Effectiveness and Tolerance of Antituberculosis Treatment Regimens Without Isoniazid and Rifampicin: Analysis of 85 Cases

José R. Tost,[a,b] Rafael Vidal,[c] José Maldonado,[d] and Joan A. Caylà[e]

[a]Servicio de Urgencias, Hospital de Terrassa, Terrassa, Barcelona, Spain
[b]Servicio de Neumología, CIBERES, Hospital Universitario Vall d'Hebron, Barcelona, Spain
[c]Servicio de Neumología, Hospital Universitario Vall d'Hebron, Barcelona, Spain
[d]Serveis Clínics, Barcelona, Spain
[e]Agència de Salut Pública de Barcelona, Barcelona, Spain

OBJECTIVE: To determine if isoniazid- and/or rifampicin-free antituberculosis treatment regimens are safe and effective and to identify any factors that might require changes in the regimens.

PATIENTS AND METHODS: We carried out a retrospective study of patients treated with isoniazid- and/or rifampicin-free regimens between 1995 and 2005 at 2 specialized hospitals in Barcelona, Spain. Predictive factors were studied by logistic regression and the odds ratio; 95% confidence intervals were calculated.

RESULTS: Eighty-five patients were included in the study: 35% were immigrants and 34% were infected with human immunodeficiency virus. The reason for omitting isoniazid or rifampicin was toxicity (53%), followed by multidrug resistance (39%). Rifampicin-free regimens were most common (42%). A change in the isoniazid- and/or rifampicin-free regimen was required in 30% of cases, but was not associated with being an immigrant. The rate of toxicity with these regimens was higher (36%), although progress was always satisfactory. Clinical course was satisfactory in 77% of patients and they were discharged.

CONCLUSIONS: Isoniazid- and/or rifampicin-free regimens with adequate follow-up showed similar treatment outcomes compared with standardized treatment regimens. Although these regimens were more toxic, patient progress was good.

Key words: *Antituberculosis drugs. Tuberculosis. Drug resistance. Drug toxicity.* Mycobacterium tuberculosis.

Efectividad y tolerancia de las pautas de tratamiento antituberculoso sin isoniacida y/o rifampicina. Análisis de 85 casos

OBJETIVO: Determinar si las pautas de tratamiento antituberculoso sin isoniacida y/o rifampicina (PsHR) son efectivas y seguras, y conocer los factores que obligan a cambiarlas.

PACIENTES Y MÉTODOS: Se ha realizado un estudio retrospectivo de los pacientes tratados con PsHR entre 1995 y 2005 en 2 centros especializados de Barcelona. Los factores predictores se estudiaron mediante regresión logística, calculándose las *odds ratio* y sus intervalos de confianza del 95%.

RESULTADOS: Se incluyó en el estudio a 85 pacientes. Un 35% eran inmigrantes y un 34% estaban infectados por el virus de la inmunodeficiencia humana. La causa de no administrar isoniacida y/o rifampicina fue sobre todo la toxicidad (53%), seguida de resistencia a fármacos antituberculosos (39%). Las pautas sin rifampicina fueron las más frecuentes (42%). Fue preciso cambiar la PsHR en el 30% de los casos y esto se asoció a no ser inmigrante. La toxicidad de las pautas fue más elevada (36%), aunque su evolución fue siempre favorable. El 77% de los pacientes tuvo una evolución satisfactoria y fue dado de alta.

CONCLUSIONES: Las PsHR, con un buen seguimiento, poseen una efectividad similar a las pautas estándar y, aunque su toxicidad es más elevada, ésta sigue una evolución correcta.

Palabras clave: *Fármacos antituberculosos. Tuberculosis. Resistencia a fármacos. Toxicidad farmacológica.* Mycobacterium tuberculosis.

Introduction

Tuberculosis continues to be highly prevalent worldwide, even though effective treatment has been available for more than 30 years.[1] The increased prevalence in the context of the human immunodeficiency virus (HIV) infection epidemic, along with toxicity and increased resistance to antituberculosis drugs, have made it difficult to control the disease around the world.[2] In Spain and other developed countries, treatment results can still be

This study was funded in part by a grant from the Catalan Society de Pneumology (SOCAP) in 2006 for the Development of Pulmonology Research.

Correspondence: Dr R. Vidal
Servicio de Neumología, Hospital Universitario Vall d'Hebron
Pg. Vall d'Hebron, 119-129
08035 Barcelona, Spain
E-mail: ravidal@vhebron.net

Manuscript received July 8, 2007. Accepted for publication January 29, 2008.

improved and the disease continues to be a relevant public health problem.[3,4]

An antituberculosis regimen is considered useful when more than 95% of patients are cured and fewer than 5% of patients develop serious intolerance. Current treatment regimens are based on the concomitant use of at least 3 first-line drugs, which should include isoniazid and rifampicin (for their greater bactericidal potential) as well as pyrazinamide (for its intracellular activity), and should last 6 months. Treatment regimens that meet these requirements and are, therefore, recommended by the World Health Organization consist of 2 months of isoniazid, rifampicin, and pyrazinamide with or without ethambutol, followed by 4 months of treatment with isoniazid and rifampicin. Because these regimens are widely used, they are considered to be the standard ones.[2,5]

Under certain circumstances, however, the main drugs used in current antituberculosis treatment (isoniazid and rifampicin) cannot be administered. The primary reasons are toxicity, drug interactions, and increased appearance of resistance around the world, even in the developed nations as a result of immigration from countries where tuberculosis and resistance are more prevalent.[1,3] The use of isoniazid- and/or rifampicin-free treatment regimens in the situations described increases the complexity, duration, toxicity, and cost[6,7] of treatment and hinders the success of these regimens, which depend on the number of first-line antituberculosis drugs used, in particular, isoniazid and rifampicin, the 2 main drugs in the arsenal due to their high bactericidal power.[8]

Isoniazid- and/or rifampicin-free treatment regimens are being prescribed more and more, yet usage recommendations are still based on expert opinion while we wait for the results of multidrug resistance studies in progress to become available. The purpose of the present study was to determine if isoniazid- and rifampicin-free treatment regimens are safe and effective and to identify the factors that oblige a change in regimen.

Patients and Methods

We retrospectively identified all patients diagnosed with tuberculosis and followed by the pulmonology department of the Hospital General of Vall d'Hebron and by a dedicated tuberculosis facility (Serveis Clínics), both in Barcelona, Spain. The patients selected were those receiving an isoniazid- and/or rifampicin-free regimen in the initial or continuation phase of treatment. The study period covered 1995 to 2005. During this period, the same physicians, all specialists in tuberculosis retreatment, were responsible for prescribing. At least 3 drugs were prescribed, in accordance with current recommendations.[9] Initially, first-line drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) were used. Then, quinolones were prescribed in the second line. The third regimen relied on injectable preparations (streptomycin, etc), and the fourth regimen included all other options (protionamide, cycloserine, etc). The drugs were prescribed according to specific recommendations for each treatment group (for isoniazid-free regimens: rifampicin, pyrazinamide, and ethambutol for 9 to 12 months; for rifampicin-free regimens: isoniazid, pyrazinamide, and ethambutol for 12 months, plus streptomycin and quinolones optionally in the first months; for isoniazid- and rifampicin-free regimens: 3 active drugs, always including an aminoglycoside for 6 months and a quinolone for 18 to 24 months if possible[5]).

The study population consisted of adult patients older than 16 years of age under antituberculosis treatment for active tuberculosis at any site. Patients followed at the Hospital Vall d'Hebron used a supervised, self-administered treatment that included checking that scheduled visits were attended, reminding patients of visits, tracking no-show patients, supplying medication free of charge and monitoring utilization, and scheduling individualized visits. Testing included general blood workup, including liver function, every month for the first 2 months and every 1 to 2 months thereafter, according to patient progress. An eye test, including fundus examination and color blindness testing, was performed on asymptomatic patients taking ethambutol and whenever optic neuritis was suspected. At Serveis Clínics, patients followed directly observed therapy (DOT) every day and remained hospitalized for months or, if discharged, they followed DOT on an outpatient basis. Patients who had completed satisfactory treatment (defined as cure or completion of the course of medication) were discharged with a follow-up visit scheduled for 1 year later.

We analyzed patient variables (age, sex, country of origin, underlying disease, HIV infection, prior history of tuberculosis, and proper treatment of such tuberculosis) and tuberculosis variables (site, microbiological diagnosis, time to negative sputum culture, drug resistance, and multidrug resistance—defined as resistance to at least isoniazid and rifampicin). We also studied the various isoniazid- and/or rifampicin-free treatment regimens, analyzing the type of regimen, indication for isoniazid- and/or rifampicin-free regimen; number of drugs withdrawn; toxicity (type, duration, and drug responsible); aspartate transaminase, glutamic pyruvic transaminase, and bilirubin levels; need and reason for a change in isoniazid- and/or rifampicin-free regimen; total number of days on treatment; and final outcome (discharge cured or after satisfactory treatment, transfer, or death). Mild-to-moderate hepatotoxicity was defined as any transaminase elevation less than 10-fold the normal values or any elevation of cholestasis parameters less than 3-fold the normal values. Severe hepatotoxicity was diagnosed when these limits were exceeded, regardless of whether hepatitis A symptoms were observed or not.

Effectiveness of the isoniazid- and/or rifampicin-free treatment regimens was determined by the percentage of satisfactory treatments. Safety was determined by the appearance of toxicity, both in comparison with the standard antituberculosis regimens used in the same population area. The isoniazid- and/or rifampicin-free regimens were analyzed in 3 groups to simplify the analysis: group 1, no isoniazid; group 2, no rifampicin, and group 3, no isoniazid or rifampicin.

Statistical Analysis

Descriptive statistics were obtained by calculating means and percentages for qualitative variables, and medians and SD for quantitative variables. For factors associated with the need for a change in the first isoniazid- and/or rifampicin-free treatment regimen prescribed, the χ^2 test was used to compare the qualitative variables and odds ratios and 95% confidence intervals were calculated to estimate association. Associated variables were analyzed by a multivariate analysis with logistic regression if *P* was less than .15, with calculation of adjusted odds ratios and the respective 95% confidence intervals.

Results

Eighty-five patients were included in the analysis. There were more men (61%) and 35% were immigrants.

TABLE 1
Characteristics of the Patients (n=85) on Isoniazid- and/or Rifampicin-Free Treatment Regimens and the Tuberculosis Disease[a]

Variables	
Sex	
Men	52 (61%)
Women	33 (39%)
Mean age (range), y	42 (17-79)
Immigrants	30 (35%)
Underlying disease	50 (59%)
HIV-infection	29 (34%)
CD_4^+/μL lymphocyte count	40 (10-84)
Prior history of tuberculosis	23 (27%)
Tuberculosis site	
Pulmonary	56 (65%)
Milium	12 (14%)
Pleural	4 (5%)
Other	13 (16%)
Tuberculosis diagnosis	
Positive sputum smear and culture	65 (77%)
Positive culture	10 (12%)
Biopsy	7 (8%)
Pleural fluid adenosine deaminase	3 (3%)
Time to negative culture (range), d	81 (11-263)
Initial therapy	
Standard	49 (57%)
Isoniazid- and/or rifampicin-free	36 (42%)
Number of isoniazid- and/or rifampicin-free episodes/patient	1.28

Abbreviations: HIV, human immunodeficiency virus.
[a]Data are given as number of patients (percentage) or mean (range).

In all cases, the cause was *Mycobacterium tuberculosis* (Table 1).

There were 109 episodes of the need for isoniazid- and/or rifampicin-free regimens in 85 patients. (A single patient could have received several such regimens in the course of treatment.) A total of 57 different isoniazid- and/or rifampicin-free regimens were observed; the most common were isoniazid, pyrazinamide, and ethambutol (15%); rifampicin, pyrazinamide, ethambutol, and streptomycin (4.6%); and rifampicin plus ethambutol (4.6%). The indications for isoniazid- and/or rifampicin-free regimens were toxicity (53%), resistance (39%), and drug interaction (8%). Multidrug resistance was detected in 26% of cases. Isoniazid- and rifampicin-free regimens were most commonly used in group 2 (no rifampicin; 42%), followed by group 3 (no rifampicin or isoniazid; 35%) and group 1 (no isoniazid; 22%).

Toxicity in isoniazid- and/or rifampicin-free regimens was observed in 40 episodes (36% of the total). Hepatotoxicity was most common; 85% of those cases were mild to moderate and 15% were severe (6 patients, 7% of the study population). Pyrazinamide was the drug withdrawn most often due to toxicity. Ocular toxicity caused by ethambutol occurred in 4 patients (10% of all toxicity episodes). More than 1 type of toxicity was observed in 11 patients (13%) during the course of treatment. The mean interval between the start of treatment and the onset of toxicity was 59 days (range, 1-365 days). All toxicity cases progressed satisfactorily.

The outcome was satisfactory in most cases and 77% of patients were discharged cured. Follow-up was incomplete for 11 patients who dropped out (compliance,

TABLE 2
Analysis of 109 Episodes With Isoniazid- and/or Rifampicin-Free Treatment Regimens in 85 Patients, According to Treatment Group Used

	Group 1 (No Isoniazid)	Group 2 (No Rifampicin)	Group 3 (No Isoniazid or Rifampicin)
Initial phase	2/23 (9%)	16/45 (36%)	2/39 (5%)
Continuation phase	21/23 (91%)	29/45 (64%)	37/39 (95%)
Reason for isoniazid- and/or rifampicin-free regimen			
Toxicity	10 (43%)	32 (69%)	15 (38%)
Resistance	13 (56%)	6 (13%)	23 (59%)
Interaction	–	8 (17%)	1 (2%)
Number of isoniazid- and/or rifampicin-free regimens	12	15	28
Types of isoniazid- and/or rifampicin-free regimens	RE (21%) RZES (21%) RZE (21%)	HZE (37%) HZEOx (9%) HZELx (9%) HZES (9%)	ZES (8%) EOxS (8%) ZEOxPtCs (8%)
Toxicity of isoniazid- and/or rifampicin-free regimens	6 (25%)	17 (37%)	17 (43%)
Type of toxicity			
Mild hepatic	4 (66%)	5 (29%)	5 (29%)
Severe hepatic	1 (16%)	3 (17%)	2 (11%)
Retinal	–	4 (23%)	–
Digestive intolerance	–	2 (11%)	6 (35%)
Drug allergy	–	2 (11%)	1 (5%)
Clinical progress			
Satisfactory	18 (75%)	23 (50%)	25 (64%)
Regimen change	2 (8%)	16 (34%)	6 (15%)
Death	1 (4%)	3 (6%)	1 (2%)

Abbreviations: Cs, cycloserine; E, ethambutol; H, isoniazid; Lx, levofloxacin; Ox, ofloxacin; Pt, protionamide; R, rifampicin; S, streptomycin; Z, pyrazinamide.

TABLE 3
Factors Associated With the Change in Isoniazid- and/or Rifampicin-Free Treatment Regimen in the 109 Episodes Occurring With the Isoniazid- and/or Rifampicin-Free Regimens Studied

Variables	Univariate Analysis			Multivariate Analysis		
	P	OR	95% CI	*P*	OR	95% CI
Age, y	16-40					
>40	.66	1-1.22	0.52-2.85	.929	1-1.04	0.42-2.58
Sex						
Men						
Women	.52	–	–	–	–	–
Origin						
Spanish						
Immigrant	.067[a]	–	–	.047[a]	0.02	0.001-0.95
Group 1 (no isoniazid)						
Yes						
No	.13	0.38-1	0.12-1.24	–	–	–
Group 2 (no rifampicin)						
Yes						
No	.01[a]	3.16-1	1.32-7.58	.043[a]	1-2.57	1.03-6.42
Group 3 (no isoniazid or rifampicin)						
Yes						
No	.262	0.54-1	0.21-1.39	–	–	–
Resistance						
Yes	.826	0.81-1	0.34-1.95	–	–	–
No						
Toxicity						
Yes	.83	0.85-1	0.36-1.98	–	–	–
No						
Interaction						
Yes	.02[a]	5.52-1	1.28-23.75	.1	3.54-1	0.75-16.59
No						

[a]Significant differences.

87%) and 3 who were transferred. The average total time on therapy was 486 days (range, 45-920 days). Mortality was 5.9% (n=5). Most who died were men (85%), young (mean age, 42 years), and HIV-infected (85%) with advanced AIDS (mean, 26 CD_4^+/µL). The characteristics of patients in the 3 different isoniazid- and/or rifampicin-free groups are shown in Table 2.

In 33 episodes (30%), clinical progress was unsatisfactory with the first isoniazid- and/or rifampicin-free treatment regimen prescribed, obliging a switch to another regimen. The reasons for this change were toxicity (69%) and resistance (30%). A univariate analysis found that the factors related to a change in isoniazid- and/or rifampicin-free regimens ($P<.15$) were being an immigrant, taking group 2 regimens, and drug interaction as an indication for the regimen. The multivariate analysis revealed only being a immigrant and using rifampicin-free treatment regimens as significant (Table 3).

Discussion

The use of nonstandard regimens in Spain has risen in recent years due to increased resistance to antituberculosis drugs, mainly as a result of cases arriving from developing countries where tuberculosis is more prevalent and drug resistance more common than in Western Europe. The switch to an isoniazid- and/or rifampicin-free treatment regimen increases the cost and duration of treatment, as well as associated morbidity, and mortality, and reduces compliance, although effectiveness is considered to be similar to that of conventional regimens.[10,11] If isoniazid cannot be used because of toxicity or resistance, a 9–to-12–month regimen based on rifampicin, pyrazinamide and ethambutol is equally effective.[11] In our study, isoniazid-free treatment regimens were more effective and required fewer treatment switches. If rifampicin cannot be used, an alternative regimen of isoniazid plus ethambutol for 12 to 18 months, with pyrazinamide in the first 2 months, would be effective.[12] In our study, rifampicin-free treatment regimens were less effective and required more treatment changes, consistent with the findings reported by authors who considered rifampicin to be the most potent antituberculosis drug.[10,13]

Isoniazid- and rifampicin-free regimens are increasingly used in multidrug-resistant tuberculosis. In our study, this group was the most heterogeneous (28 different regimens) and the one with the most toxicity, perhaps due to individualized prescription of antituberculosis drugs because standard guidelines for such situations are not available and because more toxic, second-line drugs are used.[7,14,15]

The high incidence of drug resistance and multidrug resistance and the risk of greater toxicity make it important to have management guidelines for resistant tuberculosis and careful monitoring of isoniazid- and/or rifampicin-free regimens, with antituberculosis drugs selected by a specialist. In underdeveloped countries, the success of such regimens is constrained by reduced access to second-

line antituberculosis drugs and little experience with these drugs.[15-17]

In our study, the effectiveness of isoniazid- and rifampicin-free treatment regimens was 77%, similar to that of standard regimens in the city of Barcelona (83%) and in Europe, estimated at 74%.[6] The theoretical effectiveness is considered to be above 85% and, under ideal conditions of compliance and sensitivity, 95%.[2] The 5% mortality was less than that described for Europe (6.8%)[6] or the city of Barcelona (8.5%), a finding attributable to the young age of the patients in our study (mean age, 42 years) and the therapeutic control of HIV infection. Other authors have also reported similar satisfactory results using selected nonstandard regimens.[18] Despite the high drug resistance and multidrug resistance observed (known factors of greater therapeutic failure) in isoniazid- and/or rifampicin-free regimens,[6,18] effectiveness would be explained by the use of appropriate regimens following the specific recommendations for each group and by adequate compliance thanks to DOT and monitored self-administered therapy.

The main indication for isoniazid- and/or rifampicin-free regimens was toxicity, followed by antituberculosis drug resistance. The toxicity profile of antituberculosis drugs has not changed over the years, although the incidence and severity of toxicity have been lowered by screening patients at risk and performing regular follow-up,[19] because early discontinuation of treatment at the onset of signs of toxicity improves the prognosis.[5,20]

Hepatotoxicity is the most common, most widely known type of toxicity caused by first-line antituberculosis drugs. Hepatotoxicity may manifest in several ways, from asymptomatic elevation of liver-related laboratory parameters, not requiring discontinuation, to acute liver impairment with death or need for a transplant.[5,20,21] Pyrazinamide is considered more hepatotoxic than isoniazid or rifampin (particularly at doses >30 mg/kg/d)[22]; this was perhaps the reason why this was the drug withdrawn most often for toxicity in our study. Hepatotoxicity is more common in isoniazid- and/or rifampicin-free regimens because the number of risk factors rises and more toxic drugs are used[9]; in our study, severe hepatotoxicity was observed in 7% of patients, a level that was clearly above that observed in other studies (2.5%).[20] Careful monitoring of our patients would also explain the favorable progress of all toxicity cases. Significant ocular toxicity due to ethambutol (10%) was observed, a finding possibly attributable to the inclusion of routine eye examinations. Such follow-up is recommended for patients who are on high-doses of ethambutol, have renal failure, or take the drug longer than 2 months, because this toxicity could be underdiagnosed, particularly in mild cases.[5]

Immigrants and patients infected with HIV accounted for a higher percentage of the isoniazid- and/or rifampicin-free regimens. Immigration from areas where tuberculosis is highly endemic is influencing the epidemiology of tuberculosis in Spain. In Barcelona, similar to what is observed all over Western Europe, cases reported in foreigners represent about 40% of all cases,[23] with no differences in the frequency of isoniazid- and/or rifampicin-free regimens in immigrants, despite the higher percentage of resistance and toxicity seen in these patients.[3] Immigrants were significantly less likely to switch to an isoniazid- and/or rifampicin-free treatment regimen, but did experience satisfactory progress when doing so; these results should be confirmed in future studies.

Tuberculosis is still more prevalent in patients infected with HIV than in the general population, although the prevalence has declined 10-fold in the past decade due to routine prophylaxis, closer monitoring of patients among the prison population, intravenous drug users, and patients on antiretroviral therapies.[24] In our study, patients infected with HIV accounted for nearly a third of all cases, similar to other series,[25] and presented advanced immunodeficiency, with extremely low $CD4^+$ lymphocyte counts and high mortality. Tuberculosis often presented as disseminated disease. The drug withdrawn most often in this group was rifampicin, particularly due to interactions with the antiretroviral drugs.

The present study had several limitations. For instance, results are not shown for each isoniazid- and/or rifampicin-free regimen because the high number of combinations made it impossible to analyze and compare them. Moreover, information on how long susceptibility tests were delayed was not available in the cases of resistance. Because the study was conducted at 2 different sites, the results at each site could not be compared: DOT was administered in one but not the other site, where any patient found to have factors associated with noncompliance was transferred to the program of Serveis Clínics. There, DOT was administered on either an inpatient or outpatient basis.

When follow-up is good, isoniazid- and rifampicin-free regimens have similar effectiveness as standard regimens and, although these regimens are associated with greater toxicity, symptoms tend to improve satisfactorily. Specialist follow-up of patients on isoniazid- and/or rifampicin-free treatment regimens is necessary, particularly in the case of regimens associated with antituberculosis drug resistance, in rifampicin-free regimens, and in nonimmigrants due to a higher probability of a change in the isoniazid- and/or rifampicin-free regimen.

REFERENCES

1. Fox W. Whither short-course chemotherapy? Br J Dis Chest. 1981;75:331-57.
2. World Health Organization. Treatment of tuberculosis. Guidelines for National Programmes. WHO Report 2003. Document WHO/CDS/TB 2003/313. Geneva: World Health Organization; 2003.
3. Caylà JA, Caminero JA, Rey R, Lara N, Vallés X, Galdós-Tangüis H. Working Group on Completion of Tuberculosis Treatment in Spain. Current status of treatment completion and fatality among tuberculosis patients in Spain. Int J Tuberc Lung Dis. 2004;8: 458-64.
4. Díez M, Hernández JA, Caloto T, Castells C, Domínguez A, García AM, et al. Resultados del tratamiento antituberculoso en seis comunidades autónomas españolas. Med Clin (Barc). 2001;117: 574-80.
5. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003;167: 603-62.

6. Faustini A, Hall AJ, Perucci CA. Tuberculosis treatment outcomes in Europe: a systematic review. Eur Respir J. 2005;26:503-10.
7. Chan ED, Laurel V, Strand MJ, Chan MJ, Huynh ML, Goble M, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2004;169: 1103-9.
8. Migliori GB, Besozzi G, Girardi E, Kliiman K, Lange C, Toungoussova OS, et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur Respir J. 2007; 30: 623-6.
9. Vidal R, Rey R, Espinar A, de March P, Melero C, Pina JM, et al. Tratamiento y retratamiento de la tuberculosis. Arch Bronconeumol. 1996;32:463-74.
10. Schluger NW. The impact of drug resistance on the global tuberculosis epidemic. Int J Tuberc Lung Dis. 2000;4 (2 Suppl 1):S71-5.
11. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis. 1986;133:423-30.
12. Bobrowitz ID. Ethambutol-isoniazid vs. streptomycin-ethambutol-isoniazid in original treatment of cavitary tuberculosis. Am Rev Respir Dis. 1974;109:548-53.
13. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA. 2000;283:2537-45.
14. Tahao lu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med. 2001;345:170-4.
15. Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. Int J Tuberc Lung Dis. 2006;10:829-37.
16. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/ 2006.361. Geneva: WHO;2006.
17. Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. Eur Respir J. 2005;25:928-36.
18. Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. Int J Tuberc Lung Dis. 1998;2:877-84.
19. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA. 1999;281:1014-8.
20. Tost J, Vidal R, Caylà J, Broquetas J, Díaz Cabanela D, Jiménez A. Severe hepatotoxicity due to anti-tuberculosis drugs in Spain. Int J Tuberc Lung Dis. 2005;9:534-40.
21. Vidal Pla R, de Gracia X, Gallego B, Algueró C, Bravo C. Hepatotoxicidad del tratamiento de la tuberculosis. Med Clin (Barc). 1991;97:481-5.
22. Durand F, Bernuau J, Pessayre D, Samuel D, Belaiche J, Degott C, et al. Deleterious influence of pyrazinamide on the outcome of patients with fulminant or subfulminant liver failure during antituberculous treatment including isoniazid. Hepatology. 1995;21:929-32.
23. Jiménez MA. Prevenció i control de la tuberculosi en els immigrants. Annals de Medicina. 2006;89:5-7.
24. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med. 2003;163: 1009-21.
25. Small PM, Schecter GF, Goodman PC, Sande MA, Chaisson RE, Hopewell PC, et al. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N Engl J Med. 1991;324:289-94.