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Frequency of adverse reactions to first-and second-line anti-tuberculosis chemotherapy in a Korean cohort

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SUMMARY

OBJECTIVE: To determine the frequency of and risk factors for major adverse drug reactions (MADRs) associated with anti-tuberculosis treatment at a tuberculosis (TB) referral hospital in the Republic of Korea.

METHODS: Data from an ongoing natural history cohort study were analyzed for permanent regimen changes due to adverse drug reactions and confirmed by chart review.

RESULTS: Among 655 subjects, there were 132 MADRs in 112 (17%) subjects. The most common MADRs were gastrointestinal ($n = 53$), musculoskeletal ($n = 22$), psychiatric ($n = 10$), visual ($n = 9$) and peripheral neuro-pathic ($n = 8$). MADRs were more frequent in subjects being treated with second-line regimens (16%) compared to first-line regimens (2.5%). Drugs frequently associated with MADRs were amikacin (3/10, 30%), line zolid (8/29, 28%), para-aminosalicylic acid (47/192, 24%), pyrazinamide (31/528, 5.8%), macrolides (2/44, 4.5%) and cycloserine (12/272, 4.4%). Fluoroquinolones accounted for a single MADR (1/377, 0.003%), despite widespread usage. In multivariate analysis, infection with multi-or extensively drug-resistant disease and previous history of anti-tuberculosis treatment were risk factors for MADR, with adjusted hazard ratios of respectively 2.2 ($P = 0.02$) and 1.6 ($P = 0.04$).

CONCLUSION: MADRs are common during anti-tuberculosis chemotherapy in this population, occurring in more than one in six subjects. New and less toxic agents to treat drug-resistant TB are urgently needed.

RÉSUMÉ

Déterminer la fréquence et les facteurs de risque de réactions indésirables majeures (MADR) en association avec le traitement anti-tuberculeux à l'hôpital de référence pour la tuberculose (TB) en République de Corée.

On a analysé les données provenant d'une étude cohorte actuelle sur l'histoire naturelle de la TB au sujet des modifications permanentes de régime par suite de réactions indésirables aux médicaments et on les a confirmées par une revue de dossiers.

Parmi 655 sujets, on a noté 132 MADR chez 112 (17%). Les MADR les plus courantes ont été de nature gastro-intestinale ($n = 53$), musculo-squelettique ($n = 22$), psychiatrique ($n = 10$), visuelle ($n = 9$) et neurologiques périphériques ($n = 8$). Les MADR sont plus fréquentes chez les sujets traités par les médicaments de deuxième ligne (16%) par comparaison avec les régimes de première ligne (2,5%). Les médicaments en association fréquente avec des MADR sont l'amikacine (3/10 ; 30%), le linézolide (8/29 ; 28%), l'acide para-aminosalicylique (47/192 ; 24%), la pyrazinamide (31/528 ; 5,8%), les macrolides (2/44 ; 4,5%) et la cyclosérine (12/272 ; 4,4%). Les fluoroquinolones n'ont été responsables que d'un seul MADR isolé (1/377 ; 0,003%) en dépit d'une large utilisation. Dans l'analyse multivariée, l'infection par des germes multirésistants et des antécédents de traitement TB antérieur sont des facteurs de risque de MADR, les ratios de risque ajustés étant respectivement de 2,2 ($P = 0,02$) et de 1,6 ($P = 0,04$).

Dans cette population, les MADR sont courantes pendant la chimiothérapie antituberculeuse et concernent plus d'un sujet sur six. Des agents nouveaux et moins toxiques sont nécessaires d'urgence pour traiter la TB à germes résistants aux médicaments.

RESUMEN

Determinar la frecuencia de aparición de reacciones adversas graves (MADR) al tratamiento anti-tuberculoso y los factores de riesgo que se asocian con la misma en un hospital de referencia de tuberculosis (TB) en la República de Corea.

Se analizaron los datos de un estudio de cohortes en curso de realización sobre la historia natural de la TB, en busca de modificaciones permanentes de las pautas terapéuticas debido a la aparición de reacciones adversas y se confirmaron los datos mediante el examen de las historias clínicas.

De los 655 pacientes que recibieron tratamiento, en 112 (17%) se observaron 132 MADR. Las reacciones más frecuentes fueron de tipo gastro-intestinal ($n = 53$), luego del sistema locomotor ($n = 22$), psiquiátricas ($n = 10$), visuales ($n = 9$) y las neuropatías periféricas ($n = 8$). Las MADR fueron más frecuentes en los pacientes que recibían pautas de segunda línea (16%) que en quienes seguían pautas de primera línea (2,5%). Los medicamentos asociados con frecuencia a las reacciones adversas graves fueron la amikacina (3/10; 30%), el linezolid (8/29; 28%), el ácido para-aminosalicílico (47/192; 24%), la pirazinamida (31/528; 5,8%), los macrólidos (2/44; 4,5%) y la cicloserina (12/272; 4,4%). Pese a una utilización muy difundida, las fluoroquinolonas causaron solo una reacción adversa grave (1/377; 0,003%). Según el análisis multifactorial, los factores de riesgo asociados con las reacciones adversas graves fueron la infección por una cepa multidrogorresistente o extremadamente drogorresistente y el antecedente de tratamiento antituberculoso (cociente de riesgos instantáneos ajustado 2,2; $P = 0,02$ y 1,6; $P = 0,04$ respectivamente).

En la población estudiada las MADR son frecuentes durante el tratamiento antituberculoso y se presentan en uno de cada seis pacientes. Se necesitan con urgencia nuevos medicamentos menos tóxicos para el tratamiento de la TB farmacorresistente.

Keywords

drug-resistant tuberculosis; drug toxic-ity; linezolid

TUBERCULOSIS (TB) claims an estimated 3 million lives per year worldwide.¹ This ongoing mortality is attributable not only to human immunodeficiency virus (HIV) co-infection but also to rising levels of drug resistance. Globally, it is estimated that there are approximately half a million multidrug-resistant TB cases (MDR-TB, defined as resistance to at least isoniazid and rifampicin), 10–25% of whom are believed to be extensively drug-resistant (XDR-TB, MDR-TB plus resistance to a fluoroquinolone [FQ] and to kanamycin [KM], amikacin [AMK] or capreomycin [CPM]).² Prior to widespread use of FQs in the treatment of MDR-TB, patient outcomes were unacceptably poor. In one study comparing treatment outcome and mortality in MDR-TB patients from a single institution before and after the introduction of FQs (ofloxacin given to 64%), treatment success rates increased from 56% to 75% and mortality rates declined from 37% to 12%. More recently, with the use of later generation FQs such as levofloxacin and moxifloxacin, treatment success for MDR-TB has been reported to be as high as 85%.³ As XDR-TB cases increase and the efficacy of FQs and injectable agents diminishes, a similar negative impact on treatment outcome and mortality has again been observed.⁴

In the Republic of Korea there has been an increase in the number of MDR- and XDR-TB cases over the last decade² in both public⁵ and private sector treatment facilities.^{6–8} XDR-TB in particular is associated with higher mortality rates.^{9–11} In one retrospective analysis of patient data from 273 individuals diagnosed with XDR-TB without HIV co-infection, 48% died of TB-related mortality, with a mean survival of 51 months after the time of diagnosis.¹²

In this setting of emerging drug resistance, the use of drugs other than first-line agents has become increasingly necessary, yet there is little consensus on optimal regimens or evidence of the efficacy of many of these drugs.¹³ Furthermore, agents are being used in combinations that are often tailored to drug susceptibility testing (DST) results from patient isolates without evidence regarding the long-term safety or potential antagonism of co-administration of these agents. Regimens containing these agents are recognized to be more toxic than first-line agents, and side effects requiring the interruption of these agents occur in 19–55% of exposed individuals.^{14–18} As new agents are introduced into this complex situation, a more complete understanding of the range and frequency of side effects in patients being treated for MDR- and XDR-TB is clearly necessary.

In the present study, we examined major adverse drug reactions (MADRs), defined as adverse events leading to permanent discontinuation of a drug, in a prospective cohort treated with first- and second-line anti-tuberculosis regimens at a TB referral center in the Republic of Korea.

METHODS

Study population

Study subjects were enrolled in a prospective cohort ‘TB Natural History’ study at the National Masan Tuberculosis Hospital (NMTH), a referral hospital in the Republic of Korea ([ClinicalTrials.gov](https://clinicaltrials.gov) ID number NCT00341601). The study was approved by the Institutional Review Boards of NMTH and the US National Institutes of Allergy and Infectious Diseases (NIAID). The subjects evaluated were enrolled between May 2005 and August 2009. All subjects provided informed consent, and the study was conducted using good clinical practice and independently monitored for compliance.

Data collection

Quarterly chart abstraction was performed to identify adverse events (AEs), regimen changes and reasons for regimen change. Any combination of symptoms within a single type of event was counted as one event (i.e., a subject with nausea and diarrhea was counted as having a single gastrointestinal ADR). All data were noted in case report forms (CRFs) and entered into a customized database. TB drugs used in this cohort are listed in Table 1. Regimens were prescribed as per NMTH guidelines, and for the purposes of analysis were classified as first-line, intensive second-line (including an injectable agent), and ‘other’ second-line (without an injectable agent; Figure).

Outcome determination and statistical methods

MADRs were defined as an ADR that led to permanent discontinuation of a drug. For MADR identification, the study database was queried for regimen changes attributed to an ADR. The drug to which these events were attributed was determined by comparing the regimen before and after a regimen change due to an ADR, and then the specific ADR type was determined by cross-referencing the data. This information was confirmed by chart review. Chart review of 124 subjects with suspected MADRs confirmed that 132 MADRs occurred in 112 subjects. Subjects were eliminated from the analysis based on the following: co-enrollment in an ongoing placebo-controlled trial ($n = 3$), chart review revealed that no drug/s was permanently discontinued ($n = 9$), and subjects voluntarily chose to discontinue the drug ($n = 2$).

The unadjusted (univariate) and adjusted (multivariate) hazard ratios (HRs) for a first MADR event were calculated for several subject characteristics, along with their 95% confidence intervals (CIs), using Cox proportional hazards regression. *P* values were calculated using standard Wald tests from the Cox regression. Due to missing data (mostly in the DST pattern), only 558/655 (85%) observations were used in the multivariate analysis. All tests were two-sided and performed with an alpha level of 0.05. Statistical analysis was performed using SAS (version 9.2; SAS Institute Inc, Cary, NC, USA) and *R* (version 2.11.1; R Foundation for Statistical Computing, Vienna, Austria) softwares.

RESULTS

Frequency and type of MADRs

Of 655 treated subjects evaluated, we observed a total of 132 MADRs in 112 (17%) subjects. The MADR types observed were gastrointestinal ($n = 53$), musculoskeletal ($n = 22$), psychiatric ($n = 10$), visual ($n = 9$), peripheral neuropathy ($n = 8$), hepatitis ($n = 7$), auditory ($n = 5$), hypersensitivity/rash ($n = 4$), headache ($n = 2$), vestibular (vertigo / dizziness; $n = 1$), hypothyroidism ($n = 2$), seizure ($n = 2$), injection site reaction ($n = 2$), neutropenia ($n = 1$), pancytopenia ($n = 1$), peri-oral numbness ($n = 1$), and non-specific generalized tingling after injection ($n = 1$; Table 1).

Frequency of MADRs in second-line treatment

The majority of the subjects included in this analysis were ultimately treated with second-line antituberculosis regimens that were typically administered in two phases: an intensive phase, with an injectable agent, for approximately 7 months, followed by a continuation phase without the injectable agent for a total treatment duration of 18–24 months after culture conversion to negative.¹⁹ Many subjects were initially treated with first-line agents while awaiting DST results to design an appropriate second-line regimen. For analysis, we grouped the regimen types as first-line regimens containing World Health Organization (WHO) Group 1 drugs alone or in combination; and second-line regimens containing any agent from WHO Groups 2–5 with or without any drugs from Group 1. Second-line regimens were further divided into intensive second-line regimens, i.e., those containing an injectable agent (WHO Group 2) given during the initial intensive phase of therapy, or ‘other’ second-line regimens, i.e., those without an injectable agent. In the majority of subjects, ‘other’ second-line regimens re-presented the continuation phase of therapy after the intensive phase; however some subjects, typically those with chronic XDR-TB and an extensive treatment history, never received an injectable agent while in the study, and they were also included in this group.

The 655 subjects included in the analysis were prescribed a total of 1224 regimen types (often sequentially, as noted above), of which 472 (39%) were first-line and 752 (61%) were second-line regimens. Among the second-line regimens, 351 (47%) included an injectable agent (intensive second-line regimen). Of the 1224 regimen types prescribed, 132 (11%) had an MADR during the course of treatment. Subjects receiving first-line regimens experienced only 12 MADRs (2.5%). Of the 752 second-line regimens prescribed (intensive and ‘other’), 120 (16%) resulted in an MADR. Most MADRs on second-line treatment occurred while a subject was receiving an intensive second-line regimen (110, 31%), compared to only 10 MADRs (2.5%) that occurred in subjects receiving ‘other’ second-line regimens (Figure).

Subject risk factors for development of an MADR

Table 2 presents the unadjusted (univariate) and adjusted (multivariate) HRs for a first MADR event and the corresponding 95% CIs for several subject characteristics. In the univariate analysis, the unadjusted HR of having an MADR was 1.69 fold higher (95% CI 1.10–2.61) among females than males. Previous anti-tuberculosis treatment (vs. no prior treatment) was associated with a 2.38-fold increase in the HR of having an MADR (95% CI

1.37–4.14). MDR-and XDR-TB were both associated with a significantly higher HR of an MADR than the non-MDR-/XDR-TB group. Combining the MDR-and XDR-TB groups together, an individual's HR of having an MADR was 2.11 times higher (95% CI 1.36–3.26) than for those with no MDR-/XDR-TB (data not shown). Due to the similarity of the MDR-and XDR-TB HRs in unadjusted analysis, and the relative rarity of XDR-TB, these categories were combined for the multivariate analysis.

The adjusted HRs for the occurrence of an MADR were similar to those from the univariate analysis, although the association with sex was no longer significant ($P = 0.12$). Due to missing data (mostly in the DST pattern), only 558/655 (85%) observations were used in this analysis. In the multivariate analysis, prior treatment history remained significant, with an HR of 2.18 (95% CI 1.13–4.20), as was having MDR-/XDR-TB on initial DST, which had an HR of 1.63 (95% CI 1.02–2.59) relative to those with drug-susceptible TB.

Drug-specific MADRs

The drugs or drug classes most frequently discontinued due to MADR were AMK (3/10, 30%), linezolid (LZD; 8/29, 28%), para-aminosalicylic acid (PAS; 47/192, 24%), pyrazinamide (PZA; 31/528, 5.8%), macrolides (2/44, 4.5%) and cycloserine (CYC; 12/272, 4.4%). FQs accounted for only a single MADR (0.3%, 1/377), despite widespread use. On one occasion, PAS and prothionamide were permanently discontinued simultaneously, but for all other MADRs only one drug was suspect. The MADR types seen with specific drugs, including more details, are summarized in Table 1.

DISCUSSION

Our study reveals that MADRs are common with anti-tuberculosis chemotherapy, particularly with AMK, LZD, PAS, PZA, macrolides and CYC. Subjects treated with second-line regimens are more likely to experience an MADR, particularly during the intensive phase of treatment when an injectable agent (streptomycin, KM, CPM and AMK) is included in the regimen, suggesting that these agents may potentiate the toxicity of the other anti-tuberculosis drugs used in the regimen. The specific reason for this is not clear, but may be due to polypharmacy, a known risk factor for ADR events in general.²⁰ FQs were often used and were well tolerated in this population, accounting for only a single MADR.^{18,21} Dangerous side effects of FQs, such as tendon rupture, psychosis or cardiac arrhythmias, were not seen. Furthermore, those with a regimen including AMK had a disproportionate amount of oto-toxicity compared to other injectable agents, occurring in 30% of subjects, in agreement with previous findings in the literature.²²

Other studies have reported ADRs with first-or second-line agents alone but not in a cohort treated with both first-and second-line agents; this is the first large, prospective cohort study in the Republic of Korea to report such events. In four prior reports of individuals being treated for MDR-TB with second-line regimens, between 19% and 55% experienced an MADR that led to the cessation of at least one anti-tuberculosis medication.^{11,14,15,18} In the group described here, the MADRs seen during treatment with second-line regimens was in this range, at 16%; however, if an injectable agent was included as part of the regimen, the proportion of subjects with an MADR nearly doubled, to 31%. These numbers may under-or

overestimate the risk for several reasons, and these results cannot therefore be generalized to the entire population of Koreans on anti-tuberculosis treatment. As this study population is from a TB referral hospital, and many subjects may already have been exposed to second-line agents, there may be selection bias for those who have tolerated these agents in the past and thus are less likely to have an event. This selection bias may have also led to an overestimate of MADRs, as some MADRs may result from cumulative exposure to a drug, putting those with prior exposure at an increased risk.

In two studies of individuals being treated with first-line agents, between 5.1% and 11% experienced an adverse event leading to permanent drug discontinuation, meeting our definition of an MADR.^{16,17} In our study, 2.5% of first-line regimens prescribed resulted in an MADR. This may be an underestimate of risk, as some subjects were lost to follow-up or were changed to second-line agents after the DST results became available, reducing the cumulative exposure to first-line agents. Despite the limitations of this study, it is clear that second-line TB drugs are toxic and are frequently discontinued. These findings confirm the toxicities of older TB drugs such as PZA (arthralgias), PAS (gastrointestinal and hypothyroidism), aminoglycosides (oto/vestibular toxicity, particularly AMK), ethambutol (visual), and CYC (seizure and psychiatric).²³ Furthermore, the hematologic and neurologic toxicity of LZD, a drug increasingly being used in the treatment of drug-resistant TB, are high-lighted. Anecdotally, LZD toxicity may be mitigated without losing efficacy by using lower doses, but this has not been studied in a controlled, prospective fashion.^{13,24,25} An ongoing study, 'Linezolid to treat extensively drug-resistant tuberculosis' (NCT00727844), is attempting to answer these questions.

In summary, the development of more efficacious and better tolerated anti-tuberculosis drugs is urgently needed to improve the management of patients afflicted with MDR-and XDR-TB disease. In addition, information is needed to optimize the efficacy and limit the toxicity of drugs being used for the treatment of TB, both on and off-label. Finally, with the suggestion that injectable agents may increase the risk of an MADR occurring from any drug, the development of oral alternatives to these drugs should be prioritized.

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Figure.

Number and frequency of MADRs by regimen type. Regimens are categorized based on the drugs they contain, and are often given sequentially. First-line regimens contain only WHO Group 11 drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). Second-line regimens contain at least one drug from WHO Groups 2, 3, 4 or 5; they were further divided into two categories: intensive second-line regimen, which also includes a Group 2 drug (injectable agent), and other second-line regimens, which do not include an injectable agent and are typically administered in the continuation phase after the intensive second-line regimen phase. MADR = major adverse drug reaction; WHO = World Health Organization.

Table 1

Number and frequency of MADR types due to specific drugs

WHO drug group, drug	Times prescribed *	MADR [†] n (%)	MADR types
First-line agents			
Isoniazid	479	5 (1.0)	Rash (<i>n</i> = 3), hepatitis (<i>n</i> = 1), peripheral neuropathy (<i>n</i> = 1)
Rifabutin	32	1 (3.1)	Neutropenia (<i>n</i> = 1)
Rifampicin	441	0	NA
Ethambutol	492	9 (1.8)	Visual disturbance (<i>n</i> = 9)
Pyrazinamide	528	31 (5.9)	Musculoskeletal (<i>n</i> = 22), GI (<i>n</i> = 7), [‡] hepatitis (<i>n</i> = 2)
Injectable agents			
Kanamycin	137	4 (2.9)	injection site pain (<i>n</i> = 2), auditory (<i>n</i> = 1), [§] non-specific whole body tingling (<i>n</i> = 1)
Streptomycin	166	3 (1.8)	Auditory (<i>n</i> = 1), [‡] peri-oral numbness (<i>n</i> = 1), vestibular disease (<i>n</i> = 1) [¶]
Amikacin	10	3 (30)	Auditory (<i>n</i> = 3) [§]
Capreomycin	3	0	NA
Total	316	10 (3.2)	See above
Fluoroquinolones			
Levofloxacin	186	1 (0.5)	Rash (<i>n</i> = 1)
Moxifloxacin	79	0	NA
Ofloxacin	106	0	NA
Gatifloxacin	6	0	NA
Total	377	1 (0.3)	See above
Bacteriostatic agents			
Para-aminosalicylic acid	192	47 (24)	GI (<i>n</i> = 41), [‡] hepatitis (<i>n</i> = 3), headache (<i>n</i> = 1), hypothyroidism (<i>n</i> = 2)
Cycloserine	272	12 (4.4)	Psychiatric (<i>n</i> = 10), [#] seizure (<i>n</i> = 2)
Prothionamide	260	4 (1.5)	Hepatitis (<i>n</i> = 2), GI (<i>n</i> = 2), [‡] hypothyroidism (<i>n</i> = 2)
Agents with possible anti-tuberculosis activity (third-line agents)			
Linezolid	29	8 (28)	Peripheral neuropathy (<i>n</i> = 7), pancytopenia (<i>n</i> = 1)
Clarithromycin	44	2 (4.5)	GI (<i>n</i> = 1), [‡] headache (<i>n</i> = 1)
Roxithromycin	1	0	NA
Amoxicillin/clavulanate	44	2 (4.5)	GI (<i>n</i> = 2) [‡]

* The number of times a drug was prescribed for the entire cohort.

[‡] An adverse reaction that led to the permanent discontinuation of a drug.

[‡]Includes nausea, vomiting, diarrhea, abdominal pain.

[§]Includes hearing loss and tinnitus.

[¶]Includes dizziness and vertigo.

[#]Includes depression, hallucinations, behavioral disturbance.

MADR = major adverse drug reaction; WHO = World Health Organization; NA = not applicable; GI = gastrointestinal.

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Table 2

Distribution of MADR by subgroup along with unadjusted (univariate) and adjusted (multivariate) hazard ratios ($n = 655$)

Characteristic	No MADR	MADR *	Univariate analysis		Multivariate analysis	
			MADR HR (95%CI)	P value [†]	MADR HR (95%CI)	P value ^{†,‡}
All subjects	543	112				
Sex						
Male	466	85	Reference	—	Reference	—
Female	77	27	1.69 (1.10–2.61)	0.02	1.49 (0.90–2.48)	0.12
Age, years						
20–29	89	17	Reference	—	Reference	—
30–39	110	27	1.21 (0.66–2.23)		1.34 (0.70–2.55)	
40–49	164	33	1.07 (0.60–2.93)		1.28 (0.68–2.40)	
50–59	98	20	1.10 (0.57–2.10)		1.24 (0.58–2.65)	
60	82	15	1.09 (0.54–2.18)	>0.50	1.40 (0.66–2.97)	>0.50
No diabetes	421	91	Reference	—	Reference	—
Diabetes	122	21	0.83 (0.52–1.34)	0.44	0.87 (0.51–1.49)	>0.50
No prior treatment	204	15	Reference	—	Reference	—
Prior treatment	337	97	2.38 (1.37–4.14)	<0.002	2.18 (1.13–4.20)	0.02
Subjects with initial DST available	460	99				
Non MDR-/XDR-TB	290	31	Reference	—	Reference	—
MDR-TB only	135	54	2.17 (1.38–3.40)	<0.001		
XDR-TB	35	14	1.90 (1.00–3.62)	0.05	1.63 (1.02–2.59)	0.04

* An adverse reaction that led to the permanent discontinuation of a drug.

[†] Wald test using Cox regression.

[‡] 558/655 subjects had complete data on all covariates for the multivariate analysis.

MADR = major adverse drug reaction; HR = hazard ratio; CI = confidence interval; DST = drug susceptibility testing; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.