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Isoniazid Completion Rates for Latent Tuberculosis Infection Among College Students Managed by a Community Pharmacist

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Abstract

Objectives: To document nine month and previously recommended six month treatment completion rates for latent tuberculosis infection (LTBI) in a pharmacist-managed LTBI clinic within a community pharmacy on a college campus, and to describe patient characteristics of those enrolled. **Participants:** University students diagnosed with LTBI. **Methods:** The authors conducted a retrospective review of existing pharmacy records from 2000 to 2006. Main outcome measures included six and nine month LTBI treatment completion rates, total isoniazid (INH) tablets taken, characteristics of completers versus non-completers, average time to treatment completion, and reported adverse drug events. **Results:** The overall nine month completion rate was 59% and the six month completion rate was 67%. Among those not completing treatment, 15.2% experienced fatigue and 2.2% experienced a rash ($p=0.04$ and $p=0.03$). **Conclusion**: LTBI clinics are a unique niche for community pharmacies and can provide individualized patient care to ensure LTBI treatment adherence, monitoring for disease progression, and safety of INH.

Globally, tuberculosis remains a significant cause of morbidity and mortality. It is estimated that one-third of the world's population is infected with tuberculosis while nine million new cases of disease were reported in 2004.[1, 2] In 2005, 14,097 cases of tuberculosis were reported in the United States. Of these cases, 55% occurred amongst foreign-born individuals, which represents a dominant factor in sustained rates of active tuberculosis in the United States.[3-5]

To reduce the development of active tuberculosis and help eliminate infection worldwide, individuals with LTBI must be treated appropriately. It is estimated that 9.6 to 14.9 million people in the United States have been diagnosed with LTBI and thus are at higher risk of developing active tuberculosis.[6-8] Treatment with INH daily for nine months (270 tablets) is the CDC recommended standard of therapy for LTBI; however, patients may take twelve months to finish all 270 tablets and still be considered treatment completers. Unfortunately, long term treatment with INH is problematic since individuals with LTBI generally do not feel symptomatic and thus may not feel obligated to complete treatment.[7] Nine month INH treatment completion rates are sparsely reported in the literature; however, the CDC's previously recommended six month (180 tablets) INH regimen has reported completion rates of between 50 to 60%.[7, 9, 10] Discontinuing INH treatment prematurely allows progression to active tuberculosis and the development of drug-resistance.

At our university, approximately 32,000 students are enrolled annually of which roughly 5,500 are classified as international (non-immigrant visa) students. All incoming international students are required to have a PPD placed and read in the U.S. within one year prior to their first semester of enrollment in an attempt to identify and treat those with LTBI. In August 2000 after an internal quality improvement study revealed that a large proportion of students did not

complete their full course of INH, a pharmacist-managed LTBI clinic was opened in the campus community pharmacy to help improve patient acceptance of INH and LTBI treatment completion rates.

Since research that focuses on the community pharmacist's role and outcomes of care in the management of LTBI is limited, the objectives of this study were to determine the six and nine month INH completion rates as well as the characteristics of treatment completers versus non-completers in our community pharmacy LTBI clinic.

Methods

This study was approved by our institutional review board for human subjects. Patients included in the analysis were those diagnosed with LTBI by student health clinicians, referred to the pharmacy LTBI clinic, and able to complete the full nine month INH regimen by December 2005. Successful completion of therapy was defined as taking 270 tablets within a nine to twelve month period. Six month completion was defined as taking 180 tablets within a six month period. If patients were given additional tablets to compensate for missed doses, it was recorded in the clinic's spreadsheet and the amount of INH dispensed was adjusted accordingly.

The number of tablets taken was assessed by the pharmacist's count or as self-reported by the patient if their medication vial was not available at the time of visit. We assumed the number of tablets taken equaled the number of days between clinic appointments, unless a patient reported skipping doses and/or the tablet count appeared to have been altered. Data collected also included age, sex, race/ethnicity, concurrent medications, co-morbidities, self-reported history of alcohol use, prior INH use, adverse drug events, symptoms of progression to active disease, use of vitamin B6, physician referral, time to first INH fill, amount of INH taken, and number of days of treatment. Self-reported history of any alcohol use, concurrent use of other medications,

and co-morbidities were assessed only during the initial visit, unless the patient mentioned any of these issues during subsequent visits with the pharmacist or if the pharmacist otherwise determined there was a change. Symptoms of INH-induced hepatotoxicity and other adverse events were assessed by pharmacist questioning and patient self-report. During each appointment, patients were counseled on the importance of treating LTBI and were encouraged to continue taking INH as well as keep all future appointments in the pharmacy's clinic. All appointments were scheduled in advance and a reminder was sent by email or phone one week prior to the visit.

Patients were assumed to be lost to follow-up if they withdrew from the pharmacy clinic on their own, consistently missed scheduled appointments, or if their physician withdrew them from the clinic on medical grounds.

Categorical variables were evaluated using the chi-square test and continuous variables were evaluated using the student's t-test. Statistical significance was set *a priori* at 0.05. A subsequent logistic regression analysis was preformed to identify factors associated with completion of INH. All data was analyzed using SAS version 9.1 (SAS Institute INC; Cary, North Carolina).

Results

Three hundred and forty-eight patients with completed data on INH use were available for analysis. P-values are based on a student's t-test for continuous variables and chi-square test for categorical variables. The majority of patients who enrolled in the clinic were male (56.3%), had a mean age of 24.2 ± 4.8 years, and most were of Asian ethnicity (63.5%). Patients were generally healthy as few co-morbidities (9.2%) and use of concurrent medications (8.9%) were reported. The average time from the initial screening, diagnosis, and referral at the student health

center to enrollment in the pharmacist-managed LTBI clinic was 4.6 days. Some patients experienced an adverse drug event (21.6%), but only 7.9% were referred to a student health physician for further evaluation. Overall, the six month treatment completion rate was 67%, and the nine month treatment completion rate was 59% for the five years of available data. Since patients typically started their INH regimen at the beginning of the academic year, we analyzed yearly completion rates from August to July of each year. Six month completion rates ranged from 55 to 74% and nine month completion rates ranged from 50 to 63% depending upon the year of study. Of those patients that completed 6 months of treatment, 88% progressed to complete the full nine month course of therapy in the allotted time.

Overall, 41% of patients withdrew from the clinic. Of these patients, 52.5% withdrew on their own, citing a lack of perceived treatment benefit and 41.2% were discharged back to their primary care provider for non-compliance with their scheduled follow up appointments. Only 6.3% of patients had their treatment discontinued by their physician. Over a third (36%) discontinued therapy after the first three months. Those not completing treatment were more likely than those that did complete treatment to have developed a rash ($p=0.03$) or experienced fatigue ($p=0.04$), both possible side effects to INH. In addition, referral to a physician was observed more often in non-completers ($p=0.0002$). A subsequent logistic regression analysis yielded no statistically significant factors associated with treatment completion rates.

Comment

Limited literature suggests pharmacists have a role in the management of tuberculosis.[11-13] Our 6 month INH completion rate of 67% is consistent with CDC reported rates. At 9 months, the completion rate dropped to 59%, but with little data on completion rates in the literature, it is unknown if this is expected. In the few studies available, nine month completion rates have

ranged from 65 to 100%; however, their location and population differ significantly from our own.[14-16] Additionally, research on INH completion rates within the community pharmacy or university setting have not, to our knowledge, been published.

In this study, the average time from a patient's initial evaluation and diagnosis of LTBI to enrollment in the LTBI clinic did not differ between those completing and those not completing treatment (p=0.6), suggesting that patient behavior was similar at baseline. Those patients who complained of either fatigue or rash as possible side effects to INH treatment after enrollment were less likely to complete a full course of treatment (p=0.04 and 0.03, respectively). However, the significance of fatigue causing treatment discontinuation is questionable because we were unable to determine a baseline level of fatigue prior to the initiation of INH treatment. In addition, those patients who were later referred to a physician for evaluation of fatigue or the presence of a rash, were also less likely to complete their INH regimen (p=0.0002).

While 32.8% of patients in our clinic reported alcohol use of any amount at enrollment, statistically significant differences between those that reported baseline use versus those that did not in the rates of INH-related adverse drug events such as nausea (p=0.98), vomiting (p=0.98), or jaundice (p=0.78) were not seen as one might expect with concurrent use. This suggests that patients adhered to the pharmacists recommendations to avoid heavy alcohol use while enrolled in the clinic.

Limitations

Tablet counts at pharmacy clinic visit may have been inaccurate as some patients may have discarded tablets and/or misrepresented the number of tablets taken in order to finish their treatment within nine months. To lessen this subjective assessment, dispensing records were used to calculate adherence. Another limitation was that a large percentage of foreign-born

individuals were enrolled in the clinic which may have created the potential for language and cultural barriers between the pharmacists and patients that were not accounted for, but may have impacted the outcome of this study.

Since student schedules are typically broken up by a summer break, treatment completion rates may have been affected as a 90-day supply of INH was dispensed during this break with phone and/or email follow-up. This could explain why those who completed treatment took longer than the minimum nine months to do so (mean= 10.1 months).

For the purposes of this study, those patients who dropped out, transferred, or graduated from school were considered lost to follow-up but may have in fact completed treatment elsewhere. However, this is less likely as most students get their prescriptions filled at the campus pharmacy.

The ability to generalize our results to a non-university population may be limited due to the unique characteristics of this population. However, applicability of this study to other university and college settings is high, particularly since international students comprise a significant percentage of students today nationwide. This is an important public health issue to be addressed before international students enter the United States workforce and are potentially lost to follow up.

Conclusions

With over 450,000 foreign students in U.S. universities in 2005-2006, most coming from high tuberculosis prevalent countries, rates of LTBI in this population are likely to grow as more universities implement PPD screening programs.[17]

At our university, the majority of individuals who were referred to, and enrolled in, our community pharmacy LTBI clinic were identified as foreign-born. Therefore, since our

university has the largest international student population of any U.S. university, this model of LTBI pharmacy-based clinic care could be implemented at other institutions with smaller international populations.[17]

Community pharmacy-based LTBI clinics represent a unique niche for pharmacy and can serve an important public health function by providing individuals and communities another option in which to receive comprehensive management, counseling, and support to help encourage LTBI treatment adherence and completion rates.

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