

# Miles



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August 8, 1984

John R.A. Simoons, Ph.D.  
The Rheumatoid Disease Foundation  
5140 Revere Road  
Parkwood  
Durham, N.C. 27714

Dear Dr. Simoons:

Re: Systemic Use of Clotrimazole in Rheumatoid Arthritis

As discussed over the telephone I am forwarding to you a number of comments by members of our medical research department (Drs. Vanov, Raphan, Birkett and Battye) and by the head of our statistical department (Dr. Ingram). They are very informal and given after only a short review of your protocol, but may, nevertheless, be of some value to you and Dr. Turner.

As emphasized yesterday, the study will be conducted under Dr. Turner's physician's IND while we provide reference to background data and the supply of the investigational drug (active and placebo).

Some of our comments are as follows:

- Dr. Vanov:
1. The protocol has apparently been written after a careful consideration of many study aspects. The protocol is detailed sufficiently; however, the Introduction and Background are too long.
  2. Two potential methodological problems are: the design or crossover and the use of clotrimazole as an add-on (second) drug to nonsteroidal drugs.
    - a) Crossover: I would prefer parallel group design; e.g., only the first part of the study without the washout and crossover. Reasons: i) FDA discourages crossover design for chronic disease studies, ii) rheumatoid arthritis is known to have spontaneous remissions and exacerbation in the natural history of the disease.

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Dr. Battye (cont'd):

aspect, and I think the protocol covers that fairly well, although I would agree that women of child-bearing potential should be completely excluded rather than just "pregnant women or nursing mothers".

If this study was to show tolerance and safety without patient rheumatoid deterioration, it would still have been worthwhile because it would give us confidence to explore this indication further.

Dr. Ingram: There is no justification given for the choice of a cross-over design. At ....., we had many problems with cross-over designs in rheumatoid arthritis (RA). The proposed statistical analysis appears to have been chosen so that the investigator can do it on his micro-computer. There are no rules for patient replacements.

The therapy scheme and the temporal relation between therapy and patient visit is not specified.

The primary measure of efficacy is not given. What happens if a particular joint or grip cannot be measured? How was the number of patients chosen?

Shouldn't the protocol be limited to a narrower range of Functional Capacity classifications (App D; p. 14)?

I would also like to enclose for your perusal a draft of "Proposed Guidelines For The Clinical Evaluation of Disease Modifying Antirheumatic Drugs (DMARDs)" which had been circulated recently by the PMA and which refers to letter dated June 20, 1984 by Daniel E. Furst, M.D., of the University of Iowa, Division of Rheumatology.

Best regards,

  
Paul H. Spiekermann, M.D.

PHS/ut  
Enclosures