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Future Therapeutic Directions for the Treatment of Psoriasis

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Abstract. The future management of psoriasis will depend on a number of distinct but ultimately inter-related strands of evidence, these are: (i) the interplay of genes and environment and the characterisation of psoriasis phenotypes; (ii) the role of pharmacogenetics in personalised healthcare; (iii) the translation of basic scientific discovery of relevant immune and angiogenic pathways into targeted biologic and small molecule therapies; and (iv) the recognition that the management of any chronic disease is enhanced by an understanding of psychosocial issues.
A reductionist approach to development of new therapies will be paramount but serendipity and the prepared mind will contribute, as they have always done.

Key words: pharmacogenetics, psoriasis, phenotypes, biologics, personalised medicine, biologic therapy.

FUTURO EN EL TRATAMIENTO DE LA PSORIASIS

Resumen. El manejo de la psoriasis en el futuro dependerá de una serie de parcelas diferentes pero esencialmente interrelacionadas de evidencia como: (i) la interacción de los genes y el ambiente con la caracterización fenotípica de la psoriasis; (ii) el papel de la farmacogenética en el cuidado personalizado de la salud; (iii) la traslación del descubrimiento científico básico de los procesos inmunitarios y angiogénicos a terapias biológicas y moléculas de pequeño tamaño; y (iv) el reconocimiento de que el manejo de cualquier enfermedad crónica mejora con la comprensión de los aspectos psicosociales.
Aunque un acercamiento reduccionista al desarrollo de nuevas terapias será primordial, también lo es, como siempre lo ha sido, la casualidad y una mente abierta.

Palabras clave: farmacogenética, psoriasis, fenotipo, biológicos, medicina personalizada, terapia biológica.

Psoriasis From Phenotype to Genotype

Psoriasis was recognised as a distinct clinical entity over 200 years ago[1]. Since this time it has become clear that a wide variety of clinical appearances are collectively being designated as variants of 'psoriasis vulgaris'. For example, some individuals will have predominantly large plaque type psoriasis whilst others may have smaller lesions (< 1 cm diameter), designated as either small plaque or guttate psoriasis. Sebopsoriasis, flexural and generalised pustular psoriasis also exist. Furthermore, in addition to the variation in morphology and anatomical site there is a bimodal age of onset for psoriasis with so called type I occurring before 40 years of age and type II presenting after the age of 40, with a distinct peak at 55-60 years[2]. We have suggested previously that accurate phenotyping of psoriasis is crucial to future efforts to both further understand the potentially different pathomechanisms involved in these various forms of psoriasis, and also in an effort to optimise personalised therapies which may be more suitable for specific sub-groups of psoriasis patients[3]. A classification of psoriasis vulgaris, which will aid future research, is summarised in table 1. This approach of attempting to refine the genotype to phenotype link is exemplified by two examples. Firstly, genetic evidence indicates that type I and type II psoriasis can be distinguished according to association with genes within the major histocompatibility complex (MHC) class I region on chromosome 6p, in particular HLA-Cw*0602 is associated with type I but not type II psoriasis[4]. Furthermore, recent work has also linked HLA-Cw*0602 positive patients with more extensive psoriasis of early onset[5]. Secondly, palmoplantar pustulosis is now recognised to be distinct from plaque psoriasis. The disease has different demographics to psoriasis vulgaris in that patients are predominantly women, either current or previous smokers and onset occurs in the 4th and 5th decades of life[6]. Furthermore, genetic data suggest that psoriasis

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vulgaris and palmoplantar pustulosis are distinct diseases[7]. Such efforts to classify disease based on combinations of phenotype, genotype and demographic data will require refinement over the coming years but are vital to understanding why such wide variation in therapeutic response exists in patients with the 'same condition'. Treatment response may vary not only as a consequence of disease sub-type but also because of a patients' overall genetic profile. This is where, in the future, the role of pharmacogenetics may be crucial.

Pharmacogenetics and Other Novel Technologies

A gene can be defined as exhibiting a polymorphism if the variant allele exists in the normal population at a frequency of at least 1%[8]. Pharmacogenetics, a term suggested by Vogel in 1959, is the study of relationships between genetic polymorphisms and drug response[9]. The most frequent type of polymorphism is a single nucleotide polymorphism (SNP), however, they can take on a number of forms including nucleotide repeat sequences. Polymorphisms, resulting in alteration of expression and/or function of drug metabolizing enzymes, can result in altered efficacy or toxicity of a given drug. The classic example in current dermatological practice is that of azathioprine, used to treat severe atopic dermatitis, where both a decision to use, or tailor the starting dose, is based on the genetically pre-determined enzyme activity of thiopurine methyl transferase[10]. Translation of other pharmacogenetic examples in dermatology has been slow but recently data have emerged which may optimise the use of methotrexate[11-14] and biologic agents[15] in the treatment of psoriasis. Clearly for expensive and /or dangerous therapies predictors of treatment response are desirable.

Two studies have investigated genetic variations in 10 genes relevant to methotrexate metabolism to see if they influence the outcome of psoriasis patients treated with this drug[14,16]. In total 374 psoriasis patients were characterised in respect of efficacy and toxicity with polarisation into two groups. The key findings were that SNPs in the methotrexate efflux transporter genes, adenosine triphosphate (ATP) -binding cassette, sub-family C, member 1 (ABCC1) and ATP-binding cassette, sub-family G, member 2 (ABCG2) were associated with both the efficacy and toxicity of methotrexate[14]. This work is preliminary and requires confirmation in further cohorts of patients but does highlight the potential that new technologies can bring in refining the use of a long-standing systemic drug.

Recent data suggest that a similar pharmacogenetic approach may be possible with biologic therapies such as optimising anti-tumour necrosis factor-alpha (TNF-α) agents depending on key SNPs within the TNF-α gene[15]. In patients with rheumatoid arthritis improved efficacy of a TNF-antagonist was correlated with a key SNP located in the promoter sequence of the TNF-α gene[15]. Indeed the same study showed that these effects may be drug specific in that patients carrying the rare genotype had a poorer response to etanercept but not infliximab[15]. There is currently little published data on the effects of genetic variants on treatment response of anti-TNFs in psoriasis. This is not the case with efalizumab, the anti-CD11a monoclonal antibody which inhibits T-cell activation. As this drug only achieved a high level of efficacy in around 25-30%[17] of patients it was an ideal candidate for the application of pharmacogenetics. Data suggest that those patients who are HLA-Cw*0602 positive were more likely to respond to efalizumab. This is particularly interesting as it highlights the potential role that disease specific genetics may play in predicting treatment response. Unfortunately efalizumab has recently been withdrawn as a result of 3 cases of progressive multifocal leucoencephalopathy in patients receiving the drug for more than 3 years. The reasons for the adverse event are not clear but examples exist where drugs with which there are significant safety concerns can still be utilised on the basis that the adverse event are predictable based on genotype[18,19]. This approach of personalised medicine is slowly making its way into everyday clinical practice, and with the revolution that is occurring in high throughput genotyping technologies, it is likely to become more relevant to daily practice. Further-

Table 1. A classification of psoriasis vulgaris

A	*B*	*C*
Localized	*Widespread or Other forms of widespread psoriasis*	
Flexural/intertriginous	Guttate	Stable/unstable
Facial/seborrhoeic	Generalized pustular	Thin/thick[a]
Scalp Palms/soles (nonpustular) Limbs Truncal	Erythroderma: ≥ 90% body surface involvement, ± systemic symptoms, unstable and thin	Small plaque/large plaque[b] Type I/II psoriasis[c] ± Nail involvement Follicular
+ Any of Box 'C'	+ Any of Box 'C'	

[a]Thin, ≤ 0.75 mm; thick, > 0.75 mm.
[b]Small plaque, ≤ 3 cm diameter; large plaque, > 3 cm diameter.
[c]Type I psoriasis, onset ≤ 40 years of age; type II psoriasis, onset > 40 years of age.
Reprinted with permission from Griffiths CE et al[3].

more, other complementary techniques which will facilitate the marriage of genotype and phenotype are rapidly evolving. These include metabolomics and gene expression profiling. Metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind" - specifically, the study of their small-molecule metabolite profiles[20]. This rapidly evolving field has the potential to produce an instantaneous snapshot of the different biochemical profiles which may be produced in individuals who are responding to drugs in different ways. Gene expression profiling is the measurement of the activity (the expression) of thousands of genes at once, to create a global picture of cellular function. Expression profiling experiments involve measuring the relative amount of mRNA expressed under different conditions. Such an mRNA profile may prove useful in identifying which genes are up or down regulated in response to methotrexate and thus provide novel genetic targets for investigation.

Despite all these new technologies there is little doubt that in the short term it is vital for dermatologists to maintain their keen clinical eye as it is the accurate phenotyping of patients that will be crucial to the successful application of newer technologies.

New Therapies

The identification of key immune pathways in psoriasis provided the targets for the development of effective biologic therapies for the condition and by so doing provides an excellent example of translational medicine[21]. Current approved approaches include targeting: T-cell activation eg alefacept; TNF-α eg adalimumab, etanercept and infliximab and; interleukin (IL) 12 and IL-23. It is anticipated that monoclonal antibodies to other cytokines involved in the pathogenesis of psoriasis, including IL-17 and IL-22 both of which are in phase II trials, will be developed for use. The key to advancement is the development of biologics that can be used effectively in a long-term, continuous fashion with minimal safety concerns. Biologics are by necessity delivered by infusion or by sub-cutaneous injection. Small molecules administered orally and targeted upstream of cytokines are under intensive investigation. The advantages being convenience and that topical preparations may be produced from these molecules. However, it is our belief that systemic therapies will become the norm in management of all but the most mild/limited cases of psoriasis. This statement is based on the premise that psoriasis is a systemic disease with associated co-morbidities including psoriatic arthritis and features of the metabolic syndrome such as cardiovascular disease[22]. Patients prefer the convenient option of systemic medication so long as there is a clear benefit over risk[23]. Small molecules currently in trial for the treatment of psoriasis include inhibitors of janus kinases (JAK), both oral and topical, which mitigate signalling via IL-12 and 23 amongst other cytokines and inhibition of protein kinase C (PKC), which indirectly inhibits T-cell proliferation, by an oral PKC antagonist AEB071[24].

One of the salient and significantly under-researched histological features of a plaque of psoriasis is the presence of vascular angiogenesis driven in part by overexpression of vascular endothelial growth factor (VEGF) produced by epidermal keratinocytes[25]. Despite this observation and that VEGF SNPs are associated with severe psoriasis of early onset[26] there has been no concerted investment in the use of anti-VEGF approaches for treatment of the disease. VEGF antagonists have been developed for the treatment of colorectal cancer, The utility of this approach for psoriasis management is underscored by a case report of the use of bevacizumab for the treatment of colon cancer in a patient who had concomitant psoriasis[27]. The psoriasis cleared. Although this was not strictly serendipitous, there was prior art, it should be recognized that many therapies for psoriasis have developed as a consequence of serendipity and not from a reductionist, translational approach.

Overall it is only by investing in understanding the basic pathomechanisms of psoriasis and recognition of commonality of immune targets across immune mediated diseases such as the arthritides and inflammatory bowel disease that we can truly make progress.

At the same time it should not be forgotten that management of the patient with psoriasis is and always will be at the personalized level. The way in which the disease affects the individual has to be taken into consideration in any approach to management of a chronic disease and psychological approaches[28] as an adjunct to medicine are the modern corollary of the role of art and science in the physician's armamentarium. Physical therapies such as phototherapy will be used less frequently, indeed the uptake of PUVA therapy is diminishing year on year.

Ideally the ultimate goal of psoriasis management is to prevent the development of the disease. This could only be achieved by an understanding of the genes associated with psoriasis and the environmental triggers required for phenotypic expression. An understanding that is a long way in the future, unfortunately.

Conflicts of interest
R.B. Warren has acted as a consultant or speaker to Abbott, Janssen-Cilag, Merck-Serono, Schering Plough and Wyeth all of whom manufacture treatments for psoriasis.
C.E.M. Griffiths has acted as a consultant to and/or received speaker's fees from Abbott, Centocor, Incyte, Janssen-Cilag, Merck-Serono, Novartis, Pfizer, Schering-Plough and Wyeth.

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