

Oral Isotretinoin Combined with Oral Terbinafine Versus Oral Terbinafine Alone to Treat Recurrent Dermatophytosis: An Open-Label Randomised Clinical Trial

Abstract

Background: Recurrent dermatophytosis is becoming arduous to treat. Recently, oral itraconazole with oral isotretinoin was successful in a patient suffering from recurrent dermatophytosis. **Objectives:** To evaluate if oral isotretinoin confers any added benefit over oral terbinafine in the treatment of recurrent dermatophytosis. **Materials and Methods:** This was an open-label randomized clinical trial including 100 adult patients with recurrent tinea cruris and/or tinea corporis randomized into two groups; Group A (oral isotretinoin 0.5 mg/kg/day and oral terbinafine 250 mg twice daily) and Group B (oral terbinafine 250 mg twice daily) for 4 weeks, and followed up for 3 months. Fungal culture and antifungal susceptibility testing against terbinafine, fluconazole, amphotericin B, itraconazole, and griseofulvin were performed. **Results:** Out of the 100 patients, 91 patients (44 in Group A and 47 in Group B) completed the trial. Complete cure was seen in 19/44 (43.18%) patients in Group A and 20/47 (42.55%) patients in Group B ($P = 0.951$). Recurrence occurred in 12/19 (63.1%) patients in Group A and 13/20 (65%) patients in Group B ($P = 0.904$). Cheilitis and dryness of lips were the most common adverse effects seen in 32/44 (72.73%) patients in Group A. A total of 50 cultures were grown. The commonest species isolated was *Trichophyton interdigitale* in 36 (72%) patients, having a mean minimum inhibitory concentration of 3.13 $\mu\text{g/mL}$ for terbinafine. However, for itraconazole, it was 0.13 $\mu\text{g/mL}$, and varied minimum inhibitory concentration (MIC) values were seen for fluconazole, griseofulvin, and amphotericin B. **Conclusion:** The addition of isotretinoin to terbinafine has no added benefit in treating patients with recurrent dermatophytosis.

Keywords: Dermatophyte, fungal culture, isotretinoin, terbinafine, tinea

Introduction

Dermatophytic infections are becoming increasingly common, with recent studies showing their prevalence ranging from 36.6% to 78.4% among patients attending dermatology outpatient departments.^[1] Furthermore, the standard antifungal treatment is no longer providing a satisfactory response in a large proportion of cases.^[2-4] Reports of drug resistance to oral antifungals have also emerged from various parts of the country.^[5] Dermatologists are now frequently prescribing higher than standard doses of oral antifungals and/or for prolonged durations in an attempt to increase the cure rate. Recently, a combination of oral itraconazole with oral isotretinoin was reported to successfully treat recurrent dermatophytosis in a patient.^[6] It was proposed that retinoids

lead to increased desquamation of normal epidermis resulting in rapid sloughing off of keratinocytes and removal of fungal spores, thereby decreasing the fungal load.^[6] In this randomized clinical trial, we evaluated if adding oral isotretinoin confers an added benefit over oral terbinafine alone in the treatment of recurrent dermatophytosis.

Materials and Methods

Study design

This was an open-label randomized clinical trial conducted between January 2017 and November 2018 at the Department of Dermatology and Venereology at our institute. The study protocol was approved by the Institute Ethics Committee and was registered with the national clinical trial registry (CTRI/2017/11/010471).

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Kaushal K. Verma,
Gridharan
Senthilnathan,
Saurabh Bhatia,
Immaculata Xess¹,
Vishal Gupta,
Sada Nand
Dwivedi²,
Kanika Sahni

Departments of Dermatology and Venereology, ¹Microbiology and ²Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:

Prof. Kaushal K. Verma,
Room No: 4078, Department of Dermatology and Venereology, 4th Floor, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: prokverma@hotmail.com

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Study participants

Adult patients with tinea cruris and/or tinea corporis confirmed on 10% potassium hydroxide (KOH) mount examination, with two or more episodes of dermatophyte infections in the last 12 months, were included in the study. All patients gave informed consent. Immunosuppressed patients, patients with underlying known active liver, cardiac, renal, or neurological diseases, uncontrolled diabetes mellitus, history of hypersensitivity to either isotretinoin or terbinafine, pregnant or lactating mothers, and women desiring pregnancy during or 3 months after the treatment period were excluded. Patients who received oral antifungal therapy within the last 4 weeks or topical antifungal therapy within the last 2 weeks were also excluded. In the absence of any prior similar studies, we planned to include 100 patients in our study.

Methods

The demographic, clinical, and investigation details of all the patients were recorded in a predesigned proforma. The extent of body surface area affected was estimated by using the "Rule of nines" in each patient. Skin scrapings from the active sites of the lesions were used to prepare a 10% KOH mount and were also cultured on Sabouraud dextrose agar to isolate fungal species. Antifungal susceptibility testing of the isolates against terbinafine, fluconazole, amphotericin B, itraconazole, and griseofulvin was performed using broth microdilution assay (Sigma Chemical Corporation, St. Louis, MO, USA) according to clinical laboratory standards institute approved standard M38-A2 molds.^[7] Laboratory tests consisting of complete blood count, liver and renal function tests, fasting lipid profile, and fasting blood sugars were done at baseline and repeated at the end of the treatment. Urine pregnancy test was done in female patients of reproductive age group.

Using a computer-generated simple random allocation list, the patients were assigned to either Group A (combination of oral isotretinoin 0.5 mg/kg once daily and oral terbinafine 250 mg twice daily) or Group B (oral terbinafine 250 mg twice daily) for 4 weeks. No topical treatment was given during the study period; however, oral antihistamines (Levocetirizine hydrochloride 5 mg) were allowed as required for itching. The patients were followed up at 2 and 4 weeks to evaluate the treatment response and adverse effects. Empty drug packets were verified from the patients every 2 weeks to check compliance. Complete resolution of lesions was considered as a clinical response, and a negative KOH mount at the end of the treatment period was taken as a microbiological response. Both clinical and microbiological responses were taken as cure. The patients showing incomplete clinical response were given treatment for another 2 weeks. The patients with complete cure were followed-up every month for 3 months to determine recurrence. Outcome parameters included clinical response (complete and partial), cure, and recurrence rates in both groups.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation (range), and categorical variables as frequency (%). Continuous variables were compared between the two groups using student's *t*-test/Mann-Whitney U-test as applicable, whereas categorical variables were compared using the Chi-square test. Statistical analysis was done as per protocol analysis. *P* value <0.05 was considered statistically significant. Statistical analysis was done using Stata, 14.2 (Texas, USA).

Results

One-hundred patients were randomized to Group A ($n = 48$) and Group B ($n = 52$). There were 80 males and 20 females with a mean age of 29.23 ± 9.24 (range 18–57) years, having the disease for a mean duration of 2.06 ± 1.43 (range 1–9) years. The mean affected body surface area was $4.11 \pm 3.01\%$ (range 1%–20%). The majority of patients had tinea cruris (46%), followed by tinea corporis et cruris (36%), and tinea corporis (18%). The patients included in both the groups had similar baseline clinical and mycological profiles [Table 1]. Ninety-one patients completed the study: 44 in Group A and 47 in Group B [Figure 1].

Treatment response

In Group A, 19 patients (43.18%) achieved complete cure; 13 patients (68.42%) after 4 weeks and 6 (31.58%) with additional 2 weeks of treatment. In

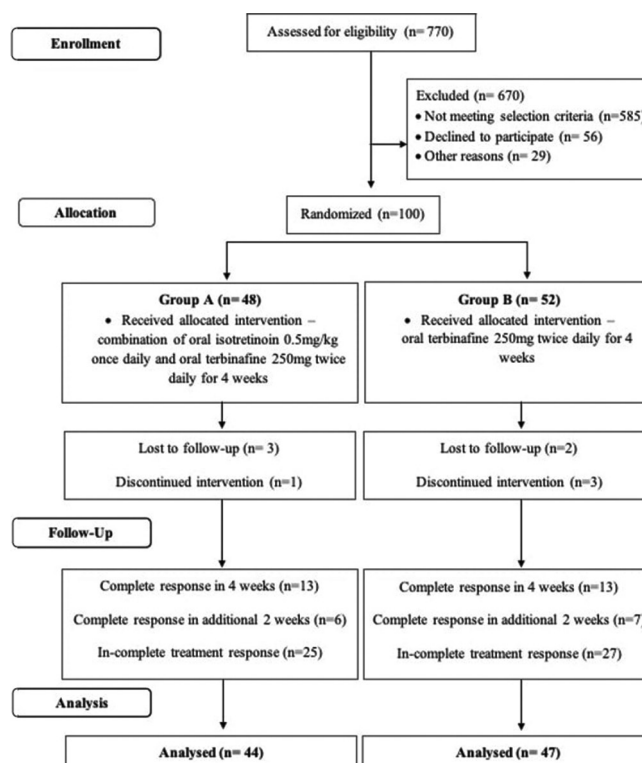


Figure 1: Flow Diagram of the study

Group B, 20 patients (42.55%) improved completely; 13 patients (65%) after 4 weeks and 7 (35%) with additional 2 weeks of treatment. The difference in treatment response between the two groups was not statistically significant ($P = 0.951$). The clinical response was comparable among the different fungal isolates [Figure 2a and b]. Out of the 39 cured patients, 25 (64.1%) experienced a recurrence, of these 12 (63.1%) were in Group A and 13 (65%) in Group B ($P = 0.904$).

Overall, no clinico-demographic variable or fungal isolate was found to be associated with recurrence. However,

the incomplete response was statistically significantly associated with a more extensive disease [Table 2].

Adverse effects

Treatment-related adverse effects were seen in 38.46% ($n = 35/91$) patients, more commonly seen in Group A than Group B (32 vs 3 patients, $P = 0.021$). Cheilitis and dryness of the lips were the most common adverse effects observed in 32 (72.73%) out of 44 patients in Group A and 1 (2.13%) out of 47 patients in Group B. Discontinuation of treatment was not required in any patient in Group A, whereas it was required in 2 patients

Table 1: Comparison between characteristics of the study patients

| | Total patients (n=100) | Group A (n=48) | Group B (n=52) | P |
|---|------------------------|--------------------|--------------------|-------|
| Age in years Mean±SD (range) | 29.23±9.24 (18-57) | 29.85±9.18 (18-48) | 28.65±9.35 (18-57) | 0.519 |
| Gender (Male/Female) | 80/20 | 37/11 | 43/9 | 0.484 |
| Tinea cruris | 46 | 21 (45.65%) | 25 (54.34%) | 0.770 |
| Tinea corporis | 18 | 10 (55.55%) | 8 (44.45%) | 0.834 |
| Tinea corporis et cruris | 36 | 17 (47.22%) | 19 (52.88%) | 0.917 |
| Duration of disease in years Mean±SD (range) | 2.06±1.43 (1-9) | 2.18±1.74 (1-9) | 1.94±1.07 (1-5) | 0.854 |
| Percentage body Surface Area involved Mean±SD (range) | 4.11±3.02 (1-20) | 4.23±3.62 (1-20) | 4.00±2.36 (1-10) | 0.705 |
| Use of soap for taking bath | 51 (51%) | 28 (58.33%) | 27 (51.92%) | 0.552 |
| Bathing frequency | | | | |
| once a day | 88 (88%) | 42 (87.5%) | 46 (88.46%) | 1.000 |
| less than once a day | 12 (12%) | 6 (12.5%) | 6 (11.54%) | 1.000 |
| Similar complaints in household contacts | 57 (57%) | 29 (60.42%) | 28 (53.85%) | 0.549 |
| Fungal isolates | 50 (50%) | 24 (50%) | 26 (50%) | 1.000 |
| <i>T. interdigitale</i> | 36 (72%) | 17 (70.83%) | 19 (73.08%) | 1.000 |
| <i>T. mentagrophyte</i> | 11 (22%) | 6 (25%) | 5 (19.23%) | 0.738 |
| <i>T. tonsurans</i> | 3 (6%) | 1 (4.16%) | 2 (7.69%) | 1.000 |

SD - Standard deviation

Table 2: Comparison of treatment responses and relapses

| | Treatment outcome at 4 weeks/6 weeks (n=91) | | | Treatment outcome at 3 months follow-up (n=39) | | |
|--|--|-------------------------------|--------|---|-----------------------|-------|
| | Complete response (n=39) | Incomplete response (n=52) | P | Relapse (n=25) | No relapse (n=14) | P |
| Males/Females | 32/7 | 40/12 | 0.551 | 20/5 | 12/2 | 0.656 |
| Age in years Mean±SD (range) | 27.61±2.78 (18-48) | 29.75±9.93 (18-47) | 0.182 | 28.40±9.39 (18-48) | 26.17±7.28 (18-40) | 0.455 |
| Disease duration in years Mean±SD (range) | 2.11±0.42 (1-5) | 1.86±1.48 (1-9) | 0.420 | 2.24±1.01 (1-5) | 2.03±1.50 (1-5) | 0.620 |
| Baseline BSA % Mean±SD (range) | 2.87±1.82% (1-8) | 5.02±3.36% (1-20) | 0.0007 | 2.55±1.80% (1-8) | 3.42±1.84% (1-6) | 0.191 |
| Use of soap for taking bath | 25 (64.10%) | 24 (46.15%) | 0.136 | 18 (72.00%) | 7 (50.00%) | 0.297 |
| Frequency of bathing less than once a day | | | | | | |
| once a day | 35 (89.74%) | 46 (88.46%) | 1.000 | 23 (92.00%) | 12 (85.71%) | 0.608 |
| less than once a day | 4 (10.26%) | 6 (11.54%) | | 2 (8.00%) | 2 (14.29%) | |
| Similar complaints in household contacts | 19 (48.72%) | 34 (65.38%) | 0.135 | 14 (56.00%) | 5 (35.71%) | 0.068 |
| Fungal isolates (n=45) | | | | | | |
| <i>T. interdigitale</i> | 12 (26.67%) | 19 (42.22%) | 0.330 | 9/12 (75.00%) | 3/12 (25.00%) | 0.895 |
| <i>T. mentagrophytes</i> | 3 (6.67%) | 8 (1.77%) | 0.265 | 2/3 (66.67%) | 1/3 (33.33%) | 0.923 |
| <i>T. tonsurans</i> | 2 (4.44%) | 1 (2.22%) | 0.397 | 2/2 (100.00%) | 0/2 (0.00%) | - |

SD - Standard deviation

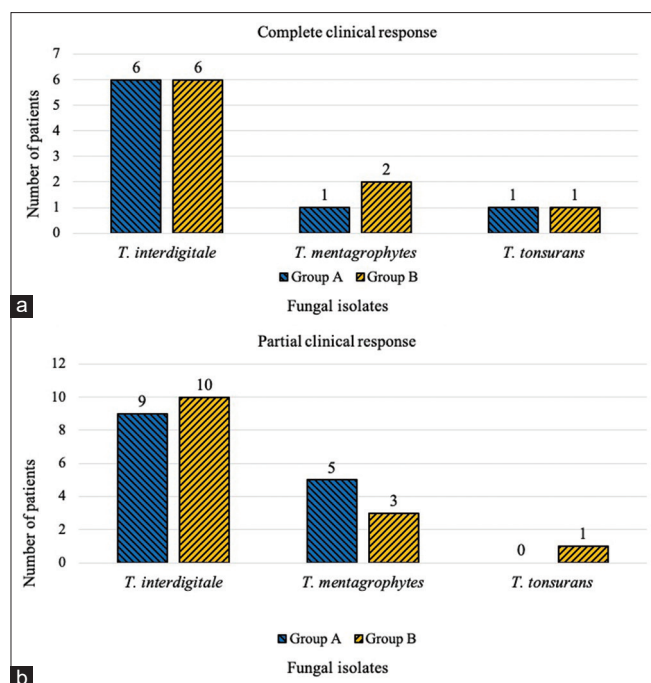


Figure 2: (a) Complete clinical response with respect to fungal isolates among the two groups, (b) Partial clinical response with respect to fungal isolates among the two groups

in Group B (1 each due to deranged liver function test and drug-induced maculopapular rash).

Antifungal susceptibility

Samples from all the patients were cultured, of which 50 samples were culture positive. The commonest species isolated was *Trichophyton interdigitale* in 36 (72%) patients, followed by *Trichophyton mentagrophytes* in 11 (22%) patients, and *Trichophyton tonsurans* in 3 (6%) patients. Antifungal susceptibility testing was performed on 39 of the 50 positive cultures (78.00%), whereas the remaining samples had poor growth in subcultures and therefore, could not be tested. The minimum inhibitory concentration (MIC) values for terbinafine in our study ranged 0.03–16 µg/mL for *T. interdigitale*, 0.06–16 µg/mL for *T. mentagrophytes*, and 0.03–16 µg/mL for *T. tonsurans*; whereas for itraconazole, it was 0.03–1 µg/mL for all three species. For fluconazole, MIC values ranged 1–64 µg/mL for *T. interdigitale*, 8–64 µg/mL for *T. mentagrophytes*, and 2–64 µg/mL for *T. tonsurans*. Similarly, MIC values for griseofulvin were 0.125–8 µg/mL, 2–16 µg/mL, and 0.25–µg/mL, respectively, whereas the values for amphotericin B ranged 0.25–20 µg/mL for *T. interdigitale*, 0.5–2 µg/mL for *T. mentagrophytes*, and 0.125–0.5 µg/mL for *T. tonsurans*. Out of 91 patients who completed the study, fungal growth was seen from 45 (49.5%) patients on the culture media.

Discussion

Dermatophytic infections are increasing world-over which has been attributed to a complex interplay between host,

fungus, drug, and environment.^[1] Other important factors include a humid and warmer climate, the unchecked use of topical corticosteroid-based combinations, increased use of broad-spectrum antibiotics, extensive use of antifungals in the agricultural industry, and the upsurge of antifungal drug resistance.^[2,3] Earlier these infections used to respond satisfactorily to standard doses and duration of topical and/or oral antifungal treatments, which are now increasingly becoming difficult to treat.^[8] Relapses after an apparent cure are also not uncommon.^[8,9] Several strategies have been tried to increase the cure rates, including hiking up the dose of antifungal drugs, increasing treatment duration,^[10] using a combination of more than one oral antifungal agent, and penetration enhancers.^[11] There was a report of successful use of a combination of oral isotretinoin (20 mg/day) and oral itraconazole (200 mg/day) in the treatment of recurrent and recalcitrant dermatophytosis.^[6] Isotretinoin increases the proliferation rate of the epidermis increasing the shedding of keratinocytes, which was hypothesized to help in eliminating the organisms. Interestingly, retinoids have also been shown to increase the skin pH thereby inhibiting the growth of dermatophytes.^[12] Therefore, we evaluated whether the addition of isotretinoin to terbinafine improved the treatment response in patients with recurrent dermatophytic infections. However, our randomized trial showed no such advantage. Failure of isotretinoin could have been due to rapid cell turnover depleting the reservoir effect of terbinafine from the skin. Further, isotretinoin reduces sebum production and may in turn decrease the concentration of terbinafine delivered by sebum at the site.^[13] Srivastava *et al.*^[14] hypothesized that the combination of itraconazole and isotretinoin may not be rational for the above-mentioned reasons. But since no statistically significant difference was found regarding the treatment outcomes and relapse rates between the two groups, it can be postulated that the addition of isotretinoin to terbinafine does not decrease the on-site concentration of terbinafine significantly so as to translate into an ineffective treatment response. Though, both the drugs have lipophilic targets that may seem to antagonize their action against the organism,^[15] systemic retinoids have been shown to have immunomodulatory effects as well^[16] which may affect the treatment outcome and may alleviate the clinical symptoms.

Earlier studies on terbinafine reported a cure rate of about 90%–93%.^[17,18] However, recent studies suggest a declining efficacy of terbinafine.^[10] Majid *et al.*,^[8] in a study on 100 patients with treatment-naive and recurrent tinea cruris/corporis, reported a cure rate of 65% with 250 mg/day terbinafine for 2 weeks, but 33.8% ($n = 22/65$) patients relapsed at 12 weeks follow up. In another study by Khurana A *et al.*,^[19] 50% (15/30) patients responded to oral terbinafine 250 mg OD for 3 weeks, whereas 20% (6/30) required additional 3 weeks treatment with terbinafine 250 mg BD; another 30% (9/30) patients had no response to Terbinafine 250 mg BD too. In patients

not cured by terbinafine OD, only 6/15 (40%) responded to Terbinafine 250 mg BD given for additional 3 weeks. All-in-all, 70% responded to either OD or BD doses of terbinafine. The lower response rate with terbinafine in our study (43%) can be explained by the inclusion of only resistant/recalcitrant cases in our study. Singh *et al.*^[10] reported a cure rate of only 30.6% ($n = 500$) with 5 mg/kg/day of terbinafine at the end of 4 weeks. More recently, a comparative trial involving 200 patients with chronic and relapsing dermatophytosis reported a cure rate of 28% with terbinafine.^[20] However, they did not correlate it with MIC values. Martinez-Rossi *et al.*^[21] used drug concentrations within tissue samples and correlated it with the activity and efficacy of a drug, especially for extracellular pathogens.

Overall, 64% of the cured patients in our study had a recurrence within 3 months. The lower cure and higher relapse rates in our study could be due to our inclusion of only patients with recurrent dermatophytosis. Further, a high proportion (56%) of patients had a history of similar illness among their household contacts.

The fungal culture positivity rate was 50% in our study. Culture positive rates have varied from 40.3% to 87.4% in previous studies.^[11,22] According to some recent studies *T. mentagrophytes* or *interdigitale* is more commonly isolated than *T. rubrum*, indicating a shift in the etiological agent.^[23] However, another study from North India reported *T. rubrum* as the most common isolate (46.4%).^[24] In our study, none of the samples grew *T. rubrum*. It has been suggested that *T. mentagrophytes/interdigitale* may be more difficult to treat, but we did not note any significant difference in the response rates between different fungal species.

Antifungal susceptibility testing was done from culture isolates of 39 patients. All the species which were tested showed significantly higher MIC values for fluconazole followed by terbinafine, griseofulvin, amphotericin, and itraconazole. In literature, MIC values of terbinafine for *T. interdigitale* range from 0.375 $\mu\text{g/mL}$ ^[25] to 2.7 $\mu\text{g/mL}$,^[2] whereas for *T. mentagrophyte*, these values ranged from 0.015 to 0.125 $\mu\text{g/mL}$.^[26] The mean MIC value of terbinafine was higher in our study as compared to the previous studies.^[2,25,26] This was expected as we included patients with recurrent and recalcitrant dermatophytosis and prolonged treatment courses have been associated with emergence of resistant isolates, requiring a higher fungicidal concentration of terbinafine.^[2] Poor response to treatment in our study group could have been due to this reason. MIC levels of itraconazole for *T. interdigitale* ranged from 0.06 $\mu\text{g/mL}$ to >16 $\mu\text{g/mL}$,^[2] whereas for *T. mentagrophyte*, these values ranged from 0.03 to 0.5 $\mu\text{g/mL}$.^[26] A wide range of itraconazole (0.06–32 $\mu\text{g/mL}$) has been reported in the literature.^[27] For *T. interdigitale*, MIC values of fluconazole have been reported to range from 0.5 $\mu\text{g/mL}$ to >64 $\mu\text{g/mL}$,^[2] whereas for itraconazole

it was 0.06 $\mu\text{g/mL}$ to >16 $\mu\text{g/mL}$.^[2] Similarly, MIC for griseofulvin has been recorded as 1 $\mu\text{g/mL}$ to 32 $\mu\text{g/mL}$.^[2] The MIC values for these antifungals were comparable to MIC values in our study.^[2,25,26] However, the MIC data might not always correlate with clinical responses.^[21]

Our study was limited by a relatively small sample size. As this study was conducted at a tertiary care institute, patients with only difficult-to-treat dermatophytosis were included, limiting the sample size. Also, the patients and investigators were not blinded to treatment and the possibility of re-infection from household contacts leading to relapse cannot be excluded with certainty. Additionally, the synergy data on use of terbinafine and isotretinoin combination would have been helpful.^[28]

Therefore, the study has shown that the addition of isotretinoin to terbinafine does not offer any added benefit to treatment outcomes in patients with recurrent/recalcitrant dermatophytosis. Also, the cure rates are limited with terbinafine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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