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Adjunctive Corticosteroid to Counteract Adverse Drug Reactions from First-Line Antituberculous Drugs

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Abstract

Several first-line antituberculosis (anti-TB) drugs, including isoniazid (H) and rifampicin (R), often produce Adverse Drug Reactions (ADRs) that may contribute to incomplete anti-TB therapy.

A retrospective study was designed to assess the impact of corticosteroid therapy on anti-TB ADRs and TB relapse following treatment completion.

TB patients who had received prednisolone during anti-TB therapy were selected. Thirty patients who had completed TB therapy using corticosteroid were compared with thirty age-, gender- and severity-matched control subjects to examine the rate of TB relapse.

Out of the 37 patients meeting the screening criteria. Twenty patients received desensitization therapy while completing the anti-TB regimen. There was one case of TB relapse both groups.

Patients receiving prednisolone derive modest benefits in reducing anti-TB ADRs, but there was no increase in the rate of TB relapse in the corticosteroid group.

Keywords: Antituberculosis (anti-TB) drugs; Adverse drug reactions (ADRs); Prednisolone

Introduction

Inclusion of H and R in anti-TB drug regimen is critical to highly effective short-duration TB treatment. Completion of anti-TB therapy is severely compromised when H or R are removed from treatment regimens. Unfortunately, H or R induces ADRs and physicians may initiate desensitization therapy to promote anti-TB therapy completion. When desensitization therapy does not mitigate the anti-TB ADRs, anti-TB therapy is often delayed. Previous studies suggest that corticosteroid adjust therapy may improve anti-TB drug ADR management. In this study, patients receiving prednisolone to counteract ADRs, despite desensitization therapy, display modest benefits in anti-TB treatment completion.

Methods

Between January 1, 1998, and December 31, 2008, 792 TB patients were admitted to the National Hospital Organization Matsue Medical Center, a 350-bed hospital with 12 TB beds, for anti-TB treatment. An extensive hospital record review was performed for thirty-seven patients who received prednisolone had more than two years pass since the completion therapy, and had TB strains sensitive to first-line anti-TB medications. Prednisolone was administered if patients presented persistent high-grade fever (temperature > 38.0°), persistent eruption or liver dysfunction (three times over normal range of ALT). Patients received an initial daily regimen of 5 or 10 mg of prednisolone, in accordance with Japanese Society for TB (JST) propositions [1] (Table 1), when desensitization therapy or withdrawal of anti-TB drugs failed to resolve ADRs. If ADRs persisted, prednisolone dosage was increased gradually by 5 or 10 mg and prednisolone therapy was terminated after ADR resolution. An age-, gender- and severity-matched comparison group of 30 subjects without corticosteroid usage was included. Severity was determined by National Tuberculosis Association (NTA) classification [2]. Positive TB samples were determined by selective staining using the fluorochrome procedure with auramine and rhodamine stains and positive smears were confirmed by Ziel-Neelsen stain.

Statistical analysis was performed using Dr. SPSS II for Windows 2003 and data were expressed as means ± SD. Two group comparisons were performed using Student's unpaired t test. Severity comparisons were performed using chi-square test.

	Isoniazid	Rifampicin
Day 1	25 (mg)	25 (mg)
2	25	25
3	25	25
4	50	50
5	50	50
6	50	50
7	100	100
8	100	100
9	100	100
10	200	200
11	200	200
12	200	200
13	300	300
14	300	300
15	300	300
16	400	400

(Japanese Society for Tuberculosis, 1997)

Table 1: Desensitization therapy for isoniazid and rifampicin.

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Male n (%)	24 (65)
Age, yr (median, yr)	73.9±14.9 (78)
Clinical diagnosis	
Pulmonary TB	26
Miliary	5
Pulmonary and pleural	4
Pleural TB	2
Initial treatment with Z n (%)	23 (62)
Main adverse effect	
Liver dysfunction	14
Eruption	9
Fever	8
Others	6
Total deaths	7
Cause of death	
Congestive heart failure	5
Renal failure	1
Cerebral infarction	1
LST (positive:negative)	10:14
Treatment completion n (%)	30 (81)
Final treatment	
HRE	25
HREZ	2
Others	3

TB: tuberculosis, LST: lymphocyte stimulation test, H: isoniazid
R: rifampicin, E: ethambutol, Z: pyrazinamide

Table 2: Characteristics of the patients.

Results

Thirty-seven TB patients receiving prednisolone (24 men, 13 women), ranging in age from 34 to 91 years (73.9 ± 14.9 years, median age 78.0 years), were included in this study. The underlying disease was pulmonary TB in 26 patients, miliary TB in five, pulmonary and pleural TB in four and TB pleuritis in two (Table 2). Sputum cultures were positive in all pulmonary TB patients, excluding two TB pleuritis cases that were diagnosed by pleural culture or polymerase chain reaction. Ten patients were diagnosed with cavitary pulmonary TB and no patients died from cavitary lesions. Fourteen patients reported a liver dysfunction adverse reaction, nine had eruption, eight had fever, and six others displayed aggravation. Independent of TB progression, seven patients (18.9%) died during the study time frame, five from congestive heart failure and one each from renal failure and cerebral infarction. Of the twenty-four patients having Lymphocyte Stimulation Tests (LST) performed, fourteen patients were negative and ten were positive with eight to H and one each to R or levofloxacin (LVFX).

Initially, fourteen patients received HRE while the 23 remaining patients were administered HRE + pyrazinamide (Z). Full doses anti-TB regimens were achieved at 29.1 ± 28.6 days. The final drug regimens of 30 patients who completed TB treatment included 25 receiving HRE, two receiving HREZ and one each receiving R + ethionamid (TH) + streptomycin (S) + LVFX, REZ + ciprofloxacin or HRS + LVFX. Due to anti-TB ADRs, desensitization therapy was used in conjunction with prednisolone in 20 patients during the treatment course. Prednisolone treatments ranged from 13-365 days (143.6 ± 108.1 days) and the average dose was 20 mg per day. Eight patients received less than 10 mg of prednisolone per day, eighteen received 10 mg, two received 15 mg, five received 20 mg, and four received 30 mg. Negative sputum culture conversion was 37.4 ± 27.2 days (Table 3).

There was one case of TB relapse both in the corticosteroid usage group and one in the age-, gender- and severity-matched control group (Table 4). The only case of TB relapse in the corticosteroid group was a diabetic man, who was administered 10 mg of prednisolone for 62 days due to liver dysfunction, had a relapse of TB fifteen months after completion of HRE therapy for twelve months. Fever subsided after anti-TB therapy was supplemented with prednisolone (Figure 1).

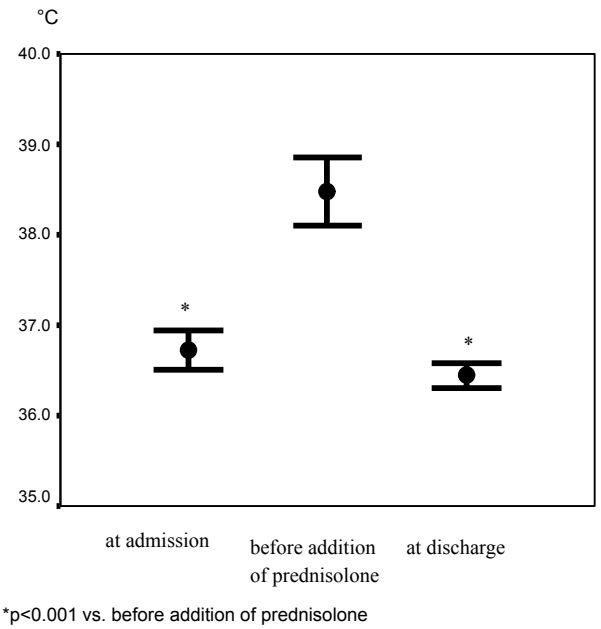
Initial dose	
Less than 10 mg	8
10 mg	18
15 mg	2
20 mg	5
30 mg	4
Average initial dose (mg)	20±0
Administration period (days)	143.6±108.1
Days to full dose of antituberculous drugs (days)	29.1±28.6
Negative sputum culture conversion (days)	37.4±29.2

Table 3: Prednisolone dosage.

Variables	Steroid group (30)	Control group (30)
Age, yr	71.1±15.0	71.3±14.9
Body weight, kg	49.3±9.5	47.6±7.4
Albumin, g/dl	3.4±0.7	3.7±0.6
Lymphocyte, 10^3/μl	1.1±0.5	1.2±0.6
Hemoglobin, g/dl	11.7±0.2	12.1±0.2
Severity (NTA) Min MA FA	 5 17 8	 5 21 4
TB relapse	1	1

NTA: National Tuberculosis Association, Min: Minimal, MA: Moderately Advanced, FA: Far Advanced

Table 4: Characteristics in the Patient Population.



*p<0.001 vs. before addition of prednisolone

Figure 1: Body temperature pre- and post-prednisolone administration.

Discussion

Previous studies suggest that corticosteroids mitigate anti-TB ADRs; however, the role of corticosteroids in TB treatment is unclear. Underlying diseases or conditions for which steroids and other immunosuppressive medications are administered may play a substantial role in TB risk enhancement [3]. According, the American Thoracic Society (ATS) /Centers for Disease Control (CDC) and Prevention Treatment of Tuberculosis Guidelines indicate that a two to three week regimen of more than 15 mg per day of prednisolone increases the risk of TB, although there is no clinical trial data to support this observation. Conversely, corticosteroid adjunct therapy may reduce persistent fever in particular forms of TB [4,5], and TB-associated inflammation may respond to steroid therapy to alter outcomes in TB meningitis or constrictive pericarditis [6,7].

The effects of prednisolone to counteract ADRs of anti-TB medications, especially H or R, are examined in this study. H and R are the two most significant first-line medications used for TB treatment in this era and each drug is critical to highly effective, short-duration treatment. As such a 6-month, all-oral, curative therapy is common with HR regimen [8]. When R cannot be administered, patients can expect a 9-month short-course treatment or longer and, if both H and R are removed from treatment regimens, anti-TB therapy success is compromised substantially [3]. In this study, prednisolone enabled H or R to be administered after the appearance of ADRs, resulting in only one TB relapse case and high treatment completion for the entire cohort. By comparison, U.S.Public Health Service Trial 21 (USPHS21) used a daily self-administered regimen of H and R for 6 months, supplemented by daily Z for the first 2 months of treatment (E was added to the regimen if patients had a history of prior treatment with H or had immigrated to the United States within the past 30 years from a country where a high proportion of patients had drug-resistant disease) [9]. The rate of ADRs for the USPHS 21 6-month regimen was 7.7%, with a TB relapse rate of 3.5% using a 24-month follow-up. Conversely, in this study the TB relapse rate was 2.8% using a 12-month follow-up period, despite the rate of cases with Z was only 6.7%. The treatment duration should be extended three months, from nine to twelve, following JTS and ATS/CDC Guidelines [10,11].

Desensitization therapy is employed when H or R cannot be prescribed due to ADRs. The initial dose of 25 mg/day of H or R is increased gradually every three days over a period of more than two weeks in the desensitization therapy proposed by JTS [1]. When desensitization therapy cannot resolve ADRs, second-line anti-TB drugs are often prescribed, even though these drugs increase duration of treatment and often produce resistant TB strains. Prednisolone may have limited effects on controlling anti-TB ADRs as one study found that patients harboring TB strains resistant to more than one first-line drug had unfavorable responses [12]. Therefore, cases demonstrating resistance to first-line drugs were omitted from the present study.

Several limitations were observed during analysis. First, this retrospective study is a non-randomized open study with a small sample size (n=37). Second, prednisolone initiation dosage and treatment duration are not consistent among all patients. Lastly, follow-up data is constrained due to the 24-month period. However, these results indicate that prednisolone provides some benefit to counteract anti-TB ADRs. Future studies should increase sample size, standardize prednisolone dosage and duration, and examine TB relapse over a longer post-treatment time period to assess the effects of prednisolone on anti-TB ADRs.

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