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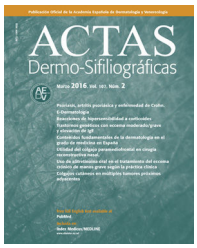

OPINION ARTICLE

# What We Know About the Clinical Course of Nonsegmental Vitiligo: Experience of a Researcher and a Dermatologist☆

## Experiencia de un investigador y un dermatólogo sobre el conocimiento del curso clínico del vitiligo no segmentario

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One of the defining characteristics of dermatology is the fact that the clinical manifestations of skin diseases—while difficult to measure—are nonetheless visible and, therefore, observable. This has led to the development of numerous clinimetric instruments that allow us to assess many aspects of the disease process, such as its impact on the patient's quality of life, the response to treatment, or the value of a diagnostic test. However, many skin diseases are chronic disorders with a multifactorial, autoimmune, or even an unknown etiology. This poses a challenge for the dermatologist and gives rise to considerable interindividual variation in the description of diseases, their manifestations, and the response to therapy. Vázquez-López et al.[1] have clearly and concisely summarized the efforts made throughout the history of our specialty to refine the methods used to measure skin disease. Since the eighteenth century, dermatologists have described the ''external characteristics of individual skin lesions'' in an entirely subjective way. Over time, they developed other methods, including the use of analogous measurements based on the comparison of lesion size or shape with objects such as pins, peas, beans, nuts, lentils, and coins. The difficulties faced by dermatologists are also reflected in the morphometric devices they have developed. These include the transparent grids used to measure the extent of the affected area and the length or shape of the lesion and, more recently, instruments designed to quantify no less important subjective or complex information, such as quality of life, activity, severity, burden of disease, and clinical course.

## Why Do We Need to Know More About the Clinical Course of Nonsegmental Vitiligo?

It is not unusual to see statements in the literature to the effect that the clinical course of nonsegmental vitiligo (NSV) ''is unpredictable''[2] and, while this is true, the reason for this unpredictability is that, to date, we have not acquired or generated the knowledge we need to define the clinical course of the condition. Greater knowledge about the clinical course of NSV will facilitate more accurate prediction of prognosis, which will be very useful for patients families, and physicians as well as for the health services. This

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better understanding will, in turn, serve to generate more knowledge, leading in time to further improvement in prognosis and treatment. This is a process that has already been shown to be successful in oncology, the field that pioneered prognostic studies.[3]

Knowledge is needed to answer many questions: the possible role of NSV as an indicator of other conditions (for example, thyroid disease), whether such conditions can be prevented or their course modified by treating vitiligo, and whether the associated morbidity influences the course of NSV. These and many other questions need to be answered if we are to gain a better understanding of the course of this disease.

## How To Define the Clinical Course of a Disease?

Prognostic studies can be divided into three phases depending on the knowledge currently available about the factors that determine the course of the disease under study. When very little information is available, as in the case of NSV today, the optimum design is a cohort study. In the second phase, when the factors influencing the course of the disease have been identified, cohort studies are undertaken to determine the weight of each one of the independent variables. In the third phase, when the results of the multivariate analyses carried out in the phase 2 studies are available, researchers can test methods for developing prediction instruments or algorithms. Each of these 3 stages has a different purpose: exploration, confirmation, and the development of understanding, respectively.[4]

Descriptive prognostic studies (phase 1) allow us to generate hypotheses about the factors that may influence a good or a bad prognosis, to identify patients with a high probability of a bad prognosis, and to provide the data needed to make more objective clinical decisions. Analytical studies (phases 2 and 3) serve to ascertain the weight of each prognostic factor and to compare the effects of each factor and each treatment on the course of the disease.[5]

A special methodology called survival analysis has been developed for prognostic studies: it is important because the outcome is a composite endpoint (time-to-event). This analysis is accompanied by a graphic representation of how the probability of the outcome decreases over time. These survival curves, calculated using the Kaplan-Meier method, are a descriptive tool used to summarize the history of a series of patients in terms of the risk of an endpoint occurring. While, in oncology the endpoint is the probability of survival, in the case of NSV it could be the probability of achieving disease stability.[5]

Another question that can be investigated using the cohort study design is the incidence of comorbidities, such as alopecia areata and other associated diseases. Survival studies can also be used to determine how the clinical course of the disease is affected by these comorbidities or by other factors, such as smoking, stressful life events, etc.

## What Resources Do We Need to Carry Out Prognostic Studies in Patients With NSV?

It should be borne in mind that this type of study is relatively costly in terms of time, money, and effort. While, the investment is, of course, fully justified by the results obtained, it is essential, before starting, to ensure that adequate measurements can be made.

The first task is to decide what endpoint should be measured and determine the most objective method of measurement.

The authors of a 2010 systematic review on the treatment of vitiligo commented that the endpoint most frequently measured was repigmentation (96%), using 48 different scales.[6] They concluded that no consensus had been reached on the methods used to measure the results of interventions in patients with vitiligo. This led to the publication of guidelines for clinical trials in vitiligo. These recommend measuring quality of life, percentage of repigmentation, cessation of spread or stabilization of disease (defined by the absence of an increase in the size and/or number of lesions and the persistence of the repigmentation achieved with treatment for at least 2 years).[7]

The treatment guidelines establish that repigmentation alone is not an appropriate endpoint since, without stabilization, it is very probable that the pigmentation regained will later be lost and that, overall, the size and number of lesions will continue to grow.[8]

In light of the above, we believe that three outcomes should be measured: progression, regression (repigmentation), and relapse (loss of regained pigmentation).[9,10]

The second task is to decide which measurement method should be used. The ideal method should combine the 3 principal characteristics of an adequate measurement instrument: feasibility, consistency, and validity.[11]

With respect to feasibility and consistency, it is important to consider the characteristic of the disease under study: in a patient with vitiligo it is common to see progression in some lesions, stability in others, and repigmentation in others,[8] a circumstance that limits the usefulness of methods based on measuring the percentage of the body surface area affected. Another difficulty facing dermatologists in the follow-up of patients with vitiligo is the task of monitoring the patient's lesions over time, a complicated undertaking even when imaging is used because the number of lesions can vary from 1 to countless. Moreover, lesion counts are likely to be inconsistent over time because of the tendency towards confluence. Measuring the area of each lesion is also an imprecise method because of the variable number and irregular and confluent nature of the macules, which range in size from a dot to large areas. Finding a practical recording method that is easy to use is important because the course of each lesion must be documented over time. Finally, all of these problems are encountered in both patients with very little vitiligo and those with involvement of most of the body surface.

Eleven instruments for measuring outcomes in patients with vitiligo were identified in a systematic review published in 2012, covering the period from 1948 to July 2011.[12] Three of these are based on the clinician's assessment: Vitiligo European Task Force assessment (VETFa), Vitiligo Area Scoring Index (VASI), and the point counting method. Six are patient reported: Skindex-29, Skindex-16, Skindex-teen, Dermatology Life Quality Index (DLQI), Patient Benefit Index (PBI), and Pictorial Representation of Illness and Self Measure (PRISM). The clinician-reported instruments assess the extent of disease by measuring lesion size; VETF also

seeks to determine disease stage and spreading or progression. Of the patient-reported instruments mentioned above, the first 4 measure quality-of-life in patients with skin disease, the PBI combines data on the patient's treatment needs and response to therapy, and PRISM combines pictorial representation of the disease with the patient's perception of suffering. One of the 2 computer-based tools was developed to determine the affected area by combining manual methods and software, and the other uses digital images to measure repigmentation.[12]

Of the instruments mentioned, only the software-based and clinician-reported tools provide ways to measure the percentage of body surface area affected and/or depigmentation by body area. However, because of their lack of precision, these methods are not useful in prognostic studies. Although the VETF was designed to assess disease stage and spread or progression, it was determined in later studies that the tool is not reliable for these variables.[13–15] None of the instruments mentioned measure relapse (depigmentation of previously repigmented areas).

An updated evaluation of the instruments available for measuring disease in patients with vitiligo is underway, including tools published between 2010 and January 2017.[16]

## Which Variables Have Been Proposed as Prognostic Factors in NSV? What Level of Evidence Supports These Proposals?

History of autoimmune disease, family history of vitiligo, Koëbner phenomenon, age of onset, mucosal involvement, leucotrichia, and confetti-like depigmentation have all been proposed as prognostic factors in NSV. However, to date there is insufficient evidence to support the hypothesis that these factors can predict the clinical course of vitiligo, and if so, how and in what time frame. Moreover, none of these studies include survival analysis and they are all subject to the problems mentioned above relating to outcome measurement.[17]

In conclusion, the phrase ''the course of disease in a patient with nonsegmental vitiligo is unpredictable'' only serves to underscore the need for prospective research using appropriate methodologies.

## Glossary

Consistency or reliability: The property of producing similar, error-free results on repeated measurements provided the conditions under which the scale is applied and the outcome measured do not change.[11]

Validity: The capacity of a tool to measure what it was designed to measure.[11]

Viability or feasibility: The degree to which an instrument is acceptable to the user, expressed as the level of difficulty in answering the questionnaire or applying the tool, the time required, the resources used, etc.[18]

Interpretability: is the degree to which the results produced by the instrument provide real insight into the health outcome being measured.[18]

## References


1. Vázquez-López F, Gotor Corrales ML, Coto Segura P, Gomez Diaz S, Perez Oliva N. Subjective and objective measurement methods in clinical dermatology from an historical perpective: The long way from Joseph Plenk to validation. Int J Dermatol. 2006;45:1242–4.
2. Yaghoobi R, Omidian M, Bagherani N. Vitiligo: A review of the published work. J Dermatol. 2011;38:419–31.
3. Simon R, Altman DG. Statistical aspects of prognostic factor studies in oncology. Br J Cancer. 1994;69:979–85, http://dx.doi.org/10.1038/bjc.1994.192.
4. Hayden JA, Côté P, Steenstra IA, Bombardier C. Identifying phases of investigation helps planning, appraising, and applying the results of explanatory prognosis studies. J Clin Epidemiol. 2008;61:552–60, http://dx.doi.org/10.1016/j.jclinepi.2007.08.005.
5. Jenicek M. Epidemiología. La lógica de la medicina moderna. Barcelona: Editorial Masson, S.A; 1996. p. 259–83.
6. Eleftheriadou V, Whitton ME, Gawkrodger DJ, Batchelor JM, Corne J, Lamb B, et al. Future research into the treatment of vitiligo: Where should our priorities lie? Results of the vitiligo priority setting partnership. Br J Dermatol. 2011;164:530–6, http://dx.doi.org/10.1111/j.1365-2133.2010.10160.x.
7. González UÀ, Whitton M, Eleftheriadou V, Pinart M, Batchelor J, Leonardi-Bee J. Guidelines for designing and reporting clinical trials in vitiligo. Arch Dermatol. 2011;147:1428–36, http://dx.doi.org/10.1001/archdermatol.2011.235.
8. Anbar T, Abdel-Rahman A, Hegazy R, El-Khayyat M, Ragaie M. Simultaneous improvement and worsening of vitiligo lesions during the course of NB-UVB phototherapy; vitiligo may not act as one unit. Dermatol Ther. 2017;30:1–6, http://dx.doi.org/10.1111/dth.12420.
9. Eleftheriadou V, Thomas KS, Whitton ME, Batchelor JM, Ravenscroft JC. Which outcomes should we measure in vitiligo? Results of a systematic review and a survey among patients and clinicians on outcomes in vitiligo trials. Br J Dermatol. 2012;167:804–14, http://dx.doi.org/10.1111/j.1365-2133.2012.11056.x.
10. Eleftheriadou V, Thomas K, van Geel N, Hamzavi I, Lim H, Suzuki T, et al. Developing core outcome set for vitiligo clinical trials: International e-Delphi consensus. Pigment Cell Melanoma Res. 2015;28:363–9, http://dx.doi.org/10.1111/pcmr.12354.
11. Terwee CB, Mokkink LB, Knol DL, Ostelo RW, Bouter LM, de Vet HC. Rating the methodological quality in systematic reviews of studies on measurement properties: A scoring system for the COSMIN checklist. Qual Life Res. 2012;21:651–7, http://dx.doi.org/10.1007/s11136-011-9960-1.
12. Vrijman C, Linthorst Homan MW, Limpens J, van der Veen W, Wolkerstorfer A, Terwee CB, et al. Measurement properties of outcome measures for vitiligo. Arch Dermatol. 2012;148:1302–10, http://dx.doi.org/10.1001/archdermatol.2012.3065.
13. Dicle O. Assessment methods in vitiligo. J Pigment Disord. 2015;2:2–3, http://dx.doi.org/10.4172/2376-0427.1000160.
14. Alghamdi KM, Kumar A, Taïeb A, Ezzedine K. Assessment methods for the evaluation of vitiligo. JEADV. 2012;26:1463–71, http://dx.doi.org/10.1111/j.1468-3083.2012.04505.x.
15. Kawakami T, Hashimoto T. Disease severity indexes and treatment evaluation criteria in vitiligo. Dermatol Res Pract. 2011;2011, http://dx.doi.org/10.1155/2011/750342, 7503427503427.

16. Peralta-Pedrero ML, Morales-Sánchez MA, Jurado-Santacruz F, García-Olguín MG, de la Torre-García M, Cruz-Peralta ES. Systematic review of clinimetric instruments to determine the severity of vitiligo. PROSPERO. 2017. CRD42017056106. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID = CRD42017056106.
17. Dave S, Thappa DM, Dsouza M. Clinical predictors of outcome in vitiligo. Indian J Dermatol Venereol Leprol. 2002;68:323–5.
18. Chren M. Giving ''scale'' new meaning in dermatology measurement matters. Arch Dermatol. 2000;136:788–90, http://dx.doi.org/10.1001/archderm.136.6.788.