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Impact of second-line drug resistance on tuberculosis treatment outcomes in the United States: MDR-TB is bad enough

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SUMMARY

SETTING: The worldwide emergence of extensively drug-resistant tuberculosis (TB) has focused attention on treatment with second-line drugs (SLDs).

OBJECTIVE: To determine the impact on outcomes of resistance to individual SLDs, we analyzed successful treatment completion and death among drug-resistant TB cases in the US national TB surveillance system, 1993–2007 (N = 195 518).

DESIGN: We defined four combinations of first-line drug (FLD) resistance based on isoniazid (INH) and rifamycin, and three patterns of SLD resistance: fluoroquinolones, injectable SLDs and other oral SLDs. We compared treatment outcomes of cases by FLD resistance, with and without each pattern of SLD resistance. RESULTS: In all but one instance, cases with FLD resistance but no SLD resistance had better outcomes than cases with SLD resistance. Rifamycin resistance, alone or with INH, resulted in a greater decline in treatment completion and greater increase in deaths than resistance to SLDs. Among patients with multidrug-resistant TB, additional resistance to injectable SLDs was statistically significant. Outcomes were better for human immunodeficiency virus (HIV) negative than HIV-positive cases for all resistance patterns, but improved among HIV-infected cases after 1998, when highly active antiretroviral treatment became widely available.

CONCLUSION: These results suggest that the effect of rifamycin resistance may outweigh the more modest effects of resistance to specific SLDs.

RÉSUMÉ

L’émergence mondiale de la tuberculose (TB) ultrarésistante a attiré l’attention sur le traitement par les médicaments de deuxième ligne (SLD).

Analyser les traitements complets couronnés de succès ainsi que les décès dans les cas de TB résistante aux médicaments dans le système de surveillance nationale de la TB aux Etats-Unis entre 1993 et 2007 (N = 195 518) pour déterminer l’impact de la résistance à l’égard des différents SLD sur les résultats.

Nous avons identifié quatre combinaisons de résistance aux médicaments de première ligne (FLD) en se basant sur l’isoniazide (INH) et les rifamycines ainsi que trois types de résistance aux SLD :

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les fluoroquinolones, les SLD injectables et d'autres SLD administrés par voie orale. Nous avons comparé les résultats du traitement des cas en fonction de la résistance aux FLD avec ou sans chaque type de résistance aux SLD.

Dans tous les cas sauf un, les résultats ont été meilleurs dans les cas avec résistance aux FLD mais sans résistance aux SLD que dans ceux avec résistance aux SLD. La résistance à la rifamycine isolée ou associée à la résistance à l'INH entraîne une diminution plus marquée des traitements achevés et une augmentation plus importante des décès que la résistance aux SLD. Parmi les patients atteints d'une TB multirésistante aux médicaments, une résistance additionnelle aux SLD injectables s'est avérée statistiquement significative. Les résultats ont été meilleurs dans les cas négatifs pour le virus de l'immunodéficience humaine (VIH) que positifs pour tous les types de résistance, mais ont été améliorés dans les cas infectés par le VIH après 1998 lorsque le traitement antirétroviral hautement actif est devenu disponible.

Ces résultats suggèrent que l'effet de la résistance à une rifamycine pourrait avoir plus de poids que les effets plus modestes de la résistance aux SLD individuels.

RESUMEN

La aparición a escala mundial de la tuberculosis (TB) extremadamente drogorresistente ha focalizado la atención en el tratamiento con los medicamentos de segunda línea (SLD).

Determinar la repercusión de la monorresistencia a SLD en el desenlace clínico; se analizó la compleción y el éxito del tratamiento y la mortalidad en los casos de TB resistente registrados en el sistema nacional de vigilancia de la TB en los Estados Unidos entre 1993 y el 2007 (*N* = 195 518).

Se definieron cuatro tipos de resistencia a medicamentos de primera línea (FLD) con base en la isoniazida (INH) y las rifamicinas y tres perfiles de resistencia a SLD: fluoroquinolonas, SLD inyectables y otros medicamentos de administración oral. Se compararon los desenlaces terapéuticos de los casos de resistencia a los medicamentos de primera línea (FLD) en presencia de cada tipo de resistencia a SLD o en ausencia de los mismos.

En todos los casos con resistencia a FLD sin resistencia a SLD se observaron desenlaces más favorables que en los casos de resistencia a SLD, con la excepción de un caso. La resistencia a las rifamicinas, ya sea exclusiva o asociada con la resistencia a INH, dio lugar a una mayor disminución en la compleción del tratamiento y a un mayor aumento de la mortalidad que la resistencia a los SLD. En los pacientes con TB multidrogorresistente, la resistencia adicional a SLD inyectables fue estadísticamente significativa. Los desenlaces terapéuticos fueron más favorables en los casos sin infección por el virus de la inmunodeficiencia humana que en los casos seropositivos, en todos los tipos de resistencia; sin embargo, el resultado mejoró en los casos coinfectados después de 1998 cuando se generalizó la administración del tratamiento antirretrovírico de gran actividad.

Estos resultados indican que el efecto de la resistencia a las rifamicinas podría pesar más que los efectos más leves de la resistencia a determinados SLD.

Keywords

drug-resistant TB; treatment outcomes; second-line resistance

MULTIDRUG-RESISTANT (MDR) tuberculosis (TB) is defined as TB caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid (INH) and a rifamycin, the two most effective anti-tuberculosis drugs. An epidemic of MDR-TB in the United States during the 1980s and 1990s led to new national guidelines recommending universal culture and drug susceptibility testing (DST) for TB suspects, as well as requirements to report initial DST results through the National TB Surveillance System.[1] This epidemic also brought attention to the uses and limitations of the second-line drugs (SLDs) required to treat MDR-TB.[1] Patients with MDR-TB must endure treatment for up to 2 years with multiple SLDs that have more severe side effects than first-line drugs (FLDs).

Since 1997, the proportion of MDR-TB in the United States has remained at around 1% of reported culture-positive TB cases with no previous history of TB.[2] The worldwide emergence of extensively drug-resistant TB (XDR-TB) has focused attention on testing drug-resistant strains of *M. tuberculosis* for susceptibility to SLDs.[3] National surveillance for drug resistance captures the results of second-line DST, but testing for resistance to SLDs is not performed routinely, but only as indicated, for example in cases with resistance to FLDs. Second-line DST results reported to the National TB Surveillance System (NTSS) have therefore not been thoroughly analyzed.

Treatment of drug-susceptible TB with FLDs is supported by decades of drug discovery, development and controlled clinical trials, quantifying the cure and death rates that can be expected with drug-susceptible TB.[4] In contrast, comparable evidence is not available for drug-resistant TB. Although SLDs are used in the treatment of drug-resistant TB, the impact of SLD resistance on treatment outcomes and mortality has not been defined. Using NTSS data, we identified cases with and without resistance to INH and/or any of the rifamycins who also had DST results available against SLDs. Among those with FLD resistance patterns, we compared cases with and without additional resistance to SLDs to determine the impact of SLD resistance on mortality and on successful treatment completion.

STUDY POPULATION AND METHODS

TB is a notifiable disease, and virtually all cases are reported to the US NTSS, described in detail elsewhere.[5–8] NTSS data represent the entire population of TB cases, not a representative subsample of TB cases. Data were analyzed from 1993 (the start of the current electronic NTSS) until 2007 (the last year for which treatment outcomes data were available at the time of this analysis). Cases reported from the 50 states and the District of Columbia who were alive at the time of diagnosis and who had culture-confirmed TB with reported DST results for INH and rifamycins were included in this analysis. Known treatment outcomes were defined according to NTSS indicators and excluded patients who had moved away, refused or were lost to follow-up. Successful treatment completion is defined as those patients completing antituberculosis treatment, regardless of duration,

which excludes all unfavorable outcomes. Death is indicated for those patients who died during treatment.[5]

Data were collected as part of routine disease surveillance. This was not human subjects research requiring institutional board review or ethical approval.

Reported TB cases from 1993 to 2007 were classified according to their pattern of resistance to four combinations of FLDs (Table 1). These four groups were then further subdivided according to three different patterns of SLD resistance: resistance to fluoroquinolones (FQs) alone, injectable SLDs (kanamycin [KM], amikacin [AMK] or capreomycin [CPM]) alone, or other oral SLDs without resistance to FQs and injectables. Thus, all cases were grouped in one of 12 combinations of FLD and SLD resistance (Table 1).

For each category of FLD resistance, we compared cases with and without additional resistance to each of the three categories of SLDs in terms of successful treatment completion and death. The χ^2 and Fisher's exact tests were used to determine statistical significance. As there were more than 10 distinct analyses, it was assumed that a *P* value of 0.005 (i.e., 10-fold lower than the customary value of 0.05) would reduce the chances of a Type I error.[9] We used stratified analysis to understand the impact of HIV and the availability of highly active antiretroviral therapy (HAART) on treatment outcomes.[10] Data were stratified by HIV status—positive, negative or unknown—to identify whether HIV infection contributed to death. It should be noted that approximately 20% of TB cases are reported by states that do not report HIV data to the Centers for Disease Control and Prevention.[5] As HAART was widely used after 1998, data were stratified by calendar time 1993–1998 vs. 1999–2007 to gauge the impact of HAART.

RESULTS

The total number of cases meeting the inclusion criteria was 195 518. The number of cases in each category of drug resistance is shown in Table 1. As a point of reference, 178 145 TB cases with known treatment outcomes were susceptible to INH and rifamycins; of these, 90% had successful treatment completion and 10% died. With one exception, every pattern of FLD resistance and TB cases with additional resistance to SLDs had lower proportions of successful treatment completion and higher mortality than cases who had the same pattern of FLD resistance but no additional SLD resistance (Table 2). The one exception was INH resistance, where additional resistance to injectable SLDs was associated with a higher proportion of successful treatment completion (92–97.8%) and lower mortality (8.0–2.2%). The remaining 11 resistance patterns were associated with worse outcomes in the presence of additional SLD resistance, but this result was statistically significant in only one pairwise comparison, between MDR-TB patients (resistance to INH and rifamycin) with vs. without additional resistance to injectable SLDs. In general, the magnitude of the difference associated with resistance to injectable SLDs was larger and the *P* value smaller than the difference associated with resistance to FQs. We stratified the results for the injectable drugs by concurrent resistance to FQs (i.e., XDR-TB), and found that additional injectable SLDs still had a greater effect on outcomes, in both strata (data not shown). As these categories were mutually exclusive, the results observed were not due to concomitant resistance to

other drugs. Data stratified by either HIV status (positive, negative or unknown) or time (1993–1998 vs. 1999– 2007) showed that, as expected, those infected with HIV during the earlier time period had worse outcomes. However, neither HIV status nor time appeared to influence outcomes in relation to SLD resistance. In other words, cases with additional SLD resistance had worse outcomes than those without additional SLD resistance (data not shown).

Even more consistent than the association of SLD resistance with outcomes was the association of rifamycin resistance with outcomes. Patients with resistance to a rifamycin had lower successful treatment completion rates and higher mortality rates than patients without rifamycin resistance for every corresponding combination of FLD resistance, both with and without every combination of SLD resistance. For comparison, among patients with INH-and rifamycin-susceptible TB, 90% had successful treatment completion and 10% died; among patients with any rifamycin resistance, 78% had successful treatment completion and 22% died (Table 2).

DISCUSSION

As these data reflect the entire population of TB cases, inferential statistics do not have their conventional meaning. Statistically significant differences have been noted, but differences among groups should be understood as actual differences regardless of *P* value. In terms of treatment outcomes, any INH resistance with additional resistance to SLDs was worse than INH resistance without additional SLD resistance, except for injectable SLDs. Similarly, in cases with any rifamycin resistance, additional resistance to the injectable SLDs was associated with worse outcomes than cases without resistance to injectable agents. In all categories, the outcomes of cases with rifamycin resistance were markedly worse, regardless of resistance to SLDs, suggesting that rifamycin resistance in itself had a singular influence on the efficacy of treatment in this population.

With one exception, every category of FLD resistance with additional SLD resistance fared worse (higher mortality and lower treatment completion) than cases without SLD resistance. The one exception was INH resistance with injectable SLD resistance, as noted above. This may be due to the small number of patients in this group ($n = 46$), in which only one person died.

Among SLD-resistant cases, mortality and successful treatment completion differed most between those with and those without resistance to injectable agents. This may be related to their intrinsic efficacy or to their long-established availability and use. The efficacy of aminoglycosides but not FQs has been documented extensively in controlled clinical trials.[11] It may be that injectables are more effective; however, they have not been compared in head-to-head trials. KM was developed in the 1950s, CPM in the 1960s, and the effectiveness of AMK against *M. tuberculosis* was noted in the 1970s, long before drug resistance surveillance was first incorporated into the NTSS. In contrast, the use of FQs and DST against FQs did not become widespread until the mid-1990s.

An important limitation of this study is that the reporting of second-line DST is not universally required; only 15% of culture-positive cases had second-line DST results reported. However, this study focuses on cases with resistance to FLDs and known DST results for SLDs. Testing for resistance to SLDs is much greater among patients with resistance to FLDs. The Clinical and Laboratory Standards Institute recommends that second-line DST be performed on isolates from patients with any resistance to a rifamycin or resistance to any two FLDs.[12] In addition, as all data are from the NTSS, any conclusions drawn from these data refer to the US population only and may not be applicable to other settings. In general, DST results were reported for 96% of culture-positive cases. However, HIV reporting was only 46% in 1993, increasing to 71% in 2009.[5] Another important limitation is that surveillance data do not capture complete treatment information, which could be important in interpreting outcomes in relationship to DST results.

The majority of patients with drug-resistant TB did not have multidrug resistance. INH resistance without rifamycin resistance is four-fold more common than MDR-TB, 6.5% vs. 1.5%.[12] When patients have any FLD resistance, the use of an SLD becomes an important consideration. For patients with FLD resistance that is not MDR, SLD resistance is associated with a higher rate of failure to complete treatment and a higher rate of death. Among patients with both first- and second-line DST results recorded in NTSS, for nearly every pattern of FLD resistance, patients with additional resistance to FQs, injectable SLDs, or other oral SLD agents had higher mortality and lower rates of successful treatment completion. However, the magnitude of these differences is substantially smaller when comparing rifamycin-susceptible with rifamycin-resistant cases, thus highlighting the crucial role of rifamycins. In virtually every instance, rifamycin resistance was associated with increased mortality and reduced successful treatment completion; this finding is expected, and lends credibility to the analysis and results. The increase in mortality and decrease in treatment completion associated with rifamycin resistance by itself was as great as or greater in many cases than that associated with resistance to any SLDs. Therefore, efforts to preserve the efficacy of rifamycins and prevent MDR-TB should be a high priority.

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Table 1

Combinations of first- and second-line drug resistance

First-line and additional second-line drug resistance	Cases *n*
INH-susceptible, rifamycin-susceptible	178 145
FQ	98
Injectable SLD	76
Other	417
INH-resistant, rifamycin-susceptible	12 894
FQ	49
Injectable SLD	46
Other	1 119
INH-resistant, rifamycin-resistant	3 300
FQ	59
Injectable SLD	201
Other	406
INH-susceptible, rifamycin-resistant	1 179
FQ	5
Injectable SLD	12
Other	31

INH = isoniazid; FQ = fluoroquinolone; SLD = second-line drug.

Table 2

Proportion of cases with outcome treatment completion or died, categorized by FLD and SLD resistance

	% of patients with reported SLD resistance vs. % of patients without SLD resistance Other SLDs					
	Fluoroquinolones		Injectables		Other SLDs	
FLD resistance	Successful treatment completion %	Died %	Successful treatment Completion %	Died %	Successful treatment completion %	Died %
INH-susceptible, rifamycin-susceptible	84.7 vs. 90.0	15.3 vs. 10.0	86.8 vs. 88.9	13.2 vs. 11.1	87.5 vs. 88.4	12.5 vs. 11.6
INH-resistant, rifamycin-susceptible	87.8 vs. 92.8	12.2 vs. 7.2	97.8 vs. 92.0	2.2 vs. 8.0	91.3 vs. 91.8	8.7 vs. 8.2
INH-resistant, rifamycin-resistant	72.9 vs. 76.1	27.1 vs. 23.9	57.2 vs. 77.1 *	42.8 vs. 22.9 *	74.9 vs. 77.8	25.1 vs. 22.2
INH-susceptible, rifamycin-resistant	60.0 vs. 68.0	40.0 vs. 32.0	50.0 vs. 67.5	50.0 vs. 32.5	64.5 vs. 67.0	35.5 vs. 33.0

* $P < 0.005$.

FLD = first-line drug; SLD = second-line drug; INH = isoniazid.