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The Treatment of Isoniazid Resistant Tuberculosis with Predominantly a Nine-Month Regimen

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Abstract

Background: Chest Clinic in Blackburn UK, a high Tuberculosis (TB) incidence area of the United Kingdom.

Methods: Retrospective analysis of a prospectively compiled database of TB notifications. The clinical characteristics and management of those cases with isonazid resistance (with or without additional streptomycin resistance) for the years 1989-2008 inclusive is described.

Results: 36 patients with proven and 3 with presumed isoniazid resistance were treated, 15 with pulmonary and 21 with non-pulmonary confirmed cultures. 35 patients (92%) were treated with a regimen of nine months rifampicin and ethambutol, supplemented by two months initial pyrazinamide (2RZE/7RE). No clinical or bacteriological relapses occurred.

Conclusion: This retrospective cohort study with a minimum of 12 months post treatment follow-up of all cases shows that a nine-month regimen, 2RZE/7RE with careful monitoring can be associated with satisfactory results in the treatment of isoniazid-resistant TB.

Introduction

Isoniazid resistance is reported throughout the world [1], and has increased in the United Kingdom (UK) from 5.6% in 1994 to 7.7% in 2006 [2]. Few controlled trial data on the treatment of isoniazid resistance are available. If isoniazid resistance is known before treatment commencement, then a supervised regimen of rifampicin (R) and ethambutol (E) for nine months, supplemented by two months initial pyrazinamide (Z) and streptomycin (S), 2RSZE/7RE, had over a 95% cure rate [3]. Case series, but not trials, have been described for isoniazid resistance diagnosed after treatment has commenced using various regimens [4-6].

Although an analysis of the results of the treatment of isoniazid resistance in the various British Medical Research Council trials suggested that isoniazid resistant TB responded satisfactorily to standard 6-month short-course chemotherapy [7], developed countries recommend stopping the isoniazid once resistance to it is diagnosed. In the UK, the Joint Tuberculosis Committee of the British Thoracic Society [8,9], and more recently the National Institute for Clinical Excellence [10], recommended an initial phase of two months rifampicin, pyrazinamide and ethambutol, followed by a continuation phase of rifampicin and ethambutol for 10 months (2RZE/10RE). In the United States, cessation of isoniazid and a treatment regimen of rifampicin, pyrazinamide and ethambutol for 6 months is recommended (6RZE) [11].

We described our experience from 1978-1999 with isoniazid resistant disease [4], and here describe additional cases, with a series from 1989-2008, where a regimen of nine months rifampicin and ethambutol, supplemented by 2 months initial pyrazinamide (Z) (2RZE/7RE) was used as standard, unless there were clinical or intolerance reasons for a longer duration of treatment.

Materials and Methods

Continuous prospective data was available on all notified cases of tuberculosis, in the Blackburn, Hyndburn and Ribble Valley local government areas for the years 1989-2008 inclusive. The database was examined and all cases resistant to isoniazid, either as isolated mono-resistance, or in combination with streptomycin, or treated for presumed isoniazid resistance were identified. In total thirty nine patients were identified and included in this study. Demographic data was obtained from the database and retrospectively reviewed. All patients had age, sex, ethnicity, country of birth, date of first arrival in the UK (if foreign born), sites of disease, regimen used, duration of follow-up, and if recurrence was diagnosed, recorded. No cases of isoniazid resistant TB were either lost to follow-up or transferred out of district.

M.tuberculosis was isolated locally, using Lowenstein-Jensen media from 1989 until May 2004, and by BACTEC 960 MGIT liquid culture from May 2004 onwards after microscopy using an auramine/rhodamine method. All isolates were sent to the Health Protection Agency Regional Mycobacterium Centre in Newcastle for identification and susceptibility testing. Drug susceptibility testing there was by the resistance ratio method [12]. This compares the MIC of test strains with the modal results of several control strains. A panel of wild strains are used as controls since the type strain (H37Rv) now

shows an unrepresentative degree of susceptibility. The advantage of this method is that slight variations in drug concentration or media preparation are unimportant. One set of dilutions of each of the first line drugs, contained in growth medium, are inoculated with ten microlitres of a standardised mycobacterial suspension along with one tube of drug free medium. The cultures are then incubated for a minimum of fourteen days. The Resistance Ratio (RR) of each test strain to each drug is calculated by dividing the MIC of the test by the Modal MIC. As doubling dilutions are used the Resistance Ratio is one (or less), two, four or eight. Those strains with an RR of one or two are reported as susceptible whilst those giving an RR of four or more as resistant. The end point is taken as a growth numbering twenty colonies or more; in practice colony numbers are usually uncountable in a resistant test. Borderline strains of 'S3' strains describe those tests where colonies number more than twenty but remain easily countable. Such results are treated with caution and repeated.

All patients had baseline liver function and visual acuity tested by Snellen test [8,9]. Visual acuity was only repeated if there visual symptoms. Treatment was given daily. Patients were seen at least monthly randomly by the TB nurses and had urine tests for rifampicin and pill-counts, throughout treatment. Patients were evaluated clinically, and by chest X-ray if they had respiratory disease, two weeks, two, four, six, and nine months after treatment commenced. If hepatotoxicity developed is was managed as per national guidance [9]. All patients were followed up at six and twelve months after treatment completion. Relapse was defined as a) either a patient developing a positive culture again or b) clinical or X-ray deterioration consistent with active TB, over their observation period.

Results

Thirty nine patients with proven (n=thirty six), or presumed (n=three), isoniazid (H) resistance, nineteen with isoniazid mono-resistance and seventeen with combined isoniazid and streptomycin (S) resistance (SH) were treated in the years 1989-2008. Fifteen of the patients were female; all of South Asian ethnic origin, of whom four were born in the UK, with a mean age of 28.9 years (range 3-59). Twenty four were male, two white, one Afghan, and twenty one of South Asian ethnic origin, including two UK-born, with a mean age of 28.7 years (range 12-72). Out of this study population, a boy of twelve who presented with a pleural effusion, and two girls aged three and nine with hilar lymphadenopathy were treated on presumption, without culture confirmation, as household contacts of parents with confirmed isoniazid resistant sputum smear-positive pulmonary disease.

Of the culture confirmed cases fifteen had pulmonary disease, eleven sputum smear and culture positive (eight cavitatory mean 1.875 zone [13,14] (range 1-3 zones); three non-cavitatory mean 1.67 zones (range 1-3 zones), four smear-negative culture positive (mean 1.25 zones: range 1-2 zones). The breakdown of the non-pulmonary cases is shown in Table 1. Thirty five of the thirty nine (92%) cases were treated with the 2RZE/7RE regimen, with the isoniazid of their initial RHZE regimen being stopped as soon as the H or SH resistance was reported, and in all cases no later than 9 weeks after RHZE treatment started. One patient who was Z intolerant was treated with 12RE, and one patient who was Z intolerant after 1 month was treated with 1RZE/8RE. The one patient with meningitis was treated with 2RZE/10RE. One patient with diabetic retinopathy was treated with 2 RZProthionamide/10 RProthionamide. The pulmonary cases were not able to produce spontaneous sputum after month two, did not have induced sputum, and so were regarded as having completed treatment, but not cured, by agreed criteria [15]. All markers of inflammation/infection as measured by CRP (C-reactive protein) or ESR (erythrocyte sedimentation rate) normalised by the end of treatment.

Site	Number
Pulmonary (smear and culture +ve)	11
Pulmonary (smear-ve, culture +ve)	4
Cervical nodes	12
Abdomen	2
Bone and joint	3
Subcutaneous abscess	1
Mediastinal nodes	1
Meninges	1
Miliary	1 (6 zone classical miliary: +ve bronchial wash)

Table 1: Confirmed sites. Three children as household contacts of smear positive disease were treated on presumption – one with pleural effusion and two with hilar lymphadenopathy

All patients were followed up at six and twelve months post treatment completion, with chest X-rays for all those with respiratory disease. There were no clinical, bacteriological or radiological relapses and no patient has subsequently been seen with recurrent disease.

Discussion

A nine month regimen, 2RZSE/7RE, is the only regimen for isoniazid resistant TB which is proven by clinical trial [3]. This however was for patients with isoniazid (H) resistance diagnosed pre-treatment, a circumstance which is not common, as the overwhelming numbers of cases are diagnosed after treatment has commenced. Although analysis of the British Medical Research Council trials suggested that using standard treatment, i.e. a continuation phase of 4RH, gave an overall satisfactory response in the presence of isoniazid resistance [7], this strategy is of considerable concern as effectively rifampicin monotherapy would be employed, which could lead to the development of rifampicin resistance, and hence MDR-TB [16]. In both the USA [11], and UK [8-10], cessation of the isoniazid after the diagnosis of resistance is advocated. Thereafter the recommended strategies and regimens differ. Each has potential advantages and disadvantages.

In the USA, a regimen of 6RZE is recommended. This has the advantage of being of only six months duration, but employs pyrazinamide throughout. In fully susceptible tuberculosis, continuation of pyrazinamide beyond the initial two months has been shown to add nothing to the efficacy of treatment [17], and pyrazinamide has the worst side-effect profile of the first-line antituberculosis drugs [18] with a near 2% hepatitis rate for 2 months treatment. Nolan et al, reporting the use of 6RHZE, i.e. the USA strategy with continuation of the isoniazid inspite of reported high-level resistance [5], showed a >5% relapse rate, and 3/44 (6.8%) patients had to stop the pyrazinamide because of intolerance. Escalente et al., reporting experience from south-eastern Texas [6],

showed twice weekly treatment regimens and treatment duration under nine months were both associated with relapse Table 2.

2RZE/7RE	Rifampicin, isoniazid for nine months with initial ethambutol for two months
2RZSE/7RE	Rifampicin and ethambutol for nine months with initial pyrazinamide and streptomycin for two months.
2RZE/10RE	Rifampicin and ethambutol for twelve months with initial pyrazinamide For 2 months
6RZE	Rifampicin, isoniazid and ethambutol for six months
12RE	Rifampicin and ethambutol for twelve months
1RZE/8RE	Rifampicin and ethambutol for nine months with initial pyrazinamide for one month
2RZProthion/10RProthion	Rifampicin and prothionamide for twelve months with initial pyrazinamide for two months
6HRZE	Isoniazid, rifampicin, pyrazinamide and ethambutol for 6 months
2RZE/4RMoxi	Rifampicin, pyrazinamide and ethambutol for two followed by rifampicin and moxifloxacin for four months
2RZMoxi/4RMoxi	Rifampicin and moxifloxacin for six months with initial pyrazinamide for two months

Table 2: Acronyms

The UK strategy is to stop isoniazid and complete an initial phase of 2RZE, then give a continuation phase of 10RE. This has the advantage of limiting pyrazinamide to the initial two months, but is of considerably longer i.e. twelve months total duration. Under neither strategy are their combination tablets of RZE, or RE. Thus drugs have to be given individually, which increases the chances of accidental or deliberate monotherapy, and hence the emergence of further drug resistance, including MDR-TB. Both strategies could however theoretically be given as thrice-weekly supervised treatment with appropriate dosage adjustments [9], but this has not been scientifically tested. This study was with self-administered treatment with frequent random monitoring and pill counts. This may not be appropriate for some isoniazid resistant patients who would require DOT because of previous poor compliance or chaotic life-styles [19].

This cohort study shows that 2RZE/7RE can be an effective regimen for the management of isoniazid resistant TB, with close patient monitoring. Although not a randomised trial, and retrospectively analysed, data was prospectively recorded, and there were no losses during treatment or follow-up, by death, transfer-out, or emigration. The results were very similar to the substantial majority of reported local case outcome [20]. In the future quinolone containing regimens may answer the dilemma of how to treat isoniazid resistant TB. Moxifloxacin has been shown to either have equivalence to ethambutol in the initial two months of treatment [21], or superiority on serial sputum colony counts [22], or in culture conversion at two months [23]. Because of this, and the better sterilising effect of rifampicin and moxifloxacin (RMoxi) in the murine TB [24], phase III studies are now underway using RMoxi continuation phases in the treatment of active disease [25,26]. If such trials confirm the utility of RMoxi in the continuation phase, then a regimen of 2RZE/4RMoxi or 2RZMoxi/4RMoxi may then be possible for isoniazid resistant disease, as the continuation phase does not depend on isoniazid susceptibility.

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Sarah Haines and Rahul Mittal examined the database and patient notes to identify patients and extract the data. They also wrote the methods and results section independently. Lawrence Ormerod was responsible for the clinical care throughout, planned the study and wrote the rest of the paper, with input from the other authors

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