The impact of initial antituberculous drug treatment choice and resistance on outcomes

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TITLE Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis

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Soon after the introduction of streptomycin in 1943 it was demonstrated that when it was used as monotherapy a streptomycin-resistant tuberculosis (TB) strain quickly emerged.[1] The use of a six-month, four-drug (isoniazid, rifampicin, pyrazinamide and ethambutol) treatment regimen has now been recommended by many world experts.[2] Initial drug resistance or monotherapy can raise increasing multidrug-resistant and extensively drug-resistant TB worldwide, which becomes a major public health threat, requires extended treatment with toxic and expensive regimens and has higher rates of treatment failure and mortality.[3]

SUMMARY

In 2004 a retrospective study on the effect of initial drug resistance, treatment outcome and acquired drug resistance in new cases receiving standardised short-course chemotherapy revealed that in patients with pretreatment pan-susceptible or streptomycin-mono-resistant strains, 13 (41.9%) of 31 cases involving treatment failures acquired new multidrug resistance.[4] This new paper by Lew et al. analyses studies published in English from 1965 to June 2007, taken from PubMed, the Cochrane Central Database of Clinical Trials and EMBASE. Additional studies were obtained from cited references with the exclusion of abstracts, book chapters, conference proceedings or correspondence. The authors also excluded studies or groups that included rifapentine or rifabutine therapy, nondrug therapy or therapies that would be considered inadequate by current standards. Studies selected were randomised, controlled trials (RCTs) and cohort studies of standardised treatment of previously untreated patients with culture-confirmed pulmonary tuberculosis. Drug susceptibility was performed on pretreatment isolates from all patients and from patients with treatment failure or relapse.

Lew and colleagues' analyses show that the cumulative incidence of failure in new cases with pre-existing resistance to one drug (single drug resistance) was 8% (confidence interval [CI] 6–11%) and resistance to two drugs (polydrug resistance) was 21% (CI 13–20%). The cumulative incidence of failure in patients with initial drug resistance who received rifampin for one to four months was more than double that of patients with the same resistance who received rifampin for five months or more. These findings indicate a very strong association between treatment failure and initial drug resistance.

The relapse rate was more than double in patients with initial drug resistance who received rifampin for four months or less, and the rate was higher in patients who were not prescribed pyrazinamide. This indicates that relapse is strongly associated with initial drug resistance. However, the failure rate and acquired drug resistance rate, which was more frequent in patients with initial polydrug resistance, did not differ in cases of pyrazinamide prescription.

OPINION

This paper involved 14,333 new TB cases in 22 trials and seven cohort studies with the inclusion of HIV-infected individuals in a few studies. The inclusion of these few studies could affect the estimated rates of failure or relapse, which were 35–40% for patients who received rifampin for two months and 20% for those who received rifampin for six months.[5,6] The most important limitation in this paper is that the authors compared different groups of RCTs with groups from other trials. Introduced bias such as age, sex, severity of disease or other comorbid conditions could have been associated with certain regimens, and identical regimens would have protected against these confounders.

Lew et al. suggest an urgent need for RCTs to assess improved standardised regimens in low- and middle-income countries with limited access to drug-susceptibility testing and moderate to high prevalence of initial drug resistance, which strongly contributes to high mortality, treatment failure and relapse.[7]

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Allopurinol and the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis

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TITLE Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel

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SUMMARY

The EuroSCAR study, a European case-control surveillance of severe cutaneous adverse reactions (SCAR), was conducted in six countries (Austria, France, Germany, Israel, Italy and the Netherlands) between April 1997 and December 2001. Patients were actively detected in a network of about 1,800 hospitals covering about 100 million inhabitants. Included were patients who developed an adverse reaction in the community, outside the hospital, and who were admitted because of symptoms of SCAR. For each case, three hospital control subjects were matched on age, sex, region and date of interview. An international expert committee, composed of the six national study coordinators (all dermatologists) who were blinded to information on drug exposure and other risk factors, validated the patients by reviewing the clinical data, photographs (available for 93% of patients) and results of the pathologic slides (available for 75% of patients).

The patients were validated by means of a predefined scoring system, which consisted of clinical and histopathologic parameters (i.e. the presence of mucous membrane erosions, skin detachment, epidermal sheets, atypical target lesions or spots, a positive Nikolsky's sign, and epidermal necrosis). The expert committee also determined the date of onset of the disease (probable index day) and checked the validity of control subjects, based on the admission diagnosis and the date of onset of their acute condition. Odds ratio (OR) and 95% confidence interval (CI) were estimated by standard methods (SAS, Version 9.1, SAS Institute Inc, Cary, NC, and StatXact-5, Cytel Software Corporation, Cambridge, Mass.). The duration of drug exposure was classified as either ≤8 weeks or >8 weeks before the index day.

Of 513 potential patients with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) who were interviewed, 379 'community-acquired' patients were analysed (SJS 134; SJS/TEN overlap 136; TEN 109). A total of 1,763 control subjects were interviewed, of whom 1,505 were enrolled in the study. Allopurinol was the high-risk drug most frequently associated with SJS or TEN, with 66 exposed patients (17.4%) and 28 exposed control subjects (1.9%) (adjusted OR=18, 95% CI: 11–32). Other drugs implicated, in decreasing order, were carbamazepine (8.2%), cotrimoxazole (6.3%), nevirapine (5.5%), phenobarbitol (5.3%), phenytoin (5%), and lamotrigine (3.7%).

The doses of allopurinol were higher in patients with SJS or TEN (median 300 mg/d, mean 258 ± 66 mg/d) compared with control subjects (median 150 mg/d,