Finally, the pace of innovation in psoriasis therapy is accelerating. For 50 years, only four systematic therapies (Methotrexate, PUVA, oral retinoids, and cyclosporine) enjoyed substantial use (Greaves and Weinstein, 1995). Although often effective, each of these therapies has associated risks. In the next few years, a large number of new systemic agents for psoriasis are likely to become available. Although differing in mechanism, many of these new treatments alter immunity and some should be considered immunosuppressive (Granstein, 2001; Griffiths, 2002). As a result, increased risks of infection and certain cancers are documented for cyclosporine in this issue of the JID and elsewhere for cyclosporine and other potentially immunosuppressive psoriasis therapies must be considered in determining the long-term safety of these agents (Paul, this issue JID; Marcil and Stern, 2001; Margolis et al, 2001).

In contrast to the codified study methodologies required for initial drug approval, uniform regulatory requirements to assess adverse events that are likely to only emerge with prolonged use are generally lacking. Rather, regulatory agencies and companies typically negotiate postmarketing safety requirements (if any) at the time a new agent is approved. The study by Paul et al published this month highlights a number of important issues concerning the evaluation of long-term safety for systematic therapies for psoriasis and other chronic dermatologic diseases. Among these issues are: (1) When is a cohort study likely to adequately quantify long-term relative and absolute risks? (2) What long-term safety issues can be adequately addressed from the study of other populations using the same drug long-term (i.e., those without psoriasis)? (3) How does the organization, financing and control of safety studies affect the likelihood that a study will provide a robust safety evaluation? (4) How can we insure the timeliness and balanced presentation of safety data for multiple competing drugs with a common therapeutic indication? These issues are important to practitioners and patients, as well as pharmaceutical and biotechnology companies who contemplate the development of systemic medications for psoriasis and other chronic diseases.

The appropriateness, feasibility, utility, and design of a cohort study meant to establish the safety of a treatment of a chronic disease such as psoriasis depends on a number of factors, including: (1) the hypothesis to be tested; (2) power desired; (3) the availability of appropriate controls or comparator data; (4) the anticipated duration of use; and (5) latency between exposure and the detection of an associated adverse event. These factors, rather than commercial considerations, should govern study design.

Advancing hypotheses provide strong guidance in study design. In the case of the new immunomodulatory agents for psoriasis, the long-term safety issues are generally similar to those for cyclosporine and have been the subject of debate for more than a decade (Stern, 1989). They include malignancy, particularly squamous cell cancer of the skin, lymphoproliferative disorders, infection, immunologic reaction to the agent itself, and autoimmune disease. For all endpoints except skin cancer, if available, data from demographically comparable populations treated with comparable dose and for similar duration for other indications should provide information that is highly likely to be applicable to patients with psoriasis.

After controlling for exposure to potential carcinogens, the risk of nonmelanoma skin cancer and melanoma among patients with psoriasis is comparable to genetically similar persons living in the same geographic areas (Stern et al, 1985). However, as a result of exposure to a variety of potentially carcinogenic therapies, patients with psoriasis who are candidates for systemic immunosuppressive therapy are likely to be at higher risk of skin cancers, particularly squamous cell carcinoma (SCC) (Stern and Laird, 1994). Further, interactions between prior therapies and subsequent immunosuppressive treatment may put some individuals at extremely high risk. We know those with high levels of exposure to natural sunlight are at particularly high risk of SCC following long-term immunosuppression. For example, the risk of squamous cell carcinomas among Australian transplant recipients is far higher than transplant patients in Europe (Ramsay et al, 2002). Long-term therapeutic ultraviolet-B exposure among psoriasis patients may have a similar effect, but this has not been systematically assessed. Paul confirms that prior exposure to PUVA is a risk factor for SCC among patients who subsequently utilize cyclosporine, but he did not examine the relation of level of dose of PUVA to this risk. An earlier study demonstrates that exposure to at least 200 PUVA treatments and subsequently use of cyclosporine was associated with extremely high SCC risk, nearly an average of nearly one SCC per year per person, an incidence equalled only by Australian transplants (Marcil and Stern, 2001; Ramsay et al, 2002). Less exposure to PUVA did not have a significant effect on SCC risk during cyclosporine therapy.

From studies in both psoriasis and the general population, we know that the risk of squamous cell cancer increases with the duration and dose of therapy of immunosuppressive therapy. The possible persistence of increased risk after immunosuppressive therapy is stopped is particularly important for younger patients using immunosuppressive therapy, but this issue has not been systematically assessed. In organ transplant patients, skin cancer risk is lower during the first two years of immunosuppressive therapy than subsequently (Ramsay et al, 2002). Therefore, the power of a study to detect important increases in risk is a function of its duration, the completeness of follow-up as well as the size and...
characteristics of the study population. Particularly important determinants of the expected incidence of SCC in a study population are age, skin type, geographic residence, total exposure to other potential carcinogens and the interval since these exposures. Although complex, robust assessments of skin cancer risk should be feasible in reasonably sized studies of psoriasis patients, the relatively low incidence of lymphoreticular malignancies in the general population makes precise risk assessment of this endpoint more difficult in psoriasis studies. In Paul's study, although not statistically significant, the incidence of lymphoma was higher in the "high" exposure group, suggesting increased risk with increased dose. In fact, detection of just one more lymphoma in this study's high dose group would have yielded a substantial (8.6-fold) increase in risk that would have been significant. Further, the lack of complete follow up raises further questions about the "lack of significance" of the study's finding concerning lymphoma in high dose patients. In assessing risk, the conservative assumption is that the incidence of adverse events is higher among those not followed than those followed. Therefore, it remains unknown whether substantial increase in the relative risk of lymphoma seen in other populations occurs at the lower doses of cyclosporine used in psoriasis (Opelz and Henderson, 1993). Paul's study does, however, permit us to exclude a high absolute risk of lymphoma with substantial confidence.

Excluding a high absolute risk of SCC among psoriasis patients and determining the relation of dose for use on the basis of Paul's report is less feasible. Especially useful in determining risk attributable to a therapy is examining variation in risk among groups followed for the same interval but who vary substantially in the level of exposure to the agent under study as well as other attributes and exposures related to skin cancer risk.

If a study's findings are to be robust, possible latency between exposure and cancer development also requires complete follow-up for a substantial period (for SCC at least 80% follow-up for 5 years seems a minimum). Because of lower baseline incidence of SCC in Europe even if all other factors are comparable, a European psoriatic study requires two to five times the number of person years of follow-up to have the same power to detect a significant increase in risk as a study in the United States. Good data on dose and duration and not just "ever used" for all relevant exposures both at entry and during follow-up is especially important if interactions between multiple therapies are to be quantified.

A long-term study with patients enrolled at 277 centers in 11 countries speaking at least 8 different languages presents a formidable challenge. When the determinants of study success are considered, such a design seems far from ideal. Paul and colleagues have done admirably well with a study of this design, but one might speculate about why the sponsors chose this design.

The design of company sponsored postmarketing "safety" studies often appears to be more marketing than science driven (La Puma et al, 1995). One can understand the temptation to a pharmaceutical company to mask a seeding study (i.e., a way to get practitioners comfortable with use of therapy) as a safety study. Since companies are likely to be the only funding source for most postmarketing safety studies, motivating companies to resist this temptation is essential if safety concerns about a drug are substantial and robust answers are desired. At present, many forces make it difficult for a company to resist the temptation to make marketing rather than safety the primary determinant of a study's design. Typically, postmarketing safety studies are a result of "Phase 4" agreements made between regulatory agencies and companies as a condition of approval. The company that conducts the more rigorous study is likely to have the findings of this study, especially if published, used against them by the competition whose apparent safety advantage might simply reflect a less rigorous study. Today, investigators face the choice of doing it the company's way or not doing it at all. In times when it is so difficult to support clinical research, there is little choice but to do it the company's way.

In view of these unfortunate circumstances, accurate quantification of the carcinogenic risk of new immunomodulatory therapies for psoriasis will require change in the ways safety studies are organized, financed and conducted. Highly motivated independent academic investigators adequately trained to design and conduct the long-term safety studies are needed. Of course this will not be enough. The ground rules and quality standards that govern long-term safety studies must change and become as rigorous as those for pre-approval studies.

Only the timely completion of well designed and executed safety studies can provide the information needed for optimal decision making in treating a chronic disease. Employees of pharmaceutical companies or contract research organizations, whose economic well being is dependent on the continued pleasing of companies (remember Enron and Arthur Anderson, respectively), should not design or conduct these studies. Clear incentives to independent investigators to collect robust, accurate and complete data are needed. These investigators must control the design of the study, the data, and be free to publish their findings. The ultimate responsibility for insuring the robustness of postmarketing safety studies rests with the regulatory authorities. If there are sufficient long-term safety concerns about a treatment to require a study, that agency should require that the results of an independently conducted high quality study be submitted in a timely manner or the drug's approval be withdrawn.

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REFERENCES