Research Article

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Adverse Drug Reactions and Their Impact on the Treatment of Pulmonary Tuberculosis

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ABSTRACT

Background: Although there have been some reports about adverse drug reactions (ADRs) in pulmonary tuberculosis treatment, there are few detailed data and the effect of age among elderly patients on ADRs and the period of medication discontinuation due to ADRs is unknown.

Purpose: We evaluated the difference in the incidence of ADRs necessitating discontinuation or a change of medication (dADR) among the different age groups and the period of discontinuation in elderly patients undergoing pulmonary tuberculosis treatment.

Subjects and Methods: We conducted a retrospective medical record survey of patients who started anti-tuberculosis medication at our hospital from April 1st, 2018 to March 31st, 2020.

Results: A total of 120 patients were recruited. There was no significant difference in the incidence of dADR among the different age groups every 10 years in patients ≥ 50 years of age ($p=0.78$). The median period of discontinuation was approximately 4 weeks for fever (29.5 days), approximately 3 weeks for rash (18.5 days), approximately 2 weeks for gastrointestinal disorders (16 days), and hepatocellular liver injury (15.5 days), and approximately 1 week for cholestatic liver injury (8 days) and eosinophilia (7 days).

Conclusion: The incidence of dADR was not different among the age groups when patients of ≥ 50 years of age were compared by age. The median times of onset were 1–3 weeks after the start of treatment. The median periods of discontinuation were 1–4 weeks, and the period of discontinuation due to allergic reactions tended to be the longest.

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Introduction

The rate of elderly patients with tuberculosis has continued to increase in Japan [1, 2]. Mortality also increases as patients become older [3-10]. Elderly patients have a poor prognosis because they usually have several comorbidities including cancer, cerebrovascular accident, aspiration pneumonia, and hypo nutrition [4, 11-23]. In addition, a poor performance status and difficulty of oral intake are associated with a poor prognosis in elderly patients [3, 24]. Thus, the management of adverse drug reactions (ADRs) during tuberculosis treatment in elderly patients is a topic of interest. It has been reported that the incidence of ADRs in patients treated with anti-tuberculosis agents is higher in patients who are ≥ 60 years of age than in those who are < 60 years of age [11, 25-28]. However, it is unclear whether the incidence of ADRs increases with age among elderly patients. Furthermore, the time of onset and the period of discontinuation of anti-tuberculosis agents due to ADRs is unclear. We therefore evaluated the difference in the incidence of ADRs necessitating discontinuation or a change of

drug (dADRs) between age groups, as well as the time of the onset of dADRs, and the period of discontinuation due to dADRs among elderly patients.

Subjects and Methods

Subjects

Patients who started pulmonary tuberculosis treatment in the Department of Respiratory Medicine, National Hospital Organization Wakayama Hospital from April 1st, 2018 to March 31st, 2020 were retrospectively recruited based on medical records. The study was approved by the local ethics committee (IRB committee of National Hospital Organization Wakayama Hospital; authorization number: 02-6, approval date: March 17, 2021), and was registered with the University Hospital Medical Information Network (UMIN000043605). The contents of this study and the opportunity to reject the agreement were explained on the website of the National Hospital Organization Wakayama Hospital.

Endpoints

The primary endpoints were the difference in the incidence of

dADRs by age among patients of ≥ 50 years of age, the time of the onset of dADRs, and the period of discontinuation due to dADRs. The secondary endpoints were the incidence of dADRs, the factors associated with the occurrence of dADRs, the difference in the time of onset among all types of dADRs, and the difference in the period of discontinuation among all types of dADRs.

Definitions

The types of dADR were defined according to the Guide for Tuberculosis of The Japanese Society for Tuberculosis [29]. The decision to discontinue treatment was basically based on the recommendation of the Japanese guideline, but the final decision was made by the attending physician. The time of onset was defined as the number of days from the start date of treatment to the date of discontinuation due to a dADR. The period of discontinuation was defined as the period from the date of discontinuation to the date on which the full dose of the effective therapeutic drug could be administered.

Statistical Analysis

The differences in demographic factors between patients with and without dADRs were analyzed using a chi-squared test or t-test.

The incidence rate by age was compared among patients of ≥ 50 years of age by a chi-squared test. The Kruskal-Wallis test was used to analyze differences in the time of onset and the period of discontinuation among the types of dADR. Types of dADR for which only one case occurred were excluded from the analysis of the time of onset and the discontinuation period. P values of <0.05 were considered to indicate statistical significance.

Results

One hundred twenty patients were recruited. The study population included 62 male patients (52%), and the average age was 79.1 years. The maximum smear amount was 2+ in 44 cases and 3+ in 42 cases. The initial treatment was Isoniazid (INH) + Rifampicin (RFP) + Ethambutol (EB) in 65 cases (54%), INH + RFP + EB, and Pyrazinamide (PZA) in 53 cases (44 %), and RFP + EB + PZA + Levofloxacin (NQ) in 1 case who was a contact person of an INH-resistant patient, and RFP + EB + PZA + Streptomycin (SM) in 1 case who had been known to be an INH-resistant patient at the start of treatment. dADRs were observed in 34 cases (28%). There was no clear difference in the demographic factors between the patients with and without dADRs (Table 1).

Table 1: Patient characteristics

	Total	Without dADR	With dADR	p value
n	120	86	34	
Sex (M/F)	62/58	44/42	16/18	0.69
Age	79.1 $\pm$ 15.9	78.8 $\pm$ 17.2	79.8 $\pm$ 12.2	0.76
Maximum smear (-/+1+/2+/3+)	13/5/16/44/42	11/4/14/28/29	2/1/2/16/13	0.31
Disease side (r/l/b)	17/11/92	10/7/69	7/4/23	0.33
Disease type (I / II / III)	16/20/84	10/14/62	6/6/22	0.64
Spread (1/2/3)	12/71/37	7/54/25	5/17/12	0.36
Initial treatment(HREZ/HRE/Other)	53/65/2	38/46/2	15/19/0	0.67

Abbreviations: HREZ, Isoniazid (INH) + Rifampicin (RFP) + Ethambutol (EB) + Pyrazinamide (PZA); HRE, INH + RFP + EB.

The incidence of dADRs in elderly tuberculosis patients ≥ 50 years of age was less affected as the age groups increased from 50-59 years of age, 60-69 years of age, 70-79 years of age, 80-89 years of age and then 90 years of age and over ($p=0.78$) (Figure 1). The 52 total dADR events included hepatocellular liver injury ($n=14$; 27%), rash ($n=12$; 23%), and cholestatic liver injury ($n=8$; 15%) (Figure 2).

Figure 1: The incidence of dADR by age

Gray columns indicate patients with dADRs; open columns indicate patients without dADRs

Abbreviations: dADR, adverse drug reaction necessitating discontinuation or change of medication.

Figure 2: Types of dADR

Abbreviations: dADR, adverse drug reaction necessitating discontinuation or change of medication

The times of onset and the period of discontinuation for each type of dADR are shown in Figures 3 and 4, respectively. The median time of onset for all dADRs was within 1–3 weeks. The median times of onset for specific dADRs were as follows: gastrointestinal disorder, 20 days; rash, 16 days; eosinophilia, 15 days; fever, 13 days; hepatocellular liver injury, 12 days. No significant difference was observed among the types of dADR ($p=0.42$) (Figure 3). The median period of discontinuation was within 1–4 weeks and did not differ to a statistically significant extent among the types of dADR ($p=0.16$). The median periods of discontinuation for the types of dADR were as follows: fever, 29.5 days (approximately 4 weeks); rash, 18.5 days (approximately 3 weeks); gastrointestinal disorder, 16 days; hepatocellular liver injury, 15.5 days (approximately 2 weeks), cholestatic liver injury 8 days, and eosinophilia 7 days (approximately 1 week) (Figure 4). Desensitization therapy was performed for fever (4/5 cases; 80%) and rash (6/12 cases; 50%). There was one treatment-associated death in a patient who experienced hepatocellular and cholestatic liver injury.

Figure 3: The time of onset of dADRs

Short vertical lines indicate the 5th and 95th percentile, the ends of the rectangle indicate the 25th and 75th percentile, and vertical line inside the rectangle indicates the median value.

Abbreviations: dADR, necessitating discontinuation or change of medication.

Figure 4: Analysis of duration of discontinuation by dADRs

Short vertical lines indicate 5 and 95 percentiles, ends of rectangle indicates 25 and 75 percentiles, and vertical line inside the rectangle indicates median value.

Abbreviations: dADR, necessitating discontinuation or change of medication.

Discussion

The incidence of dADR was not different among the age groups when patients of ≥ 50 years of age were compared by age every 10 years. The median time of onset was within 1–3 weeks and the median period of discontinuation was within 1–4 weeks. Allergic reaction tended to require the longest discontinuation period, followed by liver injury. Tuberculosis patients have been getting older. In 2019, patients of ≥ 70 years of age accounted for 61.1% of the newly diagnosed cases in Japan. According to the Statistics Bureau of the Ministry of Internal Affairs and Communications, patients of ≥ 65 years of age and ≥ 75 account for 28.4% and 14.7% of the Japanese population, respectively, while they account for 33.1% and 17.6% of the population of Wakayama Prefecture. The aged population accounts for a greater percentage of the population of Wakayama Prefecture in comparison to the Japan. In the current study, elderly patients of ≥ 70 years of age accounted for 80.0% (96/120 cases) of the study population, while patients of ≥ 80 years of age accounted for 65.8% (79/120 cases). The study population could reflect the features of tuberculosis treatment for elderly patients.

The incidence of ADRs associated with tuberculosis treatment in patients of ≥ 60 years of age has been reported to be higher than that in patients < 60 years of age [11, 25–28]. However, it is unclear whether the incidence of ADRs increases elderly patients as they grow older. In the current study, the incidence of dADRs in the patients of ≥ 60 years of age was higher (40.5 %) than in those < 60 years of age (33.3 %), although the number patients of < 60 years of age only accounted for 13.3% of the study population (16/120 cases). When patients ≥ 50 years of age were compared by age, however, the incidence of dADRs did not differ among the different age groups every 10 years ($p=0.78$). The overall incidence of dADRs was 28% in the current study. Breen et al. reported that the incidence of ADRs requiring a discontinuation of treatment was 15% [30]. Vieira et al. reported that the incidence of ADRs requiring a change of treatment was 3.7% [31]. However, the median age was 35 in the former report and the proportion of young patients of < 60 years of age was 84.2% in the latter report, which indicated the populations of these reports were younger than that of current report. Furthermore, in the latter report,

patients who discontinued medication but who could restart the same regimen were not included. These differences might have been why the incidence of ADRs was lower in comparison to our study.

The time of onset did not differ to a statistically significant extent among the types of dADRs. The median time of onset was within 1–3 weeks after the start of treatment. Sekiya et al. reported that in cases of rash, 80% of cases occurred within 1 month (median: 14 days) in patients treated with INH + RFP + EB + PZA, and 75% of the rash occurred within 1 month (median: 20 days) in patients treated with INH + RFP + EB [32]. Ministry of Health, Labour and Welfare Japan reported that liver injury often occurs until day 15 [33]. The results of these reports were consistent with our results. These results suggested that careful observation up to around 1 month might be required for elderly patients.

There are few reports about the period of discontinuation due to dADRs. In the current study, the average and median period of discontinuation were 16.3 days and 15.5 days, respectively. Although there was no statistically significant difference among the types of dADR, the median period of discontinuation due to allergic reactions (including gastrointestinal disorders, rash, and fever) was the longest (3–4 weeks), followed by liver disorders (approximately 2 weeks), and others (< 1 week). In patients with optic neuropathies and gout, the causative drugs were considered to be EB and PZA, respectively; thus, only the suspected drug was discontinued. Effective treatment with or without an alternative drug was continued. The relatively longer period of discontinuation due to allergic reactions in comparison to other types of dADR might be due to the more frequent implementation of desensitization therapy.

The present study was associated with some limitations. First, the numbers of each type of dADR were small, which may have influenced the time of onset and the discontinuation period. In the future, a large cohort should be analyzed. Second, the outcome might have been affected by the attending physician's decision to discontinue or restart the treatment. Third, the study was performed at a single facility. A multicenter study could be important to determine the

features of dADRs. Fourth, the baseline comorbidities have not been evaluated, which might affect the frequency of dADRs.

Conclusion

The incidence of dADR was not different among the age groups when patients of ≥ 50 years of age were compared by age every 10 years. The median time of onset for all types of dADRs was within 1–3 weeks, and the median period of discontinuation was within 1–4 weeks. The period of discontinuation due to allergic reactions tended to be longer in comparison to the period of discontinuation due to other reasons.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no conflicts of interest in association with the present study.

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