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Early View

Research letter

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Treatment of latent tuberculosis with 12-weeks isoniazid/rifapentine in clinical practice

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Summary

Completion rate with 12-weeks isoniazid/rifapentine for latent tuberculosis was high. Direct observed therapy was solved with flexibility. Adverse events were mostly mild, except one case of suspected nephrotoxicity, which calls for heightened attention.

Background

As part of the global End TB strategy [1-3] treatment of latent tuberculosis infection (LTBI) is now recommended in low endemic middle- and high income countries for certain risk groups, such as contacts of pulmonary TB, migrants from high endemic countries and immunocompromised individuals.

US Food and Drug Administration (FDA) approved the rifamycin rifapentine (Priftin® Sanofi) (P) for treatment of active TB in 1998 and for LTBI in 2014 (www.fda.gov). P is as effective as rifampicin (R) but with a five times longer half-life. Therefore, P is administered intermittently and should be taken together with a fat-containing meal for optimal absorption. In a recent meta-analysis, P (20-30 mg/kg, max 900mg) and high dose isoniazid (H) (15 mg/kg, max 900mg) once a week for 12 weeks (3HP) provided by direct observed therapy (DOT) was as effective as other recommended treatments for LTBI i.e. 9 month H (9H), 4 month R (4R) and 3 month H and R (3HR) (OR 0.89) and associated with higher completion rate (87.5% vs 65.9%)[4]. Overall, 3HP was associated with lowest frequency of reported adverse events (AEs) (11.5%), including hepatotoxicity (1%). However, higher frequency of flu-like symptoms have been reported, as well as severe AEs (6%) even though comparisons were limited by variability in definitions and inconsistent data [5].

In 2015, 3HP was introduced as an alternative regimen to standard treatment with 9H, 4R or 3HR for LTBI at the TB center, Karolinska University Hospital in Stockholm. 3HP is at present not recommended for pregnant or breastfeeding women or in patients with severe immunodeficiency. However, studies on 3HP vs 9H among moderately immunocompromised HIV-infected persons have shown that 3HP is more effective (0.39 vs 1.25 active TB cases per person-years) and also associated with higher completion rates (89% vs 64%)[6]. Data on pregnant women inadvertently exposed to 3HP have not shown higher frequency of fetal loss or anomalies [7]. Further studies are ongoing in more severely immunocompromised HIV-infected persons and pregnant/postpartum women (www.clinicaltrials.gov). There is also recent data available on non-DOT administrations. In a study from US, completion rate was non-inferior for self-administration as compared to DOT (77.9% vs 85.4%)[8].

P is not yet approved by the European Medical Agency (EMA) but is approved by the Swedish Medical Products Agency as a licensed drug since 2013. Our objective was to evaluate feasibility, adherence and AEs with 3HP treatment of LTBI in clinical practice.

Material and methods

This was a retrospective, observational study of 3HP as treatment of LTBI in clinical practice. HIV negative migrants from high endemic countries and pulmonary TB contacts with a positive tuberculin skin test (TST) or Quantiferon in Gold® (Qiagen) test were offered 3HP as an alternative to standard

regiments for treatment of LTBI according to current clinical recommendations [9]. 3HP (Priftin® Sanofi and Tibinide® Meda) was given as DOT on one specific day of the week for 12 consecutive weeks. Patients were provided HP by the responsible TB nurse and treatment was given under supervision together with a fat-containing nutritional drink or sandwich. Contraindications to 3HP were suspected active TB, exposure to MDR-TB, abnormal liver function tests, previous AEs to H or R, pregnancy/breastfeeding, HIV or other immunodeficiency, on-going drug abuse or unwillingness to comply with DOT. Liver function test results, AEs, adherence to DOT and exceptions from regular administration e.g. shortage of drugs, were documented on separate patient report forms every administration day and in the patient´s regular file when needed.

AEs were graded 0 - 4 according to an in-house system based on severity and duration of symptoms (0 = none, 1 = mild, less than one month, 2 = mild, more than one month, 3 = severe, pause in treatment needed, 4 = severe, discontinued treatment). The study was approved by Stockholm Ethical Review Board (2018/349-31).

Results

Between May 2015 and December 2017, a total of 30 patients initiated treatment with 3HP. During the same period about 650 patients in total initiated LTBI treatment, out of which 170 were migrants from high endemic countries and pulmonary TB contacts. As such, about 5% (30/650) of all patients and about 18% (30/170) of young migrants and contacts that initiated LTBI treatment were given 3HP, while the remaining were given standard treatment with 9H, 4R or 3HR.

Clinical characteristics and AEs for patients initiating 3HP are presented in Table 1. Most were young adults below 25 years old (median 23.8, range 17-44 years) and the majority were males. The majority were migrants from high TB endemic countries, such as Somalia, Eritrea, Afghanistan and Democratic Republic of Congo. 27/30 (90%) patients completed treatment. 21/30 (70%) patients experienced any AEs.

Most common AEs were nausea/stomach ache (n=13) and headache/vertigo (n=10), rash/itching (n=3), flu-like symptoms (n=3) and slightly elevated liver enzymes (ALT maximum 94.8 IU/L) (n=2). 3/30 (10%) discontinued due to more severe AEs. One 32-year-old woman experienced severe nausea. One 44-year-old woman developed urticaria, but no other anaphylactic symptoms. One 20-year-old man developed fever, nausea, stomach pain and elevated creatinine (180 μmol/L) six hours after the first dose of 3HP and progressive kidney failure necessitated temporary dialysis with full recovery after three months. In the diagnostic work-up it was noted that he had been admitted at the emergency department due to stomach pain and elevated creatinine (106 μmol/L) after a single dose of R one month prior to 3HP, but with full recovery within a week. This event was unfortunately overlooked prior to initiation of HP. R associated nephrotoxicity has been described previously as a rare adverse

event (<1/1000) [10, 11]. With re-exposure anti-R antibodies activate the complement cascade with target-cell damage. This has to our knowledge not been described for P alone before. However, a rifamycin immunological cross-reactivity is likely, with potential deterioration of a previous R induced nephritis.

A challenge to adherence was the necessity of DOT and long travel distances to our unit. This was solved by providing the last doses by telephone-DOT or primary health care (PHC) for two patients or public transport tickets to our clinic for three patients. Shortage of P during a limited period was another obstacle and therefore clinic routine is now to set aside a complete 12-week treatment for each patient before initiation.

Conclusion

Completion rate with 3HP was high (90%) in this group with mostly young migrants from Africa, where discontinuation with standard LTBI treatment has been a challenge at Karolinska [12]. However, the study group was small and consisted mainly of younger patients, which limits generalizability of our findings to other age groups. In addition, no control group receiving standard regimens was included and protective efficacy was not possible to evaluate. AEs were mostly mild and temporary. However, one patient developed acute kidney failure, probably induced by a previous rare AE to R, which calls for heightened attention. DOT can be challenging and alternative solutions via telephone-DOT or PHC can facilitate treatment. Despite one event with nephrotoxicity, we consider 3HP as promising alternative to longer LTBI treatments, especially in young migrants and as such an improved tool in the global effort to eliminate TB. We advocate an approval of P by the EMA to facilitate introduction of 3HP in Europe and also suggest a centralized European report system to monitor rare AEs.

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Table text

Table 1. Characteristics and AEs of patients treated with 3HP. AE grade 0 = none, 1 = mild, less than one month, 2 = mild, more than one month, 3 = severe, pause in treatment needed, 4 = severe, discontinued treatment.

	Patients treated with HP (n)	Patients that reported AEs (n)
Total	30	21
Gender:		
Male	20	12
Female	10	9
Origin:		
Europe	3	2
Africa	20	16
Asia/S-E Asia	7	3
Treatment group:		
Migrants	25	16
Contacts	5	5
AE grade:		
Grade 1		9
Grade 2		8
Grade 3		1
Grade 4		3