and the remaining 45 received 9-month therapy (Fig. 1). Follow-up of enrolled patients continued until July 2007.

Baseline characteristics. Table 1 shows patient baseline characteristics. There were no marked between-group differences in gender ratio, median age, or initial presenting symptoms. The most common symptoms were abdominal pain, weight loss, and diarrhea. The groups did not differ in frequencies of anemia, leukocytosis, thrombocytosis, elevated inflammatory markers, or hypoalbuminemia. The most common site of intestinal TB was the ileocecal area (87.8%), followed by the ascending colon (58.9%), transverse colon (27.8%), rectum and sigmoid colon (11.1%), and descending colon (10.0%), and site preference did not differ between groups. Strictures were found in

TABLE 1. Baseline clinical and laboratory characteristics of patients

Characteristic[a]	6-mo group (n = 45)	9-mo group (n = 45)	P value[b]
Gender (no. male:no. female)	18:27	22:23	0.53
Median age (yr) (range)	36 (18–71)	42 (20–71)	0.12
Symptom presentation [no. (%)]			
Abdominal pain	37 (82)	35 (78)	0.79
Diarrhea	22 (49)	18 (40)	0.53
Weight loss	24 (53)	31 (69)	0.19
Fever	6 (13)	10 (22)	0.41
Laboratory findings [no. (%)]			
Anemia[c]	21 (47)	28 (62)	0.20
Leukocytosis[d]	4 (9)	5 (11)	1.00
Thrombocytosis[e]	15 (33)	21 (47)	0.28
Elevated ESR	26 (58)	31 (69)	0.38
Elevated CRP	23 (51)	29 (64)	0.29
Hypoalbuminemia[f]	15 (33)	25 (56)	0.06
Location of lesions [no. (%)]			
Ileocecal area	38 (84)	41 (91)	0.52
Ascending colon	25 (56)	28 (62)	0.67
Transverse colon	10 (22)	15 (33)	0.35
Descending colon	4 (9)	5 (11)	1.00
Sigmoid colon	2 (4)	6 (13)	0.27
Rectum	3 (7)	4 (9)	1.00
Stricture [no. (%)]	8 (18)	10 (22)	0.79

[a] Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
[b] Calculated using Fisher's exact test.
[c] Defined as hemoglobin of <12 g/dl.
[d] Defined as a white blood cell count of $>10{,}000/mm^3$.
[e] Defined as a platelet count of $>350{,}000/mm^3$.
[f] Defined as albumin of <3.3 g/dl.

TABLE 2. Modes of diagnosis

Clinical or pathological manifestation	No. (%) of patients		*P* value[a]
	6-mo group (n = 45)	9-mo group (n = 45)	
Caseating granuloma	9 (20)	13 (29)	0.46
AFB	11 (24)	10 (22)	1.00
Mycobacterium culture	26 (58)	23 (51)	0.67
Active pulmonary TB	20 (44)	24 (53)	0.53

[a] Calculated using Fisher's exact test.

eight patients of the 6-month group and 10 patients of the 9-month group.

Mode of diagnosis. In 66 (73.3%) of the 90 patients with intestinal TB, diagnosis was made at initial workup by one or more of the following methods: histological evidence of caseating granuloma in 22 patients (24.4%), histological AFB demonstration in 21 patients (23.3%), and colonoscopic findings typical of intestinal TB associated with active pulmonary TB in 44 patients (48.9%). In the remaining 24 patients (26.7%), the diagnosis of intestinal TB was confirmed by growth of *M. tuberculosis* in culture of a biopsy specimen after a period of follow-up. The two groups were similar in clinical and pathological manifestations (Table 2).

Clinical course and follow-up. Of the 90 patients enrolled, 6 withdrew before completing treatment because of drug toxicity or intolerance (two patients in the 6-month group and four in the 9-month group). Among the 84 patients who completed scheduled treatment, complete response was achieved by 83 patients (42 of 43 patients in the 6-month group and 41 of 41 patients in the 9-month group). One patient in the 6-month group failed to achieve a complete response, and he was maintained on anti-TB medications for one additional month, thus receiving 7 months of treatment. The complete response rates did not differ between groups by intention-to-treat analysis (6-month group, 93.3%; 9-month group, 91.1%; $P = 1.00$). Per-protocol analysis also revealed no difference in between-group complete response rates (6-month group, 97.7%; 9-month group, 100%; $P = 1.00$). Seventy-nine patients were successfully followed up 12 months after the end of treatment, and the median follow-up durations were 39 months in the 6-month group and 32 months in the 9-month group ($P = 0.21$). No patient relapsed in either group except for one patient in the 6-month group who showed recurrence of the endoscopic lesion. There was thus no between-group difference in relapse rate ($P = 1.00$) (Table 3). No surgical intervention was required for any patient.

TABLE 3. Clinical courses and follow-up

Clinical course	6-mo group (n = 45)	9-mo group (n = 45)	*P* value
Dropout (n)	2	4	
Complete response (n)	42	41	
Complete response by intention-to-treat analysis (%) (no. positive/total no.)	93.3 (42/45)	91.1 (41/45)	1.00[a]
Follow-up duration after complete response (median no. of mos.) (range)	39 (6–131)	32 (10–127)	0.21[b]
Recurrence rate (%) (no. positive/no. total)	2.4 (1/42)	0 (0/41)	1.00[a]

[a] Calculated using Fisher's exact test.
[b] Calculated using the Wilcoxon rank sum test.

DISCUSSION

Attempts have been made to shorten the duration of treatment of pulmonary TB based on data from in vitro and animal experiments (19). These trials used a combination of drugs (isoniazid and rifampin) that kill actively multiplying organisms and a drug (pyrazinamide) attacking intracellular organisms, thus increasing overall chemotherapy effectiveness and permitting truncation of total treatment duration to 6 months. These data appeared to us to be applicable to the treatment of extrapulmonary TB.

Our trial was undertaken to test whether a 6-month regimen was effective in eliminating intestinal TB. To date, increasing evidence suggests that 6- to 9-month regimens that include isoniazid and rifampin are indeed effective in this regard (2, 12). Thus, a 6-month drug course is recommended for treatment of TB in any site except the meninges and, in some cases, bone, where a 9- to 12-month regimen is considered wise. However, few properly randomized trials of extrapulmonary disease treatment, featuring appropriate clinical end points, have been conducted, except for reports on tuberculous lymphadenitis (6–8) and spinal TB patients (27, 28, 30).

To the best of our knowledge, this study is the first prospective randomized trial comparing the efficacy of 6-month therapy with that of a longer treatment duration in patients with intestinal TB. All between-regimen comparisons, to the end of therapy, showed no significant differences. One patient in the 6-month group did not achieve a complete response after therapy completion. At that time, symptoms had disappeared but a tiny residual ulcer, associated with extensive granulation tissue, was seen on colonoscopy. Although the endoscopic lesion seemed to improve without further therapy, we modified the therapeutic protocol to offer our patient treatment for 7 months, as we felt it was ethical to do so. No difference in any outcome measure was seen when follow-up data (to 12 months posttreatment) were compared between groups. No patient suffered a bacteriologically or histologically confirmed relapse, even though one patient in the 6-month group was thought to have relapsed endoscopically (i.e., with one tiny ulcer on colonoscopy). Although this finding did not fulfill our diagnostic criteria for intestinal TB, the patient was retreated for 12 months with anti-TB medications identical to those previously received and later achieved complete response without any relapse.

Intestinal TB clinical presentations in our patients were in agreement with earlier reports on clinical manifestations of extrapulmonary TB. Symptoms are vague, and signs are nonspecific. Therefore, intestinal TB diagnosis can be difficult without a high degree of suspicion (24, 34). Abdominal pain was noted in 80.0% of patients, and weight loss was noted in 61.1% of patients. Other symptoms on entry to the trial included diarrhea, fever, and anorexia. Drug-related adverse effects were observed in some patients. Gastrointestinal reac-

tions such as nausea and poor appetite were most common but were effectively managed with symptomatic therapy.

We performed drug susceptibility tests on *M. tuberculosis* isolated from 33 of 49 culture-positive patients with intestinal TB (data not shown). Although isoniazid resistance was seen in five patients (two in the 6-month group and three in the 9-month group), these patients did not receive second-line drugs and achieved complete responses after their scheduled therapies. Thus, the clinical significance and use effectiveness of isoniazid and second-line drugs in a setting of low-level isoniazid resistance are not yet clear. As noted previously, isoniazid use was associated with better survival rates in patients with multidrug-resistant *M. tuberculosis* strains that were susceptible to higher isoniazid concentrations (16).

The strengths of this study are that intestinal TB diagnosis was confirmed histologically and/or bacteriologically in most patients (77%); diagnostic accuracy was thus high. Also, follow-up duration was longer than that in previous studies. Although one report from South Korea (25) compared 9-month and 15-month therapies in intestinal TB patients, that study differs from ours in that only 23% of patients showed pathognomonic histologic findings and the sample size was comparatively small. Our findings must, however, be interpreted against the background of potential limitations. First, careful consideration has to be given to outcome interpretation because the trial was not double blind. Also, we did not identify mycobacterial species other than *M. tuberculosis* in this study, so patients who might have enterocolitis caused by nontuberculous mycobacteria were not completely excluded. In addition, we excluded patients with impaired immunity, such as those with HIV infections or malignancies or patients using immunosuppressants, because their inclusion would complicate disease assessment and follow-up data. Although recommendations for TB treatment in HIV-infected patients are generally the same as those for HIV-uninfected patients (4), further work is needed to determine whether 6-month therapy is also sufficient in immunocompromised intestinal TB patients.

In conclusion, as the 6-month regimen was equal in effectiveness to the 9-month protocol, the 6-month course can be recommended for routine use in intestinal TB patients and offers the benefits of increased compliance and reduced cost. Double-blind trials are required to validate our recommendation.

ACKNOWLEDGMENT

No conflicts of interest exist.

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