Author’s reply

P Ravindra Babu, A J S Pravin1, Gaurav Deshmukh2, Dhiraj Dhoot3, Aniket Samant3, Bhavesh Kotak2

From the Consultant Dermatologist, Raga Skin Care, Bengaluru, Karnataka, 1Department of Dermatology and Venerology, Kanyakumari Government Medical College, Nagercoil, Tamil Nadu, 2Medical Services Glenmark Pharmaceuticals, Mumbai, Maharashtra, India.
E-mail: dr.gaurav.deshmukh@glenmarkpharma.com

Indian J Dermatol 2017;62(6):667-9

Sir,

We appreciate the doctor’s concerns regarding rational for drug dosimetry and duration of terbinafine in the context of recalcitrant dermatophytosis.

Kindly find the detailed explanation of the same as given below.

1. We have conducted this survey in patients with superficial fungal infections of mild-to-moderate severity with single or multiple lesions. Also, the use of terbinafine in recalcitrant dermatophytosis does not feature in our article.

2. The pharmacodynamic parameter that is most often predictive of outcome for concentration-dependent drugs is “peak/MIC,” for such drugs, single dosing strategy is a better predictor of clinical response. The pharmacodynamic parameter that is most often predictive of outcome for time-dependent drugs is “%T > MIC,” for such drugs, multidosing strategy is a better predictor of clinical response[1]

3. Hence, the sentence in the query “Drugs that are concentration dependent like terbinafine use %T > minimum inhibitory concentration (MIC) as the cardinal parameter, which essentially means that a multidosing strategy is a better predictor of clinical response; thus, a twice a day dose is better than increasing the single dose as reported in this study” is contradictory and confusing.

4. Authors of quoted reference in query to support the above claim reported that “the pharmacodynamic properties of terbinafine remain incompletely described. The pharmacodynamic parameter (T > MIC, area under the curve/MIC, or Cmax/MIC) most predictive of drug efficacy has not been properly established for terbinafine[2]

5. Also, in the same study, authors were hesitant to comment on the dosing recommendations solely based on the data produced in their study[3]

6. Dolton et al. in their study for the first time reported the pharmacodynamic parameters for different dosages of terbinafine; however in this study also, authors never made comment or recommended particular dosing regimen for terbinafine (i.e., once daily or twice daily). Authors concluded that use of higher dose of terbinafine appears promising[4]

7. As mentioned in the query, if concentration- or time-dependent pharmacokinetic parameters would have been so much clinically relevant in case of terbinafine with more emphasis on multiple dosage regimen, then once-daily dosage of terbinafine would have been clinically ineffective compared to twice-daily regimen. However, that is not the case, in a systematic review of multiple clinical trials on the efficacy and safety of terbinafine by Villars and Jones, authors reported that both once- and twice-daily dosages of terbinafine are equally efficacious and safe in the treatment of tinea infections[4]

8. The USFDA has also approved both 250 mg once daily and 125 mg twice daily dosages of terbinafine for treating tinea infections[5]

9. From the above discussion, it is quite clear that concentration- or time-dependent pharmacokinetic parameters have very little impact on the clinical effect of terbinafine and the dosing frequency has very little clinical relevance in case of terbinafine. Both once- and twice-daily dosages are equally efficacious and safe

10. As correctly mentioned in the query that even
Correspondences and reported 87% and 100% clinical cure.

11. Similarly, in the current scenario where dermatophytosis is becoming epidemic in India and becoming very difficult to treat, dermatologists in India are using higher dose of oral antifungal drugs for longer duration which tends to benefit the patients more. The same is the case with topical antifungal drugs where using drugs for longer duration is a common practice nowadays.

12. Corroboration for the need of change in the management of dermatophytosis was vividly evident from a recent paper from Verma and Madhu in which authors state that “Dermatophytosis has undergone a sea change in its clinical pattern in the past few years. The standard treatment recommendations which we have been following from the Western and Indian literature are no longer valid or even realistic. In a country like India, where there is a paucity of original studies of dermatophytosis and its treatment, it is becoming amply clear that experience-based treatment of dermatophytosis is ruling the roost and is proving to be more effective than the standard guidelines provided in current literature that one often considers most valid and evidence based.”

13. Majority of dermatologists in India are using a combination of oral antifungals, higher doses of antifungals, longer duration of treatment, and even other therapies not even approved for dermatophytosis (retinoids, tacrolimus, salicylic acid, etc.) for the management of these tinea cases.

14. We conducted our survey based on a simple questionnaire to evaluate the efficacy and safety of terbinafine 500 mg once daily. In this survey, we have collected the data depicting clinical experience of the dermatologists in real-time settings who were using terbinafine 500 mg once daily in their patients for the treatment of dermatophytosis.

15. Since it was a simple observational survey and not a randomized, comparative, controlled, prospective clinical trial, there was no question of comparative clinical arm or use of particular regimen of terbinafine for specific duration.

16. In this survey, we only tried to highlight the clinical experience and efficacy and safety of higher dose of terbinafine (i.e., 500 mg once daily) which has been commonly used nowadays by dermatologists in India.

17. Our intention was to highlight the clinical experience of dermatologists in real-time settings and not to comment on or to compare the different dosing regimens of terbinafine.

18. The observational design of the survey has been clearly mentioned as the limitation of survey. It has also been mentioned that there is a need of long-term comparative, randomized trials to address the shortcomings of this survey.

19. No reference in this article has been misconstrued or misquoted as written in the query. We have clearly mentioned that studies by Cole and Stricklin and Hay et al. reported 87% and 100% clinical cure rates, respectively, with 500 mg/day terbinafine and not as 500 mg once daily.

20. In our survey, 12% of patients reported adverse drug reactions (ADRs) associated with the use of terbinafine which is in accordance with previous results reported by various authors. Even though hepatic and optic side effects are seen with terbinafine, it is not necessary that each and every patient using terbinafine will report those side effects. Since it was an observational retrospective survey in an uncontrolled setting, many patients may not have reported the ADRs.

21. The treatment duration mentioned in the survey was based on the common practices followed by dermatologists in India. In our article, we have emphasized the fact that using terbinafine for extended periods seems to be beneficial in the treatment of dermatophytosis in the current scenario.

Conclusion

With the changing scenario of dermatophytosis in India, many dermatologists are relying on their clinical experience and practice rather than relying on the standard guidelines. Majority of dermatologists in India are using a combination of oral antifungals, higher doses of antifungals, longer duration of treatment, and even other therapies not even approved for dermatophytosis (retinoids, tacrolimus, salicylic acid, etc.) for the management of these tinea cases and these strategies are proving to be more effective than the standard guidelines provided in the current literature. In this survey, we have shared the clinical observation of the dermatologists in a real-time setting in an uncontrolled environment. Even though terbinafine at the dose of 500 mg once daily may not be rational according to standard guidelines, these guidelines hold very little clinical significance in the current scenario in India for dermatophytosis. In this survey, we have clearly found that higher dose of terbinafine (500 mg once daily) was efficacious and safe in the treatment of dermatophytosis. To further validate these findings, long-term randomized comparative studies are warranted.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am 2009;23:791-815, vii.
2. Sakai MR, May ER, Imerman PM, Felz C, Day TA, Carlson SA, et al. Terbinafine pharmacokinetics after single dose oral administration in the dog. Vet Dermatol 2011;22:528-34.
3. Dolton MJ, Perera V, Pont LG, McLachlan AJ. Terbinafine in combination with other antifungal agents for treatment of resistant or refractory mycoses: Investigating optimal dosing regimens using a physiologically based pharmacokinetic model. Antimicrob Agents Chemother 2014;58:48-54.
4. Villars V, Jones TC. Present status of the efficacy and tolerability of terbinafine (Lamisil) used systemically in the treatment of dermatomycoses of skin and nails. J Dermatolog Treat 1990;1:33-8.
5. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020539s021lbl.pdf. [Last accessed on 2017 Sep 22].
6. Majid I, Sheikh G, Kanth F, Hakak R. Relapse after oral terbinafine therapy in dermatophytosis: A Clinical and mycological study. Indian J Dermatol 2016;61:529-33.
7. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: An appraisal. Indian J Dermatol 2017;62:227-36.
8. Dogra S, Uprety S. The menace of chronic and recurrent dermatophytosis in India: Is the problem deeper than we perceive? Indian Dermatol Online J 2016;7:73-6.
9. Cole GW, Stricklin G. A comparison of a new oral antifungal, terbinafine, with griseofulvin as therapy for tinea corporis. Arch Dermatol 1989;125:1537-9.
10. Hay RJ, Logan RA, Moore MK, Midgely G, Clayton YM. A comparative study of terbinafine versus griseofulvin in ‘dry-type’ dermatophyte infections. J Am Acad Dermatol 1991;24:243-6.

How to cite this article: Babu PR, S Pravin AJ, Deshmukh G, Dhoot D, Samani A, Kotak B. Author's reply. Indian J Dermatol 2017;62:667-9.

Received: October, 2017. Accepted: October, 2017.