the morphologic counterpart of the lesion's biologic evolution rather than the expression of different clinicopathologic entities.

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NOTES & COMMENTS

Efficacy of docosanol

To the Editor: I write in response to a letter published in the Journal[1] in which Professor Spruance raised several points questioning the legitimacy of our conclusions on the efficacy of topical docosanol (n-docosanol) against cold sores.[2] The issues raised in this letter can essentially be summarized in 5 points: (1) The use of any placebo other than vehicle alone renders any study uninterpretable. (2) Demonstrations of in vitro antiviral activity aside, it is necessary to demonstrate antiviral activity in clinical trials before claiming an antiviral effect. (3) Docosanol (if one were to agree it works) might be anti-inflammatory. (4) Docosanol is ineffective in Professor Spruance's guinea pig studies. (5) Clinical trials in herpes labialis should not proceed without proof of a mechanism of action established.

Although this letter raises several important clinical trial principles, it also makes several of these "perfect world" arguments impossible to achieve. For example, we were asked to provide a look-alike, smell-alike, taste-alike, feel-alike placebo cream, absent the active ingredient. Unfortunately, this would have consisted of a clear, watery liquid, because the active ingredient itself contributes significantly to the consistency of the cream. Our polyethylene glycol (PEG) placebo, however, was very well matched and easily formed the basis of an appropriately blinded study as outlined in our report. In other words, to follow the concerns raised, this program would have been dropped entirely for lack of a "typical" placebo. Indeed, Professor Spruance points out that PEG has consistently shown itself to be inert in animal studies.[1,3] Certainly, it has never been shown to have any impact, either positive or negative, in numerous herpes clinical trials that used a PEG-based product or placebo.[3]

Similar limitations apply when assessing the antiviral activity of docosanol because of its lipophilic nature. Yes, it is different than more traditional antivirals. However, its antiviral mechanism has been elegantly demonstrated by Spear's group.[4] We did not claim to have observed an antiviral effect in our clinical trial. On the contrary, we pointed out that antiviral testing, even in larger clinical trials, has been of little help. No difference in medians was observed in Professor Spruance's topical penciclovir study[5] of 4573 enrolled patients (of whom 3057 initiated treatment), leading to the Food and Drug Administration to disallow any mention of viral shedding in the product insert. On the other hand, our reported study[2] was by far the most aggressive study of clinical assessment and follow-up in herpes labialis reported to date. Patients were clinic-initiated into fully blinded, parallel, randomized treatments before the onset of papules and then followed up twice daily. In my opinion, these clinical trial models represent significant breakthroughs in the study of self-limited infections such as herpes labialis. Recently published studies of topical acyclovir cream once again demonstrated the limitations of very large patient-initiated protocols in demonstrating clinically meaningful events.[6]

That docosanol may have mechanisms over the primary mechanism, such as an anti-inflammatory effect, cannot be ruled in or out by our study and seems to be entirely based on hypothesis. I fail to understand this issue being raised in the context of this clinical trial.

We do acknowledge, however, that docosanol has been ineffective in Professor Spruance's guinea pig studies.[7] Because we report the results of a large,

aggressive, and highly defined clinical trial, it would seem that this model was not predictive for this drug. As Professor Spruance has noted, a negative effect on herpes labialis of a PEG-based placebo is highly unlikely.[1,3] Would such a discrepancy be otherwise explained on the basis that animal models do not seek to treat recurrent disease in its prodromal stages, or that they are optimized to study topical nucleoside antivirals, or that study subject numbers are not comparable with human trials? Regardless of the myriad of possible explanation(s) for discordance with specific guinea pig protocols, however, the positive human data in 2 very large clinical trials, as we reported, remain compelling. It is relevant to add that not all animal models of docosanol have been negative. Ying et al recently presented evidence that docosanol cream reduces herpes simplex virus-1 and herpes simplex virus-2 viral titers in hairless guinea pigs and vesicle numbers in both hairless and Hartley guinea pigs ("Docosanol Treatment of Herpes Simplex Virus in Hairless and Hartley Guinea Pigs," presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Ill, December 16-19, 2001).

Finally, I simply do not agree that trials should never proceed until mechanisms of action are clear. It is normal and appropriate to formulate a rationale for a clinical trial in the absence of complete mechanism of action information. The safety of docosanol, as well as its limited potential to induce the development of resistance, on the basis of in vitro understandings of mechanism, constituted persuasive arguments in favor of commencing clinical trials.

Our studies have shown a novel approach to the study of herpes simplex labialis. As we learn to intervene earlier and more carefully in the natural history of this disease, we have become more adept at demonstrating differences that exist. Docosanol cream is a very acceptable nonprescription topical treatment alternative to prescription topical nucleoside antiviral products.

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