

METHODOLOGY AND POTENTIAL PITFALLS IN ALLERGIC DISEASES STUDY DESIGNS: MEASUREMENTS FOR THE ASSESSMENT OF THE OVERALL SEVERITY OF ATOPIC DERMATITIS – THE FOUR STEP SEVERITY SCORE` (FSSS), SCORAD-RELATED, ELECTRONIC SYSTEM, FOR THE SIMPLE AND RAPID EVALUATION OF THE SKIN AND MUCOSAL ALLERGIC INFLAMMATION

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SUMMARY: Medical statistics may contribute to ameliorate research by improving the design of studies and identifying the optimal method for the analysis of results. Sometimes, nevertheless, it could be misemployed flawing the benefit potential. Allergic diseases pathogenesis is recognized to be systemic but global initiatives such as GINA and ARIA documents define allergic asthma and rhinitis as organ diseases; such an asymmetrical view raises a set of known and unknown confounding that could influence the quality of the process of evidence-based decision-making (topic symptomatic therapeutic interventions versus systemic pathogenetic interventions).

This article shows the first scoring system for the assessment of atopic dermatitis lesions developed in the allergy-area. A four-step severity score (FSSS) was chosen in agreement with those developed for asthma and rhinitis in global initiatives, to avoid any further differences in evaluating the severity of allergic diseases. FSSS relates each step with the objective signs of the SCORAD and rates the disease course as intermittent or persistent. A devoted electronic program has been also framed to allow a quick and simple contemporary evaluation of the SCORAD Index (Section I) and of the FSSS (Section II); the program furthermore foresees a third section named ESAS (Extra Skin Allergic Signs) (Section III) in which it is possible to check whether organs other than the skin are involved by the allergic inflammation.

The limitations potential generated by a misemployment of medical statistics for clinical trials designed to establish benefits rising from specific immunotherapy for allergic diseases have been also discussed extensively.

Key-words: Atopic dermatitis, allergic disease, allergic inflammation - Classification, Four step severity score - FSSS - Assessment - Severity - Study design - Specific immunotherapy.

NATURE AND EVOLUTION OF ATOPIC DERMATITIS

A recent review about the classification of allergic skin disorders highlights the importance of a unique common nomenclature for allergic disorders of the skin (1). The authors correctly stress the concept that diseases are best defined on the pathophysiological mechanisms underlying the symptoms. Over the years, in fact, more than twenty different names have been used to indicate 'atopic eczema' or 'atopic dermatitis' raising confusion and hindering

evidence-based practice. The authors concluded that doctors, scientists and patients in the field of allergy must use one and the same terminology for allergic diseases: otherwise, confusion will be generated.

Furthermore, if pathogenetic criteria will be conveniently used for defining diseases, therapeutic guidelines should equally be framed not only to control symptoms but also to potentially modify their causes (pathogenetic interventions versus symptomatic interventions).

Atopic dermatitis (AD) is currently defined as a *chronic inflammatory skin disease* though a consistent body of compelling evidence supports its allergic pathogenesis: indeed, infiltrating cells are Th2 and IgE are increased (2-6). Psoriasis, that on the contrary is sus-

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tained by Th1 cells (7-9), is equally defined as a *chronic inflammatory skin disease*. Now, a unique definition is employed for two diseases whose pathogenesis are opposite. Such a confusion should be avoided. In fact, AD and Psoriasis do not share a common physiopathology; moreover, although immunosuppressant treatments are rational in Th1 autoimmune diseases, their use in allergic diseases could induce paradoxical effects that are beneficial on symptoms but worsening on the causes (Th2 and IgE increase), as extensively reported in literature (10-22).

Furthermore, a consistent body of direct evidence supports the view, now achieving great acceptance, that allergic diseases such as rhinitis, asthma and atopic dermatitis may represent the organ compartmentalisation of a systemic inflammation in which haemopoietic precursor cells play an important role (23-31).

Atopic dermatitis often starts the 'atopic march' that is the known sequential phenotypic expression of the allergic disease. The clinical evidences at the level of skin (AD), gut (food allergy) and bronchi (airways allergy) as well as the concept of peripheral leukocytopoiesis have recently been related with a mechanism to counterbalance a genetically based condition of immunodeficiency.

Since skin and gut epithelial microenvironments are able to sustain a lymphoid ontogeny and since respiratory epithelia are able to sustain a myeloid ontogeny, it has been proposed that the temporary sequence of the bone marrow precursor cells homing to the different microenvironments is dictated from the attempt of compensating first on the compartment most recently produced by evolution that is the lymphoid one (specific immunity) and then, if ineffective, on the most ancestral compartment that is the myeloid one (innate, non-specific immunity) (26, 32). From this viewpoint, the appearance of asthma and rhinitis in up to 80-90% of the subjects previously suffering from AD (33-36) represents the ultimate stages of the natural history of a complex but unique disease.

OBJECTIVE MEASUREMENTS OF OUTCOMES AND THE OPEN QUESTION OF PLACEBO

Clinical trials are usually based on the design comparing a new investigational therapy with the currently best available ones. It is now accepted that in evaluating *alternative* treatments, randomised placebo-controlled designs are the best choice. However, an important question rises when therapies are not alternative but *complementary* (add-on treatment) and

belong to different categories (chemical drugs versus biological drugs or Biological Response Modifiers).

Allergic diseases could be treated with drugs that have the advantage of quick controlling symptoms but do not affect the basic mechanisms underlying inflammation. As alternative biological response modifiers (BRM) could be administered, such as specific immunotherapy (SIT). BRM have a delayed effect on symptoms but have shown to be able to positively act on many factors sustaining allergic inflammation.

Thus, the complementary therapeutical intervention achieves better results than the alternative treatment.

SIT positive effects are delayed in their appearance and last in time after treatment discontinuation; thus, a conveniently designed study should evaluate outcomes for a sufficiently long time. Atopic dermatitis, as well as other allergic diseases, presents spontaneous variations in time (cyclic course) that generate order effects that have to be balanced by prolonging the observation period. Another important question regards the need for placebo in control groups. The New England Journal of Medicine recently published a set of technical articles defining the actual power of placebo as confounding and focusing its proper use (37, 38). Hrobjartsson and Gotzsche conducted a systematic review of clinical trials in which patients were randomly assigned to either placebo or active treatment. Results showed that placebo had no significant effect on binary outcomes. In trials with continuous outcomes, placebo had a beneficial effect, but such effect decreased with increasing sample size. The Authors thus concluded that little evidence exists on the fact that placebo has powerful clinical effects. Although placebo had no significant effects on objective or binary outcomes, it may have small benefits in studies with continuous subjective outcomes and in the treatment of pain (39). Furthermore, in a very impressive editorial entitled "The powerful placebo and the Wizard of Oz", Bailar JC (40) referred to misemployed placebo as an often flawing and misleading myth.

AD SEVERITY ASSESSMENT SCORING SYSTEMS

Due to the above mentioned reasons, many laboratory markers, such as eosinophil products (Eosinophil Derived Neurotoxin: EDN, Serum Eosinophil Cationic Protein: s-ECP, Urinary Eosinophil Protein X: u-EPX) have been searched for a good correlation with atopic dermatitis severity but none of them fit the goal with both low and high degrees of lesions. In fact, the

maximal correlation found was between u-EPX and subjective symptoms; it reached only a medium value of $r = 0.50$ (41). The lack of an objective measurement of the disease activity thus stimulated the study and the diffusion of several scoring systems in different geographic areas (Tab. I) to validate standardised methods for the expression of AD severity and extension (42-47).

Scoring systems developed mainly in dermatological environments evaluate objective and subjective parameters all directly or indirectly referred to the skin lesions. Each method presents advantages and disadvantages. Major topics discussed in specific literature regard their complexity (time-spending) for a broad practical use in epidemiological and clinical studies and the significant inter-observer variation in the assessment of different items. Severity scores, in fact, have been found to be not interchangeable (48-52).

The increasing number of AD severity scores has thus made the comparison of study results onerous if not almost impossible (50). Such wide variations in the outcome assessment methodology and its negative impact on the evidence-based practice have finally been systematically investigated in a recent detailed study (53).

THE AD FOUR-STEP-SEVERITY-SCORE

In the "ARIA" document (54), Allergic Rhinitis has been defined as a chronic disease of the nose (organ definition) when pathogenesis (mechanisms, section 4) is accepted to be systemic. This has induced panelists to recognize, in section 8-3-8 regarding specific immunotherapy, that "this artificial separation has led to unresolved questions, possibly because the IgE-mediated reaction has not been considered as a mul-

tiple organ involvement".

Independently of the spraining effects generated by the choice of defining an allergic disease differently from its pathogenesis, four-step classifications of severity have been developed in global multidisciplinary initiatives for Asthma (55) and Rhinitis (54). To avoid any further differences in evaluating allergic diseases severity we have developed a four-step severity score (AD-FSSS) (26, 56, 57) for atopic dermatitis that is quite homogeneous and easy to use in daily routine. FSSS, that is the first AD severity assessment tool developed in the field of allergy, furthermore relates each step with the objective signs of the SCORAD, i.e.: Extension (A) = body area involved, Grading of intensity (B) of the six items erythema, edema/papulation, oozing/crusts, excoriations, lichenification and dryness (B range 1-18) (42). It also rates the duration of lesions (months) in one year.

FSSS: Step 1 (mild intermittent): low-grade lesions (SCORAD, B: 1-6), < 25% of the body area involved; duration < 2 months a year. Step 2 (mild persistent/moderate intermittent): low-grade lesions (SCORAD, B: 1-6), < 25% of the body area involved (SCORAD, B: 1-6); duration 3-6 months a year or moderate-grade lesions (SCORAD, B: 6-12); duration < 3 months a year. Step 3 (moderate persistent/severe intermittent): moderate-grade lesions (SCORAD, B: 6-12), up to 50% of the body area involved; duration > 6 months a year or severe-grade lesions (SCORAD, B: 12-18), up to 50% of the body area involved; duration < 3 months a year. Step 4 (severe persistent): severe-grade lesions (SCORAD, B: 12-18), more than 50% of the body area involved and persisting year-round (duration > 6 months).

To allow the record of the AD severity during long-lasting clinical trials, a tailor-made electronic program

AD Scoring System	Acronyms	Speciality	Geographic Area	References
Severity Score for Atopic Dermatitis	SCORAD	Dermatology	Europe	42
Atopic Dermatitis Assessment Measure	ADAM	Technology	Australia	44
Three Item Severity Score	TIS score	Dermatology	Europe	45
Eczema Area and Severity Index	EASI	Dermatology	U S A	46
Six Area Six Signs Atopic Dermatitis	SASSAD	Dermatology	Europe	47
Four Step Severity Score	FSSS	Allergy	Europe	26

Table 1: Some among the many systems for the assessment of AD lesion severity.

has been developed. It allows a quick and simple evaluation of the SCORAD Index (Section I), of the FSSS (Section II) and furthermore foresees a third section named ESAS (Extra Skin Allergic Signs) (Section III) in which it is possible to check the presence of allergic extra-skin overt signs/symptoms (Fig. 1). If organs other than the skin are affected from the allergic inflammation with its systemic and local aspects, it should be recorded when outcomes of a pathogenetic treatment, that could rise global beneficial results, are under evaluation.

Thus, the atopic dermatitis four-step-severity score, making use of objective severity measurement parameters, only, as detailed in section # 2, allows to design studies in which controls do not need placebo. The contemporary recording of SCORAD and FSSS makes it furthermore possible to compare the results of studies performed in the allergy-area of interest with those of the dermatology area. Finally, the ESAS section permits to evaluate the overall advantages potential of a biological treatment (SIT) that, acting on the systemic mechanisms of the allergic inflammation, exerts beneficial effects not only on the skin but also on all the other mucosas affected from allergy.

Figure 1: Electronic program allowing the contemporary recording of SCORAD, FSSS and ESAS along the disease course.

CONCLUSIONS

To conclude, while a definitive consensus-based scoring system for atopic dermatitis severity evaluation is far to be near the corner, the developed electronic program for the contemporary record of SCORAD, FSSS and ESAS may represent a further useful tool to employ in AD clinical trials.

After the Smith and Pell thoughtful, hyperbolic assay focusing the common sense limitations generated by the unique use of a systematic review of randomised controlled trials (58), pressing attention has

to be paid to define the optimal study design in order to determine (A degree of EBM) the benefits rising from specific immunotherapy of allergic diseases even if we have to point out that an A degree of evidence is required for a general-practice routine treatment when specific immunotherapy is a specialty-practice sustained by the existing evidence (26).

When outcomes are objectively measured and when concerns about the bias concerning the lack of randomisation are exceeded by an optimal population sample size, a simple and not expensive design of comparison between groups (best available therapy versus best available therapy + SIT) could simply represent the right choice.

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