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Incidence and risk factors for drug intolerance and association with incomplete treatment for tuberculosis: analysis of national case registers for England, Wales and Northern Ireland, 2001–2010

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ABSTRACT

Anti-tuberculosis drug regimens are efficacious, but drug intolerance can be severe and may impact on treatment completion rates. The Enhanced Tuberculosis Surveillance (ETS) system is a case register of all new notifications of tuberculosis in England, Wales and Northern Ireland. We conducted a cohort study to estimate the incidence of, and risk factors for, drug intolerance reported through ETS between 2001 and 2010 and to assess its relationship with treatment non-completion. Reports of drug intolerance were found for 868/67 547 (1.28%) patients in the cohort, and important risk factors were female sex, older age, later case report year and white ethnicity. Drug intolerance was associated with an approximate fivefold increased odds of treatment non-completion ($p<0.001$). These results highlight the need for better-tolerated drug regimens and close case management of patients at risk of drug intolerance to improve treatment completion rates and contribute to more effective disease control.

INTRODUCTION

Ensuring that people with tuberculosis (TB) successfully complete their treatment is not only life saving for the individual but also reduces the number of infectious cases in the community, leading to population disease control.[1] One of the barriers to successful completion of therapy is poor adherence, which can result from a range of anti-TB drug intolerance conditions such as gastrointestinal upset, rash and hepatotoxicity.[2] The incidence of anti-TB drug intolerance among the population of TB patients in the UK has not been estimated previously, and there are little reported data for its effect on the overall outcome of treatment.

In this paper, we present the incidence of, and clinical and demographic risk factors associated with, reported anti-TB drug intolerance in England, Wales and Northern Ireland and determine the relationship of reported drug intolerance with non-completion of TB treatment.

METHODS

This was an analysis of the cohort of patients diagnosed with active TB and reported through the Enhanced Tuberculosis Surveillance (ETS) system between 2001 and 2010.

The incidence of reported cases of anti-TB drug intolerance was estimated by combining reports made through a categorical field for patients still on treatment at follow-up with those made through free text comments for patients with any treatment outcome. A wide set of search terms was used to query these comments, including phrases referring to specific recognised adverse events and names of anti-TB drugs.

Drug intolerance in the cohort was described in terms of reported condition and the drugs specified as the cause. Single and multivariable logistic regression analyses were used to identify risk factors for development of drug intolerance in the cohort.

The effect of drug intolerance on treatment non-completion was also investigated through logistic regression analysis. The outcome was non-completion of treatment, which included patients whose final outcomes were *still on treatment*, *died during treatment*, *lost to follow-up*, *stopped treatment* and those who had not finished treatment for an unknown reason. A multivariable model was built to determine the relationship after adjusting for other significant covariates in the data.

All analyses were conducted using Stata V.12, Stata Corporation, Texas, USA.

RESULTS

The cohort comprised 67 547 cases of TB reported in England, Wales and Northern Ireland through ETS between 2001 and 2010. This excluded 1067 cases whose diagnosis was made postmortem and 6984 with a final treatment outcome missing, as these patients would not have had intolerance recorded, and 390 with MDR TB, as the second-line treatments used to treat MDR TB are known to cause a higher frequency of adverse events.

A total of 866 reports of drug intolerance were identified, representing 1.28% of TB notifications. Of these, 265 were identified through the specified treatment outcome field and a further 601 from the keyword search of the free text comments field.

The nature of the intolerance condition was reported in 233 of the 866 records of drug intolerance, and the drug thought to be responsible in 268 records. Hepatotoxicity was the most common disorder (160, 18.5% records) and pyrazinamide the most frequently reported drug (135, 15.6%

records). Factors found to be significantly associated with reporting of adverse drug reactions at multivariable analysis were older age, female sex, white ethnicity and case report year (table 1).

A total of 10 216 of the 66 843 patients whose treatment regimen was not planned to extend beyond the follow-up period had not completed treatment at follow-up. There were 844 cases of drug intolerance in this cohort, of which 450 (53.3%) did not complete treatment, compared with 9766 (14.8%) of the 65 999 patients with no reported drug intolerance.

Logistic regression analysis gave an unadjusted OR of 6.58 (95% CI 5.73 to 7.54, p<0.001) for the effect of drug intolerance on treatment non-completion. Following adjustment for other significant covariates (age, sex, case report year, whether the patient was born in the UK, resistance to isoniazid, pyrazinamide or ethambutol), the adjusted OR was 4.95 (95% CI 4.05 to 6.05, p<0.001).

Table 1 Single and multivariable analysis of association between exposure variables and anti-tuberculosis drug intolerance

	Drug intolerance		Single variable analysis		Multivariable analysis	
Risk factor	Yes (N=866)	No (N=66 681)	OR (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age (years)						
0–14	15	3710	0.46 (0.27 to 0.77)	0.003	0.41 (0.24 to 0.70)	0.001
15–44	362	40 918	1		1	
45–64	234	12 837	2.06 (1.75 to 2.44)	<0.001	1.77 (1.49 to 2.11)	<0.001
65+	255	9211	3.13 (2.66 to 3.68)	<0.001	2.31 (1.93 to 2.78)	<0.001
Sex						
Male	318	36 700	1		1	
Female	543	29 825	2.10 (1.83 to 2.42)	<0.001	2.24 (1.95 to 2.59)	<0.001
Year						
2001	58	4914	1	<0.001*	1	
2002	66	5545	1.00 (0.71 to 1.43)		1.08 (0.76 to 1.55)	0.66
2003	38	5712	0.56 (0.37 to 0.85)		0.61 (0.40 to 0.93)	0.022
2004	56	6048	0.78 (0.54 to 1.13)		0.86 (0.59 to 1.25)	0.43
2005	64	6780	0.80 (0.56 to 1.14)		0.96 (0.67 to 1.37)	0.81
2006	78	7265	0.91 (0.64 to 1.28)		1.02 (0.72 to 1.45)	0.91
2007	84	7435	0.96 (0.68 to 1.34)		1.12 (0.80 to 1.59)	0.51
2008	129	7638	1.43 (1.05 to 1.96)		1.69 (1.23 to 2.33)	0.001
2009	158	7981	1.68 (1.23 to 2.27)		1.91 (1.40 to 2.61)	<0.001
2010	135	7363	1.55 (1.14 to 2.12)		1.80 (1.32 to 2.48)	<0.001
Ethnic group						
White	341	13 845	2.19 (1.87 to 2.56)	<0.001	1.97 (1.67 to 2.33)	<0.001
Black Caribbean	9	1633	0.49 (0.25 to 0.95)	0.036	0.55 (0.28 to 1.07)	
Black African	109	14 826	0.65 (0.52 to 0.82)	<0.001	0.80 (0.64 to 1.01)	0.078
Indian/Pakistani/Bangladeshi	298	26 520	1		1	0.058
Other	82	7944	0.92 (0.72 to 1.18)	0.50	1.04 (0.79 to 1.52)	0.59
UK-born						
No	469	44 917	1			
Yes	320	16 968	1.81 (1.57 to 2.09)	<0.001		
Site of disease						
Pulmonary	395	30 612	1			
Extrapulmonary	394	29 857	1.02 (0.89 to 1.18)	0.75		
Both	73	5995	0.94 (0.73 to 1.21)	0.65		
Neither recorded	4	217	1.43 (0.53 to 3.86)	0.48		
Previous diagnosis						
No	676	50 609	1			
Yes	85	4540	1.40 (1.12 to 1.76)	0.004		
Previous treatment						
No	16	426	1			
Yes	36	2347	0.41 (0.22 to 0.74)	0.003		
Resistance to INH, PZA or EMB						
No	450	35 235	1			
Yes	35	2354	1.16 (0.82 to 1.65)	0.39		
Sputum smear positive						
No	212	16 382	1.19 (0.96 to 1.47)	0.11		
Yes	147	13 505	1			

*p trend.
EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide.

DISCUSSION

This is the first analysis of anti-TB drug intolerance and its relationship to non-completion of treatment in England, Wales and Northern Ireland derived from the ETS system, a whole population case register of TB patients.

Intolerance to anti-TB drugs was reported in 1.28% of notifications. This figure includes records in which drug intolerance had been indicated through free text comments, a threefold increase in reports compared with those made using the dedicated drug intolerance field only. This is partly because the drug intolerance field can only be completed for patients who are still on treatment at follow-up, and therefore omits those who experienced adverse events during their treatment but who, for example, completed treatment or were lost to follow-up.

Previous attempts to measure the incidence of drug intolerance in other settings have produced higher estimates, with 8.6% patients affected in a smaller single-centre cohort[2] and 30% in a population-based study involving regular standardised collection of information regarding patients' tolerance to the TB medications.[3] This indicates that the number reports of intolerance to anti-TB drugs ascertained here are an underestimate of the true incidence of adverse events. A limitation of this method for identifying cases of drug intolerance that has contributed to this is the lack of standardisation in data entry: Drug intolerance information is not actively sought on ETS, there is no agreed system for grading side effects and completion of comments relies on retrospective recall by the case manager. It is therefore probable that only the most severe adverse events, or those that resulted in a change of treatment regimen, would prompt a case manager to comment.

Hepatotoxicity was the predominant reported adverse event caused by anti-TB drugs, and pyrazinamide was most frequently suggested as the cause. These results are consistent with previous understanding,[2 3] although details of conditions and drugs were only available for approximately 30% of the reports of drug intolerance. Important risk factors associated with drug intolerance in this cohort were female sex, older age, later case report year and white ethnicity. Other studies[2] have found similar relationships with sex and age, but it is probable that the association with year reflects a change in the way that the comments section has been used over time, rather than a real increase in incidence. There may also be residual confounding for factors that could not be controlled for in this study; notably HIV status,[2] which is not included in TB surveillance data in the UK, and alcoholism, homelessness and drug use, which have only been collected in ETS since 2009.

This study provided evidence that drug intolerance is associated with an approximate fivefold increased odds of treatment non-completion. Although this is a logical association, few attempts have previously been made to quantify it. Adverse events were associated with a twofold higher rate of unsuccessful treatment outcomes at 6 months in one study, but this was a smaller analysis of patients at a single tertiary care hospital.[4]

The crude relationship between drug intolerance and non-completion of treatment was partially confounded by a number of covariates that were included in the adjusted analysis, but, again, there may have been residual confounding from unmeasured covariates such as alcohol dependence, homelessness and refugee status.[5] The precision of our estimate of the effect of drug intolerance on treatment failure may also have been implicated by the likely underestimation of intolerance in the cohort and by the restriction of the categorical drug intolerance option on ETS to patients who are still on treatment at follow-up. This restriction would tend to increase the effect on treatment non-completion, although these reports made up a minority of the overall number of reports of drug intolerance that were ascertained.

The observed relationship between drug intolerance and treatment non-completion has consequences for the management of TB in patients with these symptoms. Such patients are more likely to have their treatment extended due to changes in drug regimens, are less likely to comply with treatment and are more likely to become lost to follow-up. As a result, they are prone to have longer disease duration, increasing their risk of death and the potential for the disease to spread. This highlights the importance of consultation with expert respiratory physicians where possible regarding management of patients with symptoms of drug intolerance and the crucial role of close case management by respiratory nurse specialists in the community so that issues can be detected early and dealt with accordingly. A more systematic way of recording instances of drug intolerance and classifying their severity would aid this, for example, by extending the dedicated drug intolerance field so that it can be completed for any case in ETS.

In conclusion, we provide evidence that intolerance to anti-TB drugs is significantly associated with failure to complete TB treatment regimens in the UK. A more accurate picture of the burden of these adverse events and the extent of the impact on treatment completion could be obtained through prospective systematic recording on ETS. Development of new, less toxic treatments should be given a high priority in order to reduce patient suffering, improve treatment completion rates and contribute to control of the disease.

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Contributors CS conducted analysis and is the lead author. IA and MR contributed to study design. LT and LA oversaw data collection. All authors contributed to the final version of the manuscript.

Competing interests None.

Ethics approval This study was carried out with national surveillance data. The Health Protection Agency was the responsible body at the time of the study and had NIGB approval to hold and analyse national surveillance data for public health purposes

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