Does Clinical Research Help Pemphigus Patients? Precautions and Suggestions

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Evidence of Limited Evidence

The review by Eleonora Ruocco et al. [1] in this issue of the journal offers a good documentation of the potential for clinical research to clarify the role of environmental factors in the development and triggering of pemphigus. In principle, non-pharmacological interventions may represent a mean to modulate disease severity. In the meantime, the review shows the limitations of our current knowledge. In fact, there is a general lack of reliable quantitative estimates of association for most of the proposed causal factors and a large part of the evidence presented comes from isolated case reports, in vitro data and previously published narrative reviews.

A balance view on the role of environmental factors is of the utmost importance to physicians and their patients. This would require thoroughly considering the quality and strength of the evidence, and the possibility of generalizing the study results from benchside to bedside, from a single case report or a clinical series to the patients’ population or, more simply, from one geographic area to another. Although much has been learned about the pathogenesis of acquired blistering disorders, little is known about key events in the interplay of environmental and genetic factors of these disorders [2].

Risk Assessment

The best way to assess risk factors in humans is by epidemiological studies, i.e. ecological correlations and analytical studies. In particular, analytical studies, i.e. cohort and case-control studies, can provide an estimate of the probability (risk) of developing a given disorder in people exposed to a candidate risk factor, adjusting, in the meantime, for confounding variables, i.e. underlying factors which may distort the association under study being connected both with the disease and the exposure of interest. In addition, these studies may offer clues to identify biological interactions and allow to model risks, taking into account the combined effect of two or more supposed risk factors. For example, analytical studies may provide an estimate of the probability of developing pemphigus on exposure to a given drug, controlling in the meantime for drug indications and other potential confounding factors, e.g. exposure to other drugs, age, sex, occupation etc. Moreover, if these studies are large enough, they may permit to explore variations in risk estimates according to the presence or absence of genetic traits which may predispose to the disease (effect modification).

In principle, both cohort and case-control studies are suited to produce risk estimates. However, when the dis-
ease is rare, as is the case with pemphigus, case-control studies may represent the only practical option. Table 1 in the review of Ruocco et al. [1] offers a good summary of those factors which may be worth of exploration in a large-scale case-control study involving newly diagnosed pemphigus patients and a suitable control group, i.e. subjects who come from the same ‘study base’ [3] as cases but do not present the disease of interest. Drugs could be analysed individually or grouped according to different hypotheses concerning the relation between the chemical structure and the biological activity, e.g. the thiol drug hypothesis. It should be noted that for a drug like penicillamine, an induction rate of pemphigus foliaceus as high as 6–7% after 6 months of treatment has been proposed [4]. If that is the case, long-term cohort studies of patients treated with the drug could be feasible, looking at clinical and subclinical manifestations, and at potential pathomechanisms (molecular epidemiology).

Expanding the Research Agenda

The last few decades have seen an impressive increase in the number of randomized clinical trials carried out in dermatology. However, to the best of my knowledge, not a single randomized clinical trial has dealt with the treatment of pemphigus. Even if a large consensus exists concerning the use of systemic steroids, the timing, starting dosage and duration of treatment are still a matter of controversy. Equally unaddressed is the effectiveness of drug combinations. Factors affecting the long-term outcome and the responsiveness to drugs are also poorly understood.

The situation is similar to what is observed with many other rare disorders. It may be explained by several factors, including the limited resources available, practical difficulties with establishing collaborative research networks on rare diseases, and, to some extent, the dominant influence of the market on clinical research [5]. The research agenda should be set, more firmly, according to unanswered clinical questions and the patients’ needs.

Signals of a Change?

In spite of the rather frustrating situation outlined above, there are signals of a possible change. In particular, there are attempts to create international networks for clinical and epidemiological studies. In Europe, an international randomized clinical trial (the Pempuls trial) has been set up to assess the effectiveness of adjuvant intravenous high-dose steroids, added to a standard combination treatment of prednisone and azathioprine, in newly diagnosed pemphigus patients. Information on this trial can be found at the website www.pempuls.nl. Partly overlapping with such an initiative, the project Pemprisk, aiming at assessing risk factors for pemphigus through an international case-control study, has been delineated. The success of such initiatives, still at their feasibility stage, relies, to a large extent, on the commitment of conscientious and motivated clinicians. It would be highly desirable that they could find adequate support and resources at the European central level.

References