Using Adverse Events in a Tuberculosis Trial to Describe the Tolerability of Standard Therapy

Introduction and Objectives

The current standard treatment for pulmonary tuberculosis (TB) has been in use for several decades and the major risks associated with each of the four drugs (HRZE) are well recognised. However, large prospective trials with regular review and documentation of adverse events while taking HRZE are lacking.

We used the incidence of grade 3 and 4 adverse events (AEs) and serious adverse events (SAEs) in patients taking HRZE in the REMoxTB trial to investigate the overall tolerability of the regimen.

Methods

Grade 3 or 4 AEs and SAEs (of any grade) for patients taking standard TB therapy were analysed. Events were labelled as occurring in the intensive phase, continuation phase or in follow-up (up to 18 months after enrolment). ANOVA and chi-square testing was used to test for significant differences in the incidence of events across the treatment phases. Logistic regression was used to investigate associations between baseline characteristics and on-treatment SAEs and withdrawal from treatment, death or relapse/treatment failure.

Results

201 (31.5%) of 639 patients taking standard therapy experienced grade 3/4 AEs or SAEs during treatment. AEs, SAEs, and withdrawals from treatment occurred most frequently in the intensive phase (see Table). Of 116 SAEs reported 84 (72.4%) improved or resolved and were most commonly respiratory (16.4%), gastrointestinal (6.9%), and infection (5.2%) related. There were 10 deaths in follow-up due to suicide, trauma, TB relapse, and acute illness. Logistic regression detected a significant association between on-treatment SAEs and withdrawal ($p<0.001$) or death ($p<0.001$), but not relapse/treatment failure ($p=0.611$). HIV-positive status (OR 4.25, $p=0.016$) and lower baseline weight (OR 1.46, $p=0.023$) were associated with the reporting of on-treatment SAEs.

Discussion

AEs and SAEs were predominantly reported in the intensive phase, probably due to a combination of TB and effects of medication. However most deaths occurred in follow-up and were unrelated, emphasising the impact that social circumstances have on TB patients. The lack of significant association between SAEs during treatment and relapse/treatment failure provides reassurance that a complicated treatment period can end with successful treatment of TB. The association between SAEs on treatment and lower weights at baseline and HIV infection reinforces the need to monitor these patients closely.

		Intensive Phase (Month 0-2) n=639	Continuation Phase (Month 3-6) n= 596	Follow Up Phase (Month 7-18) n= 569	P value
No of Grade 3 AEs Reported		66	31	19	***
No. Grade 4 AEs Reported		19	6	3	***
System Organ Class of Reported Grade 3 & 4 AEs					
	Musculoskeletal	14	7	0	0.102
	Metabolism & Nutrition	11	0	6	0.006
	General Disorders	7	3	1	0.838
No of Grade 3 or 4 AEs per Patient					
	0	578	574	554	<0.001
	1	49	18	9	
	2	9	2	4	
	≥3	3	2	2	
No of Patients with ≥1 SAE (Considered Related)		32 (21)	18 (6)	20 (2)	0.168
Mean No of SAEs per Patient		1.78	1.39	1.60	0.092
No of Withdrawals		38	26	1	<0.001
No of Deaths		5	1	10	0.014