Genetic screening test for psoriatic arthritis and UVB irradiation potential responders: A new tool to identify psoriasis subpopulation patients?

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ABSTRACT

Psoriatic arthritis (PsA) is a psoriasis-associated inflammatory disease of the joints and enthuses. The occurrence of PsA is linked to the complex interplay of gene environment, and immune system. Genetic factors have long been recognized to play an important role in PsA. Genes within the major histocompatibility complex (MHC) region have been shown to be associated with PsA. These include genes coded in the HLA region, (especially Class I antigens) and non-HLA genes (i.e., MHC class I chain-related antigen A, *MICA*, and TNF-α genes). Association studies in PsA have also identified a number of genes outside MHC region, including interleukin-1 (IL-1) gene cluster, killer-cell immunoglobulin-like receptors (KIRs), and IL-23R genes. Established systemic treatments for moderate-severe psoriasis and PsA may be potentially dangerous and usually time consuming for the patient and often expensive for the National Health Systems. Tests which could predict which subset of psoriatic patients could develop the most severe forms of the disease (i.e., PsA) or will respond to well-established (UVB irradiation) or other systemic treatments are now required. The goal of genetic test screening is to rapidly and safely identify subjects for preventive or early treatment or extended surveillance prior to the onset of signs and symptoms. Genetic tests today represent a reliable investigation procedure which could rapidly and consistently improve the diagnostic ability of the dermatologist and contribute to the early and correct treatment of the different subsets of PsA.

Key words: Psoriatic arthritis, genetic test, UVB-responders, MICA-A9

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INTRODUCTION

Current understanding see psoriatic arthritis (PsA) as a seronegative inflammatory disease of the joints, enthuses and periarticular connective tissue, associated with any clinical type of psoriasis. PsA has been included in the group of HLA-B27-associated spondyloarthropathies as it shares many clinical features with them.[1]

PsA is more common in white persons than in persons of other races; it typically develops in persons aged 35-55 years with equal sex distribution. Recent data indicates that the incidence of PsA in the general population has been rising over the past 30 years in both men and women with an annual incidence rate of 7.2/100.000. Similarly the PsA prevalence in patients with psoriasis has varied widely during the past decade with estimated rates of 6% and 19% in 2009, and of 11% in 2005. Reasons for this increase are not clear: it may be related to a true change in incidence or a greater overall awareness of the diagnosis by physicians.[2]

The pathogenesis of PsA remains unknown but much information has been gathered. The occurrence of PsA is linked to the complex interplay of genes, environment, and immune system.[3] A genetic predisposition is commonly accepted and the role of genetic factors is evident when considering the strong heritability of PsA.[4] In addition to the genetic influences, environmental factors and immunological mechanisms (in which CD8+ T cell and T-cell-derived cytokines play crucial roles) are thought to be prominent in the development, amplification, and perpetuation of the disease.[5]

PsA is characterized by a wide variety of articular, periarticular, and extra-articular features, along with comorbidities that may complicate the disease course.[6] Articular and periarticular features include arthritis,enthesitis and dactylitis. Regarding diagnosis of enthesitis ultrasonography (US) allows detailed assessment of both tendinous and bony-side subclinical involvement.[7,8] Early US signs of enthesitis include hypoechoic swelling of the tendon insertion, increase of blood flow detectable with power Doppler, and bursal enlargement [Figure 1]. Considering articular involvement, PsA can be classified in axial disease (with or without peripheral arthritis) and peripheral disease, which include five patterns: asymmetrical olygoarthritis, symmetrical polyarthritis, distal interphalangeal arthropathy, and arthritis mutilans.[6,7] Extra-articular features comprise involvement of the skin, the nails [Figure 2], and the eye (iridocyclitis, conjunctivitis, and other anterior uveitis in most cases), followed by less common involvement such as inflammation of the aortic valve, IgA nephropathy, or amyloidosis.[9] Psoriasis vulgaris [Figure 3] is the main form of psoriasis associated with PsA but pustular psoriasis, flexular psoriasis, and guttate lesions have also been recognized.[9,10] Pustular psoriasis was thought to be associated with more severe PsA. Nail changes include onycholysis, hyperkeratosis, transverse ridging, nail pitting [Figure 4], oil drop discoloration, and splinters; all these features refer to the definition of psoriatic onychopathy [Figure 5]. It is often reported that when the nail organ is involved in nail psoriasis, a secondary affection of the joint may develop and vice versa; this is because the nail is functionally integrated with enthesis associated with the distal phalanx.[10-12] Moreover, when skin and joint disease begin simultaneously, nail involvement is frequently present at the onset, and severe deforming arthritis of the hands and feet is frequently associated with extensive nail involvement.[10,11]

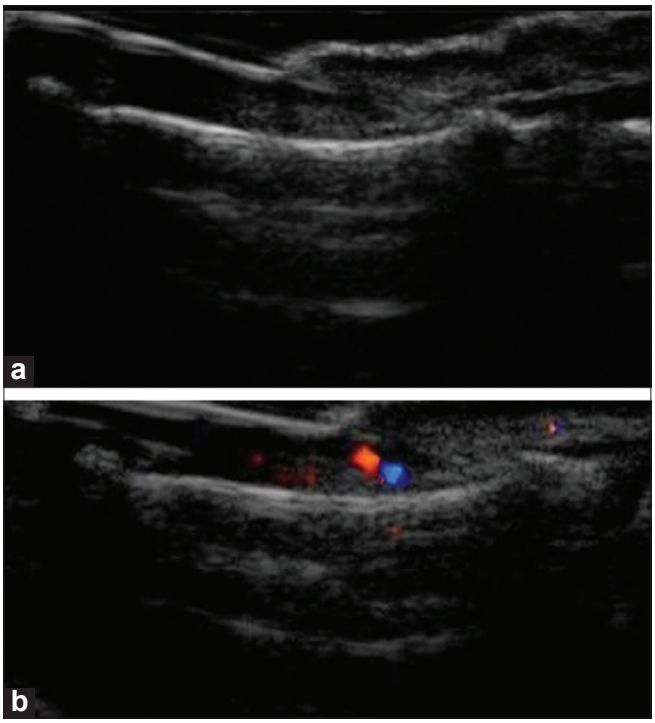

Figure 1: US imaging of the nail in a patient with PsA: (a) loss of the normal tri-laminar appearance of the nail plate, which appears with an irregular shape; (b) nail bed is clearly thickened and power Doppler US reveals a marked signal indicative of an increase of blood flow at the nail bed level

The natural course of PsA is characterized by flares and

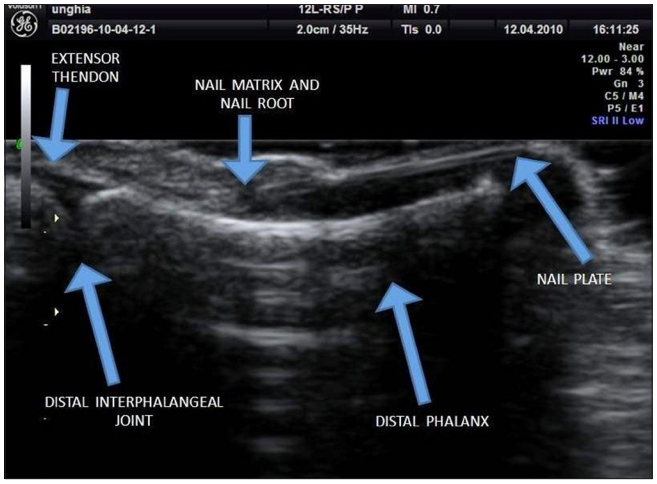

Figure 2: An ultrasound image of a healthy nail

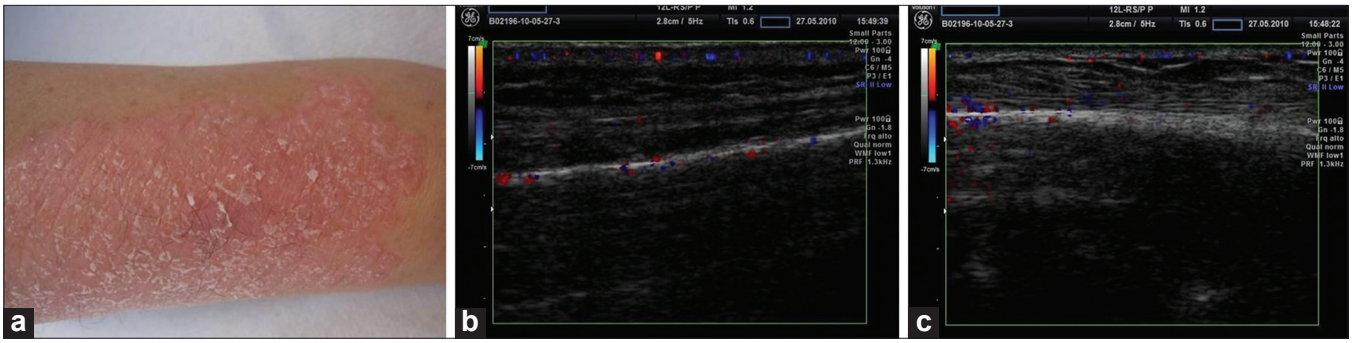

Figure 3: Psoriatic plaque (a), related US findings of lesional skin (b) and perilesional healthy skin (c) showing increased neoangiogenesis in the lesional skin

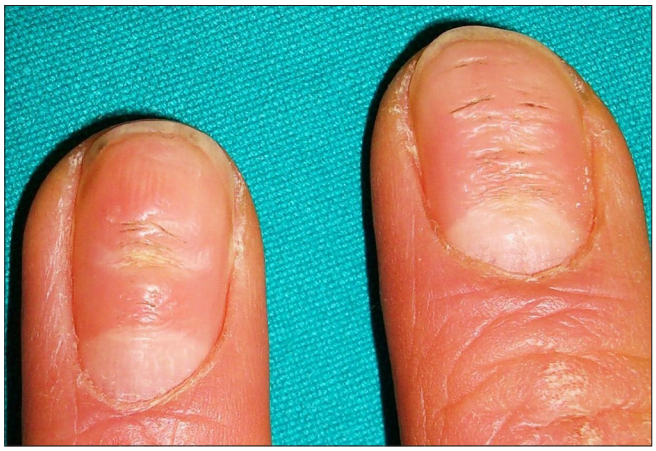

Figure 4: Nail pitting and transverse ridging in a patient with psoriasis

remissions.[1] The following factors influence the severity of the disease and are related to a more aggressive course:[9,10] onychopathy, specific clinical subsets (e.g., arthritis mutilans, symmetric polyarthritis), involvement of five or more joints at onset, female sex, family history of arthritis, and HLA markers (especially HLA-B39 and HLA-B27 in the presence of HLA-DR7).[4,7,9,12] Moreover, the use of medication before the first clinical visit, evidence of radiologic damage, and elevated erythrocyte sedimentation rate have been related to significantly increased mortality.[8,9,13] Finally, research over recent years has highlighted that moderate to severe PsA and psoriasis are linked to cardiovascular disease, the metabolic syndrome, and increased mortality.[14-16]

Between 6% and 42% of patients suffering from psoriasis will develop PsA, with over two-thirds developing psoriasis usually 10 years before articular involvement.[12,13] Otherwise, approximately 15% of patients develop articular manifestations, especially arthritis, before the onset of psoriatic skin lesions.[1,8,11,12] Nearly 50% of patients affected by PsA develop erosive joint disease.

Juvenile PsA generally develops in children aged 9-10, with a female predominance, and it accounts for 8-20% of childhood arthritis. In 52% of cases, arthritis precedes psoriasis onset, and usually children have a higher frequency of simultaneous onset of psoriasis and arthritis than adults.[17]

GENETIC OF PsA

Genetic factors have long been recognized to play an important role in PsA. Identifying genes underlying disease susceptibility involves a series of complex investigations beginning with familial aggregation studies followed by segregation analysis, linkage analysis, association analysis and functional studies to identify and characterize genes. Moll and Wright were the first to demonstrate familial aggregation of PsA.[18] Strong heritability

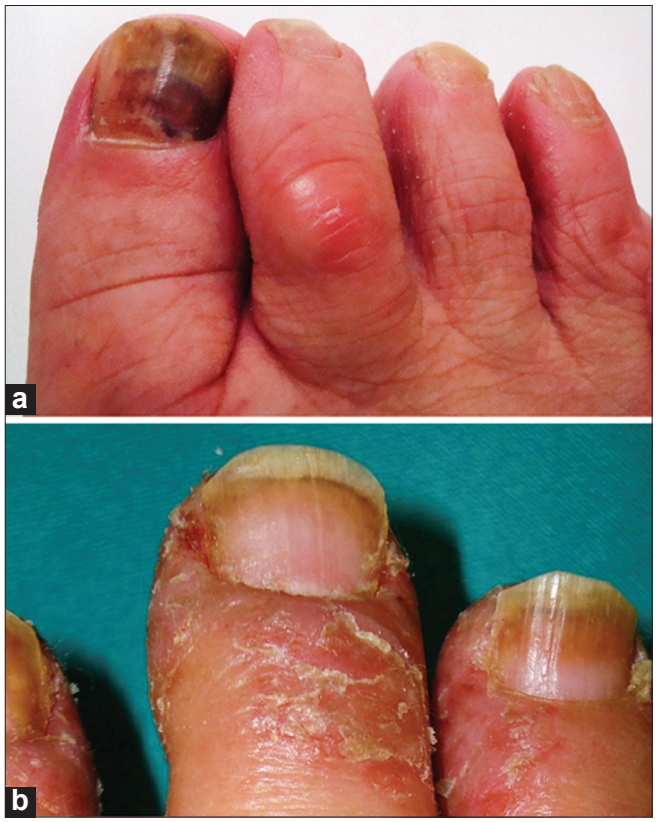

Figure 5: Clinical presentations of psoriatic onychopathy in two patients (a, b) with PsA

was also demonstrated in a recent study from Iceland.[19] Moreover, compared with most other rheumatic diseases, heredity plays a particularly strong role in the development of PsA.[20]

The genetic factors underlying susceptibility to PsA are closely intertwined with that of cutaneous psoriasis since almost all patients diagnosed with PsA have either personal or family history of psoriasis. The immune system is a tightly regulated network of cells and cytokines, and genetic factors that lead to immune alterations may likely tip the balance toward inflammation in the skin and synovium of psoriasis and PsA, respectively.

Multiple genes contribute to susceptibility with some interaction of effects. Recent advances in genetics have confirmed previous associations and new loci have been discovered. However, many genetic factors remain to be identified.[21,22] Thus, PsA has a strong genetic component involving loci within or outside the major histocompatibility complex (MHC) region.

GENES WITHIN THE MHC REGION

Polymorphisms in the genes coded in the HLA region on chromosome 6p have been shown to be associated with PsA.

This dense region codes for a number of genes important in the immune response, including HLA and non-HLA alleles. Class I antigens (HLA-B13, HLA-B57, HLA-B39, HLA-Cw6, HLACw7) have consistently shown a positive association with psoriasis and PsA.[23] While HLA-B13, -B16, and its splits -B38 and -B39, B17, and Cw6 are associated with psoriasis, with or without arthritis, B27 and B7 are specifically associated with PsA.[24] Associations with Class I alleles are stronger with HLA-B than HLA-C alleles. The association of HLA-C with PsA was found to be due to association with early onset psoriasis, since no association was found in patients with PsA and late onset psoriasis.[25]

HLA antigens may also identify patients with a particular pattern of PsA: HLA-B27 with spinal involvement, and B38 and B39 with peripheral polyarthritis. HLA antigens were identified as prognostic factors in patients with PsA. HLA-B39 alone, HLA-B27 in the presence of HLA-DR7, and HLA-DQw3 in the absence of HLA-DR7, each conferred an increased risk for disease progression. HLA-B22 was found to be protective for disease progression.[23] The "rheumatoid arthritis (RA) shared epitope" was found to be associated with radiological erosions among patients with PsA.[26] Recently, patients with PsA carrying both HLA-Cw6 and HLA-DRB1*07 alleles were found to have a less severe course of arthritis, as measured by the number of damaged and involved joints.[25] Non-HLA genes within the MHC region have also been proposed to be associated with PsA. These include *MHC class I chain-related antigen A (MICA)* and *tumor necrosis factor alfa (TNF-α) gene.*

MICA is one of the most polymorphic non-HLA genes in the human genome. It lies 47 kb centromeric to the HLA-B locus, within the heart of the MHC complex. MICA expression is induced by cell stress. Its protein product is expressed in a wide variety of epithelial cells, the skin and the synovium and interacts with the natural killer-cell receptor (KIR) NKG2D to activate the immune response. MICA has two main forms of polymorphism: a "GCT" triplet repeat in the transmembrane region and a large number of single nucleotide polymorphisms (SNPs) in the part of the gene that encodes the extracellular binding domains.[27,28] Some studies have found an association between PsA and the MICA-A9 (MICA allele which has nine GCT repeats), but relatively small numbers of patients have been studied considering the complexity of the condition. In a Spanish population, the trinucleotide repeat polymorphism MICA-A9 corresponding to the MICA-002 allele was associated with PsA (but not psoriasis), independent of HLA Cw*0602. Similar associations have been shown with Jewish, Croatian, and British patients.[29-33]

Another high-priority candidate is the TNF-α gene, which is located 250 kb centromeric from the HLA-B locus.[21] TNF-α is a key inflammatory cytokine in psoriasis and PsA and is found in high levels in the serum, synovial fluid, and synovial membrane of patients with PsA.[27] Associations have been reported between the TNF-α–308 polymorphism in the promoter region of the TNF-α gene and PsA.[34] The TNFα–308 polymorphism has been associated with the presence of joint erosions, progression of joint damage, and early age of the onset of PsA.[35]

Subsequent studies have also confirmed an association between TNF-α–238 and -857 polymorphism and PsA.[36,37]

Patients show marked clinical response to treatment with biological and it would be interesting to investigate whether these polymorphisms can be related to responsiveness to treatment with anti-TNF agents. It would appear that any association with the TNF genes and PsA is more linked with disease severity and clinical expression than overall disease susceptibility.[27]

GENES OUTSIDE THE MHC REGION

Association studies in PsA have identified a number of genes outside chromosome 6p including *interleukin-1 (IL-1) gene cluster* (chromosome 2q), *killer-cell immunoglobulin-like receptors (KIRs) genes* (chromosome 19q), and *IL-23R* (chromosome 1p).

IL-1 is up-regulated in the serum and synovium of patients with PsA.[38] An association with the IL-1α-889 was first reported in 2004.[39] Subsequently, a study revealed two regions contributing independently to risk of PsA: a region spanned by markers rs3783547, rs3783543, and rs17561 in IL-1A, and a region near the end of IL-1B.

KIRs are one of two groups of receptors on natural killer (NK) cells. NK cells are key effector cells in psoriasis and PsA. There is a high degree of polymorphism and complexity in the genes that encode the KIRs. A particular KIR haplotype encodes a distinct set of receptors for an individual's NK cells. Each NK cell has a combination of inhibitory and activating receptors that interact with certain HLA alleles to influence the immune response. In addition, MICA is also a ligand for an NK receptor (NK2GD). Polymorphism within this gene may also influence susceptibility to PsA through altered interactions with NK cells.[27] Moreover, two publications reported an association between the activating KIR2DS1 receptor and PsA. Interestingly, the association between KIR2DS1 and PsA was only found if the HLA ligand for the corresponding inhibitory receptor (KIR2DL1) was absent.[40,41]

Finally, three loci were associated recently with PsA when compared with normal controls. There was a statistically significant difference between PsA and psoriasis alone at three loci; HLA-C and IL-23R were more strongly associated with psoriasis alone, and IL-12B with PsA.[42] However, an

adequately genome-wide association study on PsA has not yet been done.

Thus, a number of susceptibility loci for PsA have been described, but many others remain to be identified. These discoveries can help us to understand pathogenesis, identify drug targets, and predict the disease course or the response to pharmacotherapy.

A GENETIC SCREENING TEST FOR PsA

The goal of genetic screening is to identify subjects for preventive or early treatment or extended surveillance prior to the onset of symptoms. Therefore, the sensitivity of the test should be high and similarly, high specificity is desired to increase the efficacy of the screening and minimize the number of subjects who will be treated unnecessarily.

Current PsA screening techniques identify symptomatic patients after the onset of inflammatory arthritis. Identifying PsA in an earlier or a pre-clinical stage will allow treatment to be initiated at a time when intervention has a greater likelihood of succeeding. Early screening combined with tailored treatment will help preventing disease progression and irreversible slow joint destruction. The need for early screening and medical intervention for PsA is underscored by the fact that PsA becomes more severe when left not properly treated or untreated, leaving patients with significant joint damage, functional impairment, and reduced quality of life.

Therefore, a genetic screening test has been recently developed in order to identify patients at a high risk for developing PsA prior to the onset of arthritic symptoms. The genetic screening test is most appropriate for individuals with psoriasis who have not yet developed PsA. It is also useful to assess the risk for individuals who have a family history of psoriasis or PsA.

A genetic sample is collected using a cheek swab, and the sample is mailed for analysis at a certified laboratory. There are no known risks associated with using this test.

The genetic screening test for PsA provides information on the presence of a specific variation (a triple repeat polymorphism) on the MICA immune response gene located on chromosome 6p, a variant called MICA-A9. Thus, the test shows whether a person has the high or low risk variant of the MICA gene. Patients with MICA-A9 variant have a higher risk for PsA; patients without this variant have a lower risk.

The clinical validity of genetic screening test has been demonstrated using standard statistical methods. The authors pooled data from two independent published studies (on Jewish and Spanish populations) that demonstrated statistical significant association between the MICA variants measured by this genetic test and PsA.[30,31] A total of 316 individuals were genotyped. The data reported by the studies are presented in Table 1. Based on these data, they calculated

- sensitivity (the probability that a person with PsA will test positive) = TP/(TP+FN) = 59%
- specificity (the probability that a person without PsA will test negative) = TN/(TN+FP) = 71%
- positive predictive value = TP/(TP+FP) = 60%
- negative predictive value = TN/(TN+FN) = 70%

Using this genetic test, a physician can conclude that a patient who tests positive for the MICA-A9 variant has approximately 60% chance of developing PsA; thus, the patient will likely benefit from early treatment. Similarly, a physician can conclude that a patient that tests negative has approximately 70% chance of not developing PsA; thus, the patient may be able to avoid costly treatment.

However, due to the limitations of the test to identify all the psoriasis patients who will ultimately develop PsA, the genetic screening test for PsA should be used as an adjunct to currently used diagnostic criteria to determine the need for medical therapy.

Unlike traditional medical diagnostics, genetic tests may have no immediate clinical benefit, but may have great utility for the patients and the society as well as the social, economic, and health impact on the individual.

GENETIC FACTORS AND UVB TREATMENT

Response to UVB treatment could be genetically related according to a recent Irish study.[43] Ryan *et al*. assessed clinical parameters as predictors of the number of exposures of narrow-band ultraviolet B (NB-UVB) needed to clear psoriasis and of the duration of remission. The influence of the *Fok1*, *Apa1*, *Bsm1*, *Taq1,* and rs4516035 polymorphisms of the vitamin D receptor (VDR) gene on treatment response was also evaluated.

Vitamin D_3 is a potent anti-proliferative and pro-differentiation factor for keratinocytes and modulates immunological processes such as T-cell activation, cytokine secretion, and dendritic cell maturation. Vitamin D_3 exerts the majority of

Table 1: Association between PsA and the MICA variants measured by PsoriasisDX Genetic Test®

MICA-A9 allele	Psoriatic arthritis	Non-psoriatis arthritis	Total
A9+	TP = 78	FP = 53	131
A9-	FN = 55	TN = 130	185
Total	133	183	316

TP: True positive, FP: False positive, TN: True negative, FN: False negative

its effects by binding to the vitamin D receptor (VDR) which belongs to the nuclear hormone receptor superfamily of receptors. There are several polymorphisms of the gene encoding the VDR which may alter its activity. In this study, the authors investigated whether polymorphisms which modify the effects of NB-UVB-induced vitamin D may have an influence on treatment response.

Authors used NB-UVB to treat 119 patients with chronic plaque psoriasis until clearance was achieved and then monitored the patients for up to 1 year or until relapse occurred. In all, 105 of the patients completed the course of phototherapy. The median number of exposures to clear psoriasis was 26 and the median remission duration was 16 weeks.

The *Taq1* polymorphism of the VDR gene was shown to be predictive of remission duration. Patients homozygous for the C allele, which is associated with the decreased activity of the VDR, had a shorter remission duration than those heterozygous for the allele and those homozygous for the T allele. As yet, routine testing for VDR polymorphisms has been considered too expensive for use in clinical practice.

This is the first prospective study to demonstrate that both clinical and genetic parameters may predict therapy response and remission duration in patients with psoriasis treated with NB-UVB. While NB-UVB was shown to be a very effective treatment in the majority of patients, a subset of patients was identified who demonstrated an inefficient treatment response. As NB-UVB treatment is time consuming, expensive, and potentially carcinogenic, the ability to predict patients who will clear quickly with prolonged remission would be useful in terms of patient care and health economics.

CONCLUSION

Systemic treatments for moderate-severe psoriasis and PsA can not only be potentially dangerous and time consuming for the patient but also very expensive for the National Health Systems.

The ability to predict which subset of patients will develop the most severe forms of the disease (i.e., PsA) or will respond to well-established (i.e., UVB irradiation) or other systemic treatments is now required by physicians and patients' associations.

Genetic tests today seem to represent a reliable investigation procedure which could rapidly and safely improve the diagnostic ability of the dermatologist and contribute to the early and correct treatment of the different subsets of psoriatic patients, especially regarding the identification of patients with PsA. These genetic tests, if properly adopted, could highly reduce the potentially dangerous side effects of systemic treatments of psoriatic patients, allow physicians to start in the earliest phase the correct treatment for the different subsets of patients, and eventually drastically reduce the cost of the optimal treatment of psoriatic patients.

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