Safety and Tolerability of 12 Weekly Doses of Isoniazid and Rifapentine for Treatment of Latent Tuberculosis Infection in Programmatic Settings in the United States

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Background

- Treatment of latent tuberculosis infection (LTBI) in high-risk populations is an important strategy for tuberculosis (TB) prevention and elimination in the United States (U.S.).[1]
- Systemic drug reactions were associated with the 12-dose LTBI regimen of once-weekly isoniazid (900 mg) plus rifapentine (900 mg) (INH-RPT) in a large clinical trial, "PREVENT TB".[2,3]

Objective

- To assess safety and tolerability of directly observed INH-RPT in the U.S. as part of a national post-marketing surveillance activity.

Methods

- Data were collected from an observational prospective cohort during July 1, 2011 - December 31, 2013 using standardized review instruments.
- INH-RPT administered by directly observed therapy (DOT) was started in 3,307 persons with LTBI from 16 U.S. sites following CDC guidelines and local program practices.
- Patients were instructed to report symptoms during treatment at each DOT visit.
- Rates for treatment discontinuation were calculated.
- We assessed the association of development of symptoms with treatment completion by univariate analysis.

Affiliations

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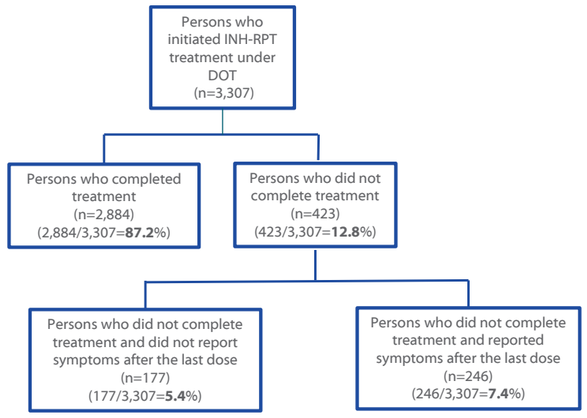
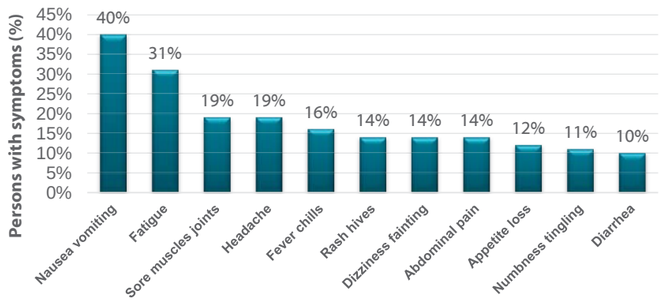
INH-RPT Treatment Under DOT in the U.S. Post-marketing Surveillance Activity



Frequency of Symptoms During the Administration of INH-RPT Treatment Regardless of Discontinuation of Treatment (n=1,207)



Symptoms developed during INH-RPT treatment

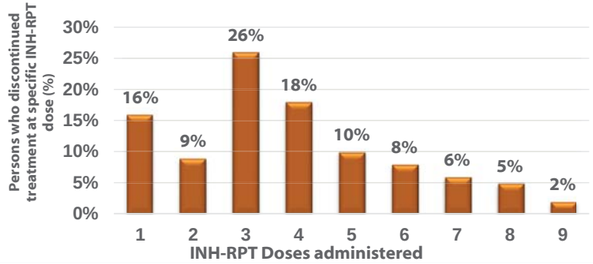
List of symptoms solicited at each visit, except for headache, which was self-reported

Univariate Analysis of Demographic Characteristics in Persons who did not Complete INH-RPT Treatment, by Report of Symptoms (n=423)

Characteristics	Did not complete treatment (n=423)		OR (95% Confidence Interval)	P-value
	Persons who did not report symptoms after the last dose (n=177) n (%)*	Persons who reported symptoms after the last dose (n=246) n (%)*		
Gender				
Male (n=1,768) *ref*	111 (6.3)	100 (5.7)	*ref*	*ref*
Female (n=1,539)	66 (4.3)	146 (9.5)	**2.46 (1.65, 3.65)**	**<.0001**
Age groups (years)				
2-17 (n=167) *ref*	4 (2.4)	5 (3.0)	*ref*	*ref*
18-30 (n=1,037)	57 (5.5)	56 (5.4)	0.79 (0.20, 3.08)	0.73
31-44 (n=957)	55 (5.7)	65 (6.8)	0.95 (0.24, 3.70)	0.94
45-64 (n=945)	51 (5.4)	87 (9.2)	1.37 (0.35, 5.31)	0.65
>=65 (n=201)	10 (5.0)	33 (16.4)	2.64 (0.59, 11.75)	0.20
Race/Ethnicity **				
Hispanic (n=754) *ref*	31 (4.2)	38 (5.0)	*ref*	*ref*
Non-Hispanic White (n=543)	36 (4.9)	91 (12.5)	**2.1 (1.12, 3.8)**	**0.02**
Non-Hispanic Black (n=1,200)	81 (6.7)	80 (6.7)	0.81 (0.46, 1.42)	0.45
Non-Hispanic Asian (n=729)	25 (4.6)	34 (6.3)	1.11 (0.55, 2.24)	0.77
Non-Hispanic Other (n=74)	4 (5.4)	3 (4.1)	0.61 (0.13, 2.94)	0.54
Special populations				
Contact of a TB case (n=827)	27 (3.3)	44 (5.3)	1.21 (0.72, 2.04)	0.48
Converter (n=806)	36 (4.4)	95 (11.8)	**2.46 (1.58, 3.85)**	**<.0001**
Incarceration (n=519)	43 (8.3)	23 (4.4)	**0.32 (0.19, 0.56)**	**<.0001**
Homeless (n=181)	23 (12.7)	11 (6.1)	**0.26 (0.11, 0.61)**	**0.002**
Foreign-born (n=1,297)	56 (4.3)	70 (5.4)	0.85 (0.56, 1.31)	0.48
Refugee (n=132)	6 (4.5)	13 (9.9)	1.59 (0.59, 4.27)	0.36
Health Care Worker (n=502)	30 (5.9)	54 (10.8)	1.38 (0.84, 2.26)	0.20
Student (n=130)	5 (3.9)	2 (1.5)	0.28 (0.05, 1.47)	0.13

*Percentages of total persons for each characteristic **7 missing values

INH-RPT Dose After Which Persons Discontinued Treatment, Among Persons who did not Complete Treatment and Reported Symptoms



Results

- Among 3,307 persons who received INH-RPT, 54% were male, 37% black, and 0.8% were infected with HIV. The median age was 36 years.
- The overall treatment discontinuation rate was 12.8% (423/3,307) and the rate of treatment discontinuation among participants who reported symptoms was **7.4**% (246/3,307).
- The proportion of persons who reported symptoms and were female or white non-Hispanic were higher than those who did not report symptoms (p-value = <.0001 and 0.02, respectively, see table).
- A total of 1,207 (36.5%) persons reported at least 1 symptom after one of the first 10 doses. Nausea vomiting (40%), fatigue (31%), sore muscle joins (19%), headache (19%), fever/chills (16%) were the most frequently reported symptoms.
- INH-RPT Dose 3 was the most frequent dose after which treatment was discontinued (26%), among persons who did not complete treatment and reported symptoms.
- The odds of not completing treatment were 4.5 times higher for those reporting at least one symptom, compared to those who did not report any symptoms after one of the first 10 doses (95% CI: 3.6, 5.6).
- No deaths or permanent sequelae attributed to INH-RPT were reported.

Conclusions

- Findings in this programmatic surveillance activity were very similar to those reported in the PREVENTTB trial.
- INH-RPT administered by DOT for LTBI treatment in programmatic settings was well tolerated and safe.

Acknowledgement

Post-implementation 12-Dose INH-RPT Assessment Project Group

References

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