RESPONSE TO SHORT-COURSE CHEMOTHERAPY OF PATIENTS WITH INITIAL RESISTANCE TO ANTITUBERCULOSIS DRUGS[1]

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INTRODUCTION

In 1978 a series of controlled studies were undertaken in the health services of the Santiago Metropolitan Region and Valparaíso that dealt with use of short-course chemotherapy for pulmonary tuberculosis. These studies sought to identify a tuberculosis treatment regimen suitable for use as the standard official therapeutic regimen in Chile's National Tuberculosis Control Program—one that would be highly effective, well-tolerated, and as inexpensive as possible. Accordingly, the studies tried to obtain information that was mainly operational in nature—on such things as rates of inactivation, treatment failures, lethality, toxicity, abandonment of treatment, and relapses observed in the follow-up period *(1-4)*.

Besides this information, however, the studies also yielded a substantial amount of additional bacteriologic and operational data *(5, 6)*. The purpose of the present review was to use these data for evaluating one subject of concern—the presumed negative influence of mycobacterial resistance (present in some study subjects) upon the results of short-course chemotherapy. More specific objectives were as follows:

- to analyze the overall influence of mycobacterial resistance at the beginning of treatment—in terms of the failures and relapses occurring among patients with sensitive and resistant strains;
- to evaluate the respective roles of two major drugs, streptomycin and isoniazid, in the genesis of failures and relapses; and
- to determine whether or not there were differences in the responses of patients with primary resistance as compared to ones with secondary or acquired resistance.

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MATERIALS AND METHODS

The courses of treatment used during the study period are indicated in Table 1. All of the patients included in the study had pulmonary tuberculosis diagnosed by positive direct examination. Some had new cases that had never received antituberculosis therapy, while others had been treated previously but had either abandoned their previous treatment or had experienced a relapse under one of the classic regimens that did not include rifampin or pyrazinamide.

TABLE 1. The short-course (SC) treatment regimens provided for the six groups of study subjects. The numbers after the letters "SC" indicate the year when each regimen was first instituted among the study subjects. The drugs employed are indicated as follows: S = streptomycin; H = isoniazid; R = rifampin; and Z = pyrazinamide.

Identifying code	Regimens[a]
SC-78	$2SHRZ/4S_2H_2R_2$[b]
SC-80	$2SHRZ/4S_2H_2R_2$ $2SHRZ/4S_2H_2$
SC-81	$2SHRZ/5S_2H_2Z_2$ $1SHRZ/6H_2R_2$
SC-82	$2SHRZ/3H_2R_2Z_2$ $2SHRZ/3H_2R_2$
SC-83	$1SHRZ/5H_2R_2$ $1HRZ/5H_2R_2$
SC-84	$1SHRZ/5H_2R_2$ $1SHRZ/4H_2R_2$

[a] The dosages of each drug given to patients weighing 50 kg or more were as follows: streptomycin, 0.75 g in daily phase, 1 g in intermittent phase; isoniazid, 300 mg in daily phase, 800 mg in intermittent phase; rifampin, 600 mg in daily phase, 600 mg in intermittent phase; and pyrazinamide, 2 g in daily phase, 3.5 g in intermittent phase. In patients weighing less than 50 kg, the dosage was adjusted to the patient's weight.

[b] The numbers before each regimen indicate months, while the subscripts indicate times per week during the intermittent phase (e.g., $2SHRZ/4S_2H_2R_2$ indicates two months of streptomycin, isoniazid, rifampin, and pyrazinamide daily followed by four months of streptomycin, isoniazid, and rifampin twice a week.)

For purposes of this study, initial resistance was considered to be resistance shown by the patient's tuberculosis strain(s) at the beginning of treatment, regardless of whether this was primary resistance (in new cases) or secondary (acquired) resistance in patients treated previously who had abandoned treatment or relapsed.

Because of the study's focus on operational research, the standard procedure of the National Tuberculosis Control Program was overridden and all entering patients were tested for sensitivity at the time of diagnosis. These tests were conducted at the central and national reference laboratory of the Chilean Institute of Public Health's Tuberculosis Control Section. The low-cost version of the proportions method described by Canetti, Rist, and Grosset *(7)* was used to test for sensitivity to streptomycin-isoniazid and rifampin, while the Wayne method *(8)* was used to test for sensitivity to pyrazinamide. The results of these tests were not made available to the attending physicians, nor were the therapeutic regimens modified when resistance to one or more of the drugs was encountered.

The six groups of study subjects receiving the regimens shown in Table 1 included a total of 2,978 patients. For purposes of the analysis presented here, the following among them were excluded: (1) patients who died during treatment; (2) patients who abandoned treatment; (3) patients who developed adverse side-effects that called for a change in the therapeutic regimen; and (4) patients who did not take the initial sensitivity test, either for bacteriologic

reasons (the culture was contaminated or negative) or for administrative ones (failure to ask the patient to take the test or failure to send the strain to the central laboratory). In addition, all the patients were excluded who did not have a complete series of bacteriologic control tests or who were not followed for 18 months after completing the prescribed course of treatment.

All of this excluded 1,008 patients, leaving a total of 1,970 study subjects. Of these 1,970, the great majority (1,781) had infections that were initially sensitive to the treatment drugs; 189 showed initial resistance—73 to streptomycin alone and 116 to isoniazid or the isoniazid-streptomycin combination.[4] No cases of resistance to rifampin or pyrazinamide were detected.

Results

Table 2 shows the percentages of failures and relapses observed in each of the six trials among the 1,970 study subjects with sensitive and resistant infections. These figures clearly indicate a larger percentage of failures among the patients with resistant infections. Higher percentages of relapses were also found among the patients with resistant infections, but this finding was not consistent in all six trials.

Overall, only 0.6% of the patients with sensitive infections experienced treatment failures, as compared to 8.5% of those with resistant infections. This difference was found to be statistically significant ($p < 0.01$). On the other hand, the difference in the rate of relapses observed (4.2% in the patients with inactivated sensitive infections versus 5.8% in those with inactivated resistant infections) was not found to be statistically significant.

Table 3 shows the results obtained with patients whose infections were sensitive, resistant to streptomycin alone, or resistant to either isoniazid alone or isoniazid plus streptomycin. These results show that resistance to streptomycin alone was not a determining factor in chemotherapy failures, and that the relapse rate among streptomycin-resistant cases was similar, on the whole, to that of sensitive cases.

As this implies, the cases with initial resistance to isoniazid or isoniazid plus streptomycin accounted for nearly all the failures, the proportion of failures in this group (13.8%) being statistically significant ($p < 0.01$) relative to the proportion of failures among the cases that were sensitive (0.6%) or resistant only to streptomycin (0%). The percentage of relapses was also higher among cases resistant to isoniazid or isoniazid plus streptomycin (7.0% versus 4.2%), but this difference was not statistically significant.

In this same vein, it should be noted that one of the 1983 regimens (see Table 1) did not use streptomycin in the initial phase. However, this regimen did not yield a significantly higher percentage of failures among isoniazid-resistant cases than did the other regimens used that included streptomycin. (A total of 139 patients completed the regimen without streptomycin. Nine of these cases showed initial resistance to iso-

[4] No effort was made to analyze the cases resistant only to isoniazid versus those resistant to both isoniazid and streptomycin because there was no noteworthy difference between these resistant cases with regard to failures and relapses.

TABLE 2. Data indicating the influence of initial resistance upon the results of treatment among the 1,970 study subjects.

Code	Initial sensitivity	Infections rendered inactive		Treatment failures		Subsequent relapses[a]	
		No.	(%)	No.	(%)	No.	(%)
SC-78	Sensitive	416	(98.6)	6	(1.4)	25	(6.0)
	Resistant[b]	48	(90.6)	5	(9.4)	5	(10.4)
SC-80	Sensitive	260	(100.0)	0	(–)	17	(6.5)
	Resistant	11	(78.6)	3	(21.4)	1	(9.1)
SC-81	Sensitive	341	(99.4)	2	(0.6)	5	(1.5)
	Resistant	33	(89.2)	4	(10.8)	2	(6.0)
SC-82	Sensitive	311	(100.0)	0	(–)	5	(1.6)
	Resistant	32	(96.9)	1	(3.1)	0	(–)
SC-83	Sensitive	225	(98.7)	3	(1.3)	13	(5.8)
	Resistant	29	(90.6)	3	(9.4)	1	(3.5)
SC-84	Sensitive	217	(100.0)	0	(–)	9	(4.1)
	Resistant	20	(100.0)	0	(–)	1	(5.0)
Total sensitive (1,781)		1,770	(99.4)	11	(0.6)	74	(4.2)
Total resistant (189)		173	(91.5)	16	(8.5)	10	(5.8)
All study subjects (1,970)		1,943	(98.6)	27	(1.4)	84	(4.3)

[a] Among the patients with infections rendered inactive
[b] Resistant to one or more of the treatment drugs.

TABLE 3. Data indicating the influence of initial streptomycin resistance and initial isoniazid (or isoniazid plus streptomycin) resistance upon the results of treatment.

Initial sensitivity	Infections rendered inactive		Treatment failures		Subsequent relapses[a]	
	No.	(%)	No.	(%)	No.	(%)
Sensitive infections	1,770	(99.4)	11	(0.6)	74	(4.2)
Infections resistant to streptomycin	73	(100.0)	0	(0)	3	(4.1)
Infections resistant to isoniazid or to isoniazid plus streptomycin	100	(86.2)	16	(13.8)	7	(7.0)

[a] Among the patients with infections rendered inactive.

niazid, seven showed resistance only to streptomycin, and 123 were sensitive. There was failure in only one (0.8%) of the sensitive cases, but in two of the nine isoniazid-resistant cases (22.2%). The small number of patients with resistance to isoniazid does not permit definitive conclusions to be drawn from these data.)

Table 4 provides a comparison of the results obtained with cases showing primary resistance (new cases) and cases showing secondary or acquired resistance (previously treated cases). Although the percentages of failures and relapses were higher in the latter group, the differences involved were not found to be statistically significant.

Since five of the regimens employed (one of the 1981 regimens and both of the 1983 and 1984 regimens) had an initial intensive daily phase lasting only one month (providing 26 doses of the indicated drug combinations because supervised antituberculosis regimens in Chile are generally administered on Monday through Saturday), it seemed appropriate to compare the results obtained with these regimens to those obtained with the six regimens that had an initial intensive daily phase lasting two months. This comparison, presented in Table 5, did not reveal any statistically significant differences between the results obtained with the two types of regimens.

Finally, Table 6 indicates the impact of drug resistance upon the effectiveness of the chemotherapy provided for all the study subjects. These figures support the conclusion that initial resistance was not a determining factor in the relapses, even though a relatively high percentage of treatment failures was found among the resistant cases. Overall, the negative impact of resistance appears to have been slight, there being only 16 treatment failures among the resistant cases, representing only 0.8% of all the 1,970 study patients treated.

DISCUSSION AND CONCLUSIONS

Ever since the beginning of tuberculosis chemotherapy, the problem of mycobacterial resistance has been a matter of concern and an ongoing challenge for those who have had to select the therapeutic regimens and design the strategies for control of the disease. It is also a problem that has sometimes been

TABLE 4. A comparison of the results obtained with "new" cases showing primary resistance and previously treated cases exhibiting secondary or acquired resistance.

	Infections rendered inactive		Treatment failures		Subsequent relapses[a]	
Resistant cases	No.	(%)	No.	(%)	No.	(%)
New cases (primary resistance)	128	(92.1)	11	(7.9)	7	(5.5)
Previously treated cases (secondary or acquired resistance)	32	(86.5)	5	(13.5)	5	(15.6)

[a] Among the patients with infections rendered inactive

TABLE 5. Results obtained with sensitive and resistant cases among patients whose regimens (as indicated in Table 1) had an initial intensive daily phase lasting only one month, as compared to the results obtained with regimens that had an initial intensive daily phase lasting two months.

Case sensitivity and length of initial daily phase of treatment	Total No. of cases	Treatment failures		Subsequent relapses[a]	
		No.	(%)	No.	(%)
Initially sensitive cases with a daily treatment phase of:					
One month	573	4	(0.7)	23	(4.0)
Two months	1,138	7	(0.6)	49	(4.3)
Initially resistant cases with a daily treatment phase of:					
One month	68	5	(7.4)	2	(2.9)
Two months	107	11	(10.3)	9	(8.4)

[a] Among the patients with infections rendered inactive.

TABLE 6. Impact of initial resistance to one or more of the drugs used upon the effectiveness of treatment.

Initial sensitivity of infections	Successful treatments (infection rendered inactive, no relapse)		Treatment failures		Relapses		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Sensitive	1,696	(95.3)	11	(0.6)	74	(4.1)	1,781	(100.0)
Resistant to one or more drugs	163	(86.3)	16	(8.4)	10	(5.3)	189	(100.0)
Total	1,859	(94.3)	27	(1.4)	84	(4.3)	1,970	(100.0)

overvalued; for, as the Hong Kong trials *(9)* demonstrated, conventional drug regimens employing reasonable combinations of drugs regularly administered have generally been able to deal adequately with the initial resistance found in a proportion of the tuberculous patients treated. These trials also showed that it was possible to dispense with the sensitivity tests commonly given before starting treatment. Theoretically, short-course chemotherapy using rifampin and pyrazinamide should further improve the situation—a hypothesis confirmed by Mitchison's exhaustive review *(10)* and corroborated in our environment by the present analysis. All of this had made it possible to firmly establish the following points:

- Patients with resistant mycobacterial strains are unquestionably at greater risk of treatment failure than those with initially sensitive strains, as shown by the data in Table 2.
- Initial resistance does not have a significant influence upon the relapse rate after treatment has been completed (see Table 2). This affirms that the risk implied by resistance exists princi-

pally in the early phase of treatment, when large bacterial populations including an important number of resistant organisms are present. The risk is clearly lower in the sterilizing phase, partly because the bacterial populations are smaller and partly because of the activity of rifampin, and, to some extent pyrazinamide, during this phase.

- The negative influence of resistance upon the results of therapy can be seen when the resistance was to isoniazid or isoniazid plus streptomycin. However, as the data in Table 3 indicate, resistance to streptomycin alone does not appear to have played a causal role in failures. This finding is especially important in our country, where the predominant form of resistance among patients with primary resistance is to streptomycin alone *(11)*. These patients with primary resistance are numerically of greatest interest, since more than 80% of the tuberculosis cases reported annually are in new patients who have never received antituberculosis drugs.
- The trials analyzed here (see Table 4) showed a higher proportion of failures among patients with acquired resistance than among those with primary resistance, but the difference was not statistically significant. In other words, patients who had received chemotherapy before appeared to run a slightly greater risk of failure under the short-course regimens. However, this higher risk was small enough so that the research findings support the policy of the National Tuberculosis Control Program—which recommends the same therapeutic regimen for new patients and for those who previously received conventional chemotherapy *(12)*.
- The shortness of the initial intensive one-month phase of treatment was not a determining factor in most cases of failure among resistant patients (see Table 5). This finding lends support to regimens with an initial one-month daily phase, including the official regimen of the National Tuberculosis Control Program ($1SHRZ/6H_2R_2$). Also, no negative influence was observed among resistant patients when streptomycin was eliminated from the 1983 regimen, even though the number of resistant patients involved was so small as to preclude any definitive conclusions.
- Finally, the data in Table 6 indicate that, from an operational viewpoint, the influence of initial resistance on the overall results of treatment was minimal, affecting less than 1% of all the patients—only 16 out of the total of 1,970 who received short-course chemotherapy. This again supports the policy adopted by the National Tuberculosis Control Program several years ago to dispense with the routine sensitivity test at the start of therapy.

It should be emphasized that the stated findings and conclusions emanating from this review are valid for the situation in our environment, where during the study period the rate of primary resistance was between 9.5% and 7.9%, and that of secondary resistance was between 28.2% and 28.9% *(13)*. The conclusions might be quite different in countries or regions where these rates are substantially higher, and might also be quite different if there were an increase in the initial resistance to rifampin, as demonstrated by Mitchison *(10)*, since this creates a much less favorable situation for the patients. These possible scenarios warn us not to be overconfident about the effectiveness of current short-course chemotherapy and to continue reviewing the rationality of the regimens

being used and the regularity of their administration—so as to avoid failures caused by inappropriate regimens and irregular administration, and to prevent "creation" of multiply resistant infections and infections resistant to the currently irreplaceable rifampin.

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Summary

Trials with a variety of short-course tuberculosis treatment regimens employing streptomycin, isoniazid, rifampin, and pyrazinamide were conducted by the health services of Valparaíso and the Santiago Metropolitan Region from 1978 through 1984. Data from these Chilean trials were later used to assess the impact of initial resistance upon the outcome of treatment. This article reports the results of that assessment.

The total number of people participating in the trials was 2,978. However, only those who took the initial sensitivity test, survived the treatment period, completed the full course of treatment, received a full series of bacteriologic control tests, and were followed for 18 months after completing treatment were included in the assessment. This reduced the study population to 1,970.

Among the study subjects, cases initially sensitive to all four drugs were less prone to treatment failure than those initially resistant to isoniazid or isoniazid plus streptomycin. But resistance to streptomycin alone did not appear to play a causal role in failures, nor did initial resistance appear to have a significant influence upon the relapse rate after treatment was completed.

Resistant cases that had received chemotherapy before seemed more prone to failure than resistant cases not previously treated, but the difference observed was not statistically significant. Similarly, comparison of short-course regimens with intensive initial daily phases of one month versus two months did not reveal any significant differences with respect to treatment failures.

In general, the role of initial resistance appeared minimal, accounting for less than 1% of all the treatment failures. This finding lends support to the established national policy of not performing any routine sensitivity test at the start of therapy. However, it should be emphasized that the conclusions reached, while valid for the conditions prevailing in the study population, could be quite different if rates of primary and secondary resistance were substantially higher, or if there were an increase in initial resistance to the currently irreplaceable rifampin.

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