Recurrence of Fungal Nail Disease and the Dissociation of Relapse from Re-infection

Sir,

Although the newer drugs for onychomycosis are more effective than their predecessors, they still leave much room for improvement; we can therefore expect more, if not better, drugs. Their gestation will inevitably be subjected to the usual battering by tedious double-blind, randomized "placebo"-controlled studies, procedures which lose as much in understanding as they give in assurance. Drug regulatory agencies will inevitably ask for comparisons of relapse rate with different drugs, the obvious and necessary information which we should have had long ago (1), but still fail to provide. Of course, recurrence rate is essential to the comparison of the efficacy of drugs, particularly for chronic infections such as onychomycosis. But the problem which immediately becomes apparent, and which is implicit in the definition of recurrence, is the need to dissociate its twin components: relapse and re-infection. Yet awareness of need, let alone understanding of how it can be achieved, is not listed in the task books of mycology, pure or applied (2). This paper is an attempt to rectify that omission, by considering ways in which these two distinct entities can be measured.

Relapse is simply the re-appearance of the same episode of disease, *whatever time has elapsed*; re-infection is the re-appearance of a new episode of the same disease caused by a new infection. If a recurrence is the re-appearance of the very same disease by the very same causal organism, this implies that the disease has never completely gone. The somewhat disturbing alternative is a recrudescence from a nest of the original infectious agent that has persisted *in the absence of clinical disease* – a reservoir rather than an infection, although, pathologically, this is a re-infection, not a relapse. One of the essential pilot studies, therefore, entails careful structural and mycological studies of nails which have apparently been "cured", to establish whether or not there is persistence of minor pockets of residual disease, or of fungi sequestered without disease. The relative prevalence of these two entities could be critical to the development of a recurrence.

Re-infection turns out to be no less complex. Only when an infection is cured, the causal organism is eradicated and the involved tissues heal, will the likelihood of new re-infection necessarily be the same as in the general population? If it is not, there must have been an abnormal propensity for development of the disease either before the infection or subsequent, and presumably consequent, to it. We therefore need to know whether an infective episode decreases the rate of re-infection, as commonly occurs with disease-provoked immunity, or enhances the risk of re-infection from, say, a residual structural abnormality such as secondary nail dystrophy. It is clear that for the efficacy of drug treatment of onychomycosis, relapse rather than re-infection will be the major consideration.

Having teased out some of the subtleties of the deceptively innocent definition of *relapse* and *re-infection* from the process of *recurrence*, can we now apply the simple working definition of relapse as a recurrence not due to a re-infection to the measurement of both events? Sadly, as will become apparent, this simple method resembles the parental definitions in having a deceptive simplicity, which in this case hides the problems of clinical observation and mycology.

Measurement of relapse and re-infection rates

The essence of the method is to establish the time to re-appearance of clinical and mycological evidence of disease in patients who have had their onychomycosis cured. From this, a group prevalence of re-appearance of the nail condition and mycological infection can be plotted against time. If *relapse* has any therapeutic significance its rate would have to be greater than that of *re-infection*. Therefore we can predict a single curve for recurrence formed by the superimposition of the discrete curves for relapse and re-infection. Since the slope of the cumulative curve for relapse would, by definition, be steeper than that for re-infection, the combination of the two curves, which is the plot of the raw data collected for recurrence, would have a double, camel hump, course. From this cumulative curve of recurrence, the slope of each underlying single curve could then be calculated, giving the rates for both relapse and re-infection. But, alas, the devil is in the detail, from clinical observation to mycology and study organization, as will now be discussed.

Clinical observations

Detection of the earliest *clinical* change of recurrent onychomycosis is in large part guesswork. The main problem with clinical assessment of early or minimal disease is its indistinguishability from trivial, non-infective nail changes, which is why it is usually given mycological support. Nevertheless, the clinical observation of disease re-appearance has to be made independently of mycology with photographic recording, together with a note of site, severity, causal organism of fungal disease elsewhere, with evidence of predisposition, such as fungal load and ease of delivery to the site of infection.

Mycology

The incomplete reproducibility of microscopic examination of KOH preparations for hyphae, and the even worse reproducibility of mycological culture, together with the uncertain significance of both after drug therapy (1), seriously limits their value. If, as seems likely, culture is only half as reproducible as KOH, if not less, it follows that a minimum of two independent samples should be used for KOH examination and four for culture. Of course, all such studies would be enormously enhanced by an improved mycological methodology (1).

Study organization

The study group must be homogeneous for factors which may influence disease re-appearance, e.g. type (including mycological) extent of disease, time taken to complete cure and its subsequent duration, and site and nature of fungal disease elsewhere. Since the group size required must be large enough for group analysis, yet cannot be predicted in advance, the study would have to be expanded and analysed continuously, independently of the examining clinician who would need to be kept unaware of the cumulative findings. Finally, either a single drug is used for therapy, or the groups must be large enough for separate analysis of each drug.

It will be apparent that both the clinical and pathological demands of such a study are impossibly excessive, and that a practical compromise would be essential.

Other methods

Other methods include carrying out a thorough investigation of nails which have been classified as clinically and mycologically cured by drug therapy. The prime purpose would be to find the basis of relapse, since this must be due to a continuing, but hidden, focus of disease. Likewise the relationship to this of a re-infection from a fungal reservoir without infection. To achieve this, "cured" nails will have to be re-investigated in detail in the first weeks of "cure" and subsequently. This re-investigation would entail repeated examination of nail clippings and subungual keratin for the identification of nests of onychomycotic disease. Such a study would include the development of a mycology which could define with precision both presence and vitality of causally associated fungi (1).

An altogether more interesting methodology would follow if it were possible to define chemical – including genetic chemical – characteristics of a new infection in an individual. Although it would then be possible to decide whether a recurrence was due to a relapse or a re-infection, such a characterization of individual fungal infections seems more desirable than likely. What could be done, however, is to use chemical characteristics to define a group of patients with the same discretely characterizable infections, and then to show whether or not the group size changes with re-appearance of disease.

Conclusions

Although the questions we have asked are trivial, the answers, and the clinical task in providing them, are surely essential to the development of new drugs which go beyond cure, to the prevention of relapse and re-infection.

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