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SHORT COMMUNICATION

Is stopping secondary prophylaxis safe in HIV-positive talaromycosis patients? Experience from Myanmar

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Objectives

The aim of the study was to determine whether it is safe to stop secondary prophylaxis in patients with talaromycosis after immune reconstitution with a sustained increase in CD4 count to ≥ 100 cells/μL after antiretroviral therapy (ART).

Methods

A retrospective cohort analysis was performed in HIV-infected patients treated for talaromycosis between June 2009 and June 2017 in Medical Action Myanmar (MAM) clinics.

Results

Among a cohort of 5466 HIV-infected patients, 41 patients were diagnosed with and treated for clinical talaromycosis. All the patients were on ART and had a CD4 count < 100 cells/μL. Of these 41 patients, 24 patients (71%) were skin smear positive for talaromycosis, while results were negative in 17 patients. Median CD4 count and haemoglobin concentration were 24 cells/μL and 7.7 g/dL, respectively. Seventy-three per cent (30) were male. Among the 41 patients, 11 (27%) died and six (15%) were transferred to other centres. Twenty-four patients (58% of the total diagnosed) stopped itraconazole secondary prophylaxis after starting active ART with CD4 counts > 100 cells/μL for at least 1 year. Throughout the duration of follow-up post itraconazole cessation, the observed incidence of relapse was zero with a total follow-up of 93.8 person-years (95% confidence interval 0–4 per 100 person-years). The median (25th, 75th percentile) duration of follow-up post-prophylaxis discontinuation was 2.8 (2.1, 6.3) years.

Conclusions

Secondary prophylaxis can be safely stopped in patients with talaromycosis after immune reconstitution with a sustained increase in CD4 count to ≥ 100 cells/μL after highly active antiretroviral therapy.

Keywords: HIV, secondary prophylaxis, talaromycosis

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Talaromycosis, a systemic mycosis caused by *Talaromyces marneffei*, is most commonly found in Southeast Asian countries. It develops most commonly in HIV-positive patients with CD4 counts of ≤ 100 cells/μL. Common clinical manifestations include fever, nonproductive cough, hepato-splenomegaly, weight loss, anaemia, and generalized skin papules with central umbilication. A presumptive diagnosis can be made following the identification of characteristic septate yeast-like organisms under microscopic examination of Wright or Giemsa-stained samples with a sensitivity of approximately 70% [1]. This can be confirmed by culture if facilities are available. Treatment with intravenous amphotericin B for 2 weeks followed by oral itraconazole for 10 weeks is effective and safe but the mortality rate can still be > 25% [2]. Relapse rates as high as 57% were described without itraconazole maintenance therapy in the pre-antiretroviral therapy (ART) era [3]. The optimal duration of antifungal prophylaxis to prevent relapse remains

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Table 1 Baseline characteristics of talaromycosis patients

Baseline characteristic	Skin smear positive (n = 24)	Skin smear negative (n = 17)	Patients who had stopped itraconazole prophylaxis (n = 24)
Male	17/24 (71)	13/17 (76)	16/24 (67)
Age (years)	32 (26, 35)	32 (27, 36)	35 (27, 38)
Weight (kg)	42 (36, 45)	40 (36, 44)	40 (34, 44)
CD4 count (cells/μL)	23 (14, 38)	27 (14, 38)	27 (14, 39)
Haemoglobin (g/dL)	7.5 (6.7, 8.9)	7.7 (7.0, 9.8)	8.2 (6.9, 9.8)
ALT (IU/L)	35.5 (23.9, 54.1)	39.8 (28.0, 53.0)	39.9 (29.5, 48.4)
Temperature (°C)	37.6 (37.3, 38.7)	38.1 (37.7, 38.9)	37.9 (37.6, 38.7)
History of fever	20/22 (91)	14/17 (82)	20/24 (83)
Lymphadenopathy	6/22 (27)	3/12 (25)	5/24 (21)
Respiratory symptoms	8/24 (33)	5/17 (29)	7/24 (30)
Hepatomegaly	15/24 (63)	12/17 (71)	16/24 (67)
Splenomegaly	1/24 (4)	4/17 (24)	5/24 (21)
Bone joint pain	3/19 (16)	6/15 (40)	5/24 (21)
Abnormal CXR	13/20 (65)	9/13 (69)	9/24 (38)
Duration of ART before diagnosis of talaromycosis (days)	−27 (−40, 11)	−22 (−61, 11)	−19 (−41, 56)
Duration of secondary prophylaxis before discontinuation (days)	Not relevant	Not relevant	346 (267, 456)
CD4 count at discontinuation (cells/μL)	Not relevant	Not relevant	255 (190, 297)

Values are median (25th, 75th percentile) or n/total (%)
ALT, Alanine aminotransferase; ART, antiretroviral therapy; CXR, Chest X Ray.

unclear [4]. Studies reporting the discontinuation of antifungal prophylaxis in HIV-infected patients responding to ART are few and involved small case numbers [5,6,7,8].

Medical Action Myanmar (MAM) is a nonprofit medical organization which operates 10 HIV integrated out-patient clinics for the poor, marginalized and vulnerable population in Myanmar. A retrospective cohort analysis was conducted to determine the relapse rate of talaromycosis after the discontinuation of itraconazole secondary prophylaxis in ART-treated patients between June 2009 and June 2017 in MAM clinics. Diagnosis was clinical with confirmation by Giemsa staining of a skin slit smear from characteristic papular skin lesions where possible. Culture was not available. All patients were treated with amphotericin (0.7 mg/kg/day) for 2 weeks and itraconazole (400–600 mg/day) for 8 to 10 weeks, followed by itraconazole 200 mg as secondary prophylaxis until they had maintained a CD4 count of > 100 cells/μL for at least 1 year on ART.

Among a cohort of 5466 HIV-infected patients, 41 patients were diagnosed with and treated for clinical talaromycosis. All the patients were on ART and had CD4 counts < 100 cells/μL. Of these 41 patients, 24 patients (71%) were skin smear positive for talaromycosis while results were negative in 17 patients. The median CD4 count and haemoglobin concentration were 24 cells/μL and 7.7 g/dL, respectively. Seventy-three per cent (30) were male. The demographic and clinical characteristics of skin smear positive and negative patients were similar (Table 1). Among 41 patients, 11 (27%) died and six (15%) were transferred to other centres, from which no clinical data could be obtained. Twenty-four patients (58% of the total diagnosed) stopped itraconazole secondary prophylaxis. The mean CD4 count of discontinued patients was 296 cells/μL, with a maximum of 751 cells/μL and a minimum of 132 cells/μL. Throughout the duration of follow-up post itraconazole cessation, the observed incidence of relapse was zero with a total follow-up of 93.8 person-years (95% confidence interval 0–4 per 100 person-years). The median (25^{th}, 75^{th} percentile) duration of follow-up post-prophylaxis discontinuation was 2.8 (2.1, 6.3) years with a range of 0.5–7.3 years for smear-positive and 1–6.5 years for smear-negative patients.

These findings contribute to the evidence that secondary prophylaxis can be discontinued safely in patients with talaromycosis after immune reconstitution with a sustained increase of the CD4 count to ≥ 100 cells/μL after highly active antiretroviral therapy.

Limitation

As plasma HIV RNA testing was not available in the project, we could not measure HIV RNA at the time of discontinuation and during follow-up.

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