

Keynote Lecture by Howard Maibach

Clinical Challenge in Percutaneous Absorption

Professor Howard Maibach from University of California, San Francisco is one of the leading figures in dermatology in the world. His research in the fields of contact dermatitis, dermatotoxicology and dermatopharmacology has been groundbreaking. He has published over 1,200 refereed articles and over 200 textbooks. His articles have been cited over 29,000 times. Professor Maibach has given postdoctoral training in his laboratory in San Francisco for several Nordic dermatologists, including Jan Wahlberg, Klaus Andersen, Arto Lahti, Kaija Lammintausta and Peter Andersen.

His talk in Nordic Dermatology Congress was entitled “*Clinical Challenges In Percutaneous Absorption*”, a topic that he has been working on for over 50 years. In his talk he described 15 determining factors for percutaneous absorption, related to local skin and systemic absorption of topically applied substances. These factors were (i) release from vehicle, (ii) kinetics of skin penetration, (iii) excretion kinetics, (iv) tissue disposition, (v) substantivity to skin, (vi) wash effects, (vii) rub effects, (viii) effect of clothing, (ix) exfoliation, (x) volatility, (xi) binding to skin layers, (xii) appendage effects, (xiii) lateral spread, (xiv) vascular perfusion and (xv) cutaneous metabolism. The talk highlighted the most important function of skin, acting as barrier between outside world and living body. Several conditions compromise this function and may cause several diseases from eczema to systemic toxicity and anaphylaxis.

Professor Maibach continues his research work in his laboratory and clinic and travels globally to give expert advice and lectures to various audiences, from dermatologists and toxicologists to government departments and international societies and expert groups.

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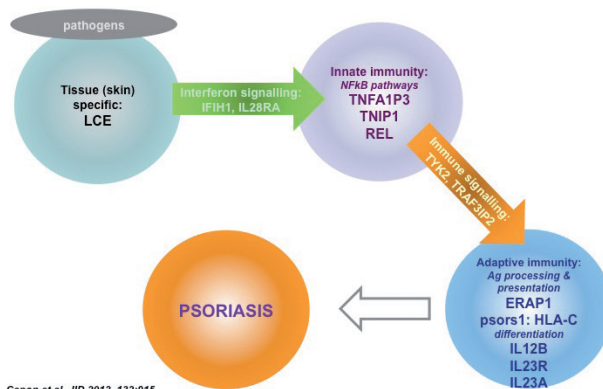
Leena Koulu and Howard Maibach at the Congress dinner.

Psoriasis and Comorbidities

Plenary Lecture by Jonathan Barker: From Genetic Discovery to Clinical Utility

Historically, attempts to identify susceptibility genes in common, complex diseases such as psoriasis have relied on a candidate gene approach. In general these have been unsuccessful in great part due to inadequate knowledge of disease pathogenetic mechanisms and small sample sizes. The explosion of genetic information created by the human genome mapping project and subsequent initiatives has led to development of methodologies that permit in a robust way detection of common genetic variants predisposing to many diseases. Such techniques have been applied with great success to psoriasis. These studies reveal multiple candidate genetic loci which cluster around specific mechanisms. These are: epidermal barrier candidate = LCE3, innate immunity (e.g. IFIH1, TYK2, TRAF3IP2), antigen processing and presentation (ERAP-1 and HLA-C) and T-cell differentiation down IL23/IL17 pathway (IL23R, IL12B).

Interestingly there is overlap with other immune-mediated inflammatory disorders including inflammatory bowel disease and ankylosing spondylitis, and intriguing parallels with atopic dermatitis, another inflammatory skin disorder in which barrier defects and immune dysregulation are also important. There are also key differences with certain phenotypic variants of psoriasis. Pustular forms appear to have a different genetic background. In some patients this relates to mutations in an interleukin-1 family member termed IL36RN, which is not observed in plaque forms of the disease. These findings are also consistent with a number of clinical observations, including the association between interferon- α and flare of psoriasis and also explain why targeted therapies inhibiting TNF α and IL12/23 and IL17 are so effective. They provide important data on which to base future drug design, including small molecules. Currently it is unclear why there is variation in response of patients to specific drugs. Pharmacology is likely to play a key role, for example development of anti-drug antibodies. However, genetic heterogeneity is also likely to be involved raising the potential of genetic testing as a co-diagnostic with use of



Capon et al. JID 2012, 132:915

Fig. 1. Pathogenetic mechanisms in psoriasis: A genetic's viewpoint.

new drugs. This may have the effect of not only maximising efficacy but also of minimising toxicity and cost.

Epidemiology and Pathogenesis of Metabolic Syndrome and its Consequences in Psoriasis

The World Health Organisation recently concluded that chronic disease is a major cause of mortality in large part through associated cardiovascular disease. Emerging evidence indicates that psoriasis, particularly when severe, should be included in this list of diseases. There is overwhelming evidence that psoriasis is associated with the metabolic syndrome with obesity, hypertension, dyslipidemia, type 2 diabetes; all being more frequently observed in psoriasis. Further, obese children and young adults are more likely to develop psoriasis and weight gain increases the risk further. This translates into an increased incidence of cardiovascular events including myocardial infarction and stroke especially in young patients with severe disease. Some evidence suggests that the risk in these patients is in part independent of traditional risk factors and that there may thus be a primary association. Intriguingly, the immunopathology of atherosclerosis and psoriasis share several common features including migration of lymphocyte subsets into inflamed tissue and release of pro-inflammatory cytokines.

It has been suggested that better treatment of the immunopathology underlying psoriasis may help avoid these comorbidities but further studies are required to confirm or refute this. In the meantime it is important that the patient pathway should include assessment of co-morbidities including metabolic syndrome. Some national guidelines, for example in United Kingdom, highlight this and provide guidance on how to intervene (www.nice.org.uk/cg153).



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The Effect of Psoriasis Treatment on the Cardiovascular Risk

When regarding the increased risk for cardiovascular diseases in psoriatic patients, the interesting question is whether the efficient treatment of psoriasis – and systemic inflammation – could decrease this risk. It is also important to know if there are differences between different treatments in this respect.

In rheumatoid arthritis, methotrexate has been shown to associate with a lower risk of both overall cardiovascular diseases and specifically for myocardial infarction. In rheumatoid patients, TNF inhibitors have been either better or equally effective than other antirheumatic medications.

There are 7 original studies and a few meta-analyses where the effect of psoriasis treatment on the cardiovascular risk has been evaluated. In most studies the number of patients has been considerably high, but the biggest challenge is how to differentiate between disease and its treatment. Looking at these studies, it is reasonable to say that methotrexate seems to reduce the cardiovascular risk in patients with psoriasis. TNF-inhibitors seem to have the same kind of positive effect, but the evidence is still weak. At this moment, the cardiovascular safety of IL-12/23 inhibitors is not yet clear.

Future studies will clarify whether methotrexate and TNF inhibitors are equally beneficial if the inflammation is adequately controlled, and whether retinoids and phototherapy are inferior to methotrexate and biological drugs, even if they offer good treatment response and disease control. It is obvious that the cardiovascular effects of the new becoming biologicals are also of great interest and importance.



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The Higher Proportion of Men With Psoriasis Treated With Biologics May Be Explained By More Severe Disease in Men

The sex ratio of the prevalence of psoriasis is balanced. In recent years several reports have documented that men receive more systemic or UV treatment than women, and different hypotheses were made. In PsoReg, the national registry for systemic treatment of psoriasis in Sweden, we have, like other European registries, observed a predominance of men (59%), especially of men treated with biologics (63%). The objective of this study was to analyse if women are discriminated by not having the same access to the high-priced biologics.

A population-based cohort study using data from a nationwide quality register of psoriasis patients included 2,294 patients with moderate to severe psoriasis receiving systemic treatment from a specialist in dermatology. The main outcome measures: time to initiation of biologic treatment. A multiple Cox proportional hazard's regression was performed, with time to initiate a biological treatment as the outcome in order to assess the

independent role of the patient's sex in initiating such therapy. The psoriasis severity was defined as a time-varying variable.

The results showed that men had more severe psoriasis than women according to the Psoriasis Activity and Severity Index (PASI), regardless of age at enrolment, and throughout the study period. The analysis of the multiple Cox regression show that age, psoriasis severity and psoriasis arthropathy were relevant factors for initiating biological therapy, whereas sex is not.

Although as many women as men are believed to suffer from psoriasis, men seem to be more severely affected by psoriasis. The asymmetry in allocation of biological therapy thereby probably reflects the differing disease activity between the sexes, and is not a discrimination of women per se.



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cause prominent follicular plugging, follicular cysts and milias, and hyperkeratotic skin reactions. Local retinoids and acitretin have been used to control these side-effects with good results in case studies. The new MEK inhibitors, such as trametinib (Mekinist®), which is FDA approved for advanced melanoma, can be used together with B-RAF inhibitors. This combination causes less dermatological side-effects in trials when compared to B-RAF single drug treatment.

However, trametinib and other MEK inhibitors cause an EGFR inhibition and can cause the same side-effects as EGFR inhibitors.



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Danish Association of Dermatology Residents & Cardiovascular Risk Assessment in Patients with Severe Psoriasis vs. Severe Atopic Dermatitis

Danish Association of Dermatology Residents: A brief history of the Danish Association of Dermatology Residents were presented and the current status of the organisation and important goals were mentioned. All this is covered in detail in the latest issue of Nordic Forum of Dermatology and Venereology (Forum for Nord Derm Ven 2013; 18: 44–45).

Cardiovascular Risk Assessment in Patients with Severe Psoriasis versus Severe Atopic Dermatitis: Psoriasis is a common inflammatory disease of the skin and joints with a characteristic inflammatory pathogenesis based on a T-helper (Th)-1, Th-17 and Th-22 cell-mediated mechanism. Severe psoriasis is thought to be a systemic inflammatory disease linked to a range of comorbidities. A link between severe psoriasis and atherosclerotic disease has been proposed and the body of literature on the area is rapidly expanding.

Atopic dermatitis is another common inflammatory skin disease. In atopic dermatitis the inflammatory response seen during flares seems to be driven primarily by a Th-2 response. In a subset of patients with severe disease, there is a lifelong constant inflammatory response in the skin with evidence of systemic inflammation as well.

In this current study we utilise the technique of coronary computed tomography to assess the risk of cardiovascular disease in patients with severe psoriasis and severe atopic dermatitis. Non-invasive coronary computed tomography is a well established method of risk assessment and a diagnostic tool in suspected coronary artery disease.

Young Dermatologists

Update on Dermatological Side-effects of Novel Targeted Cancer Therapies

Many new targeted biological cancer therapies have recently come to market. They offer better efficacy, longer survival and fewer side-effects in general. Many of the targeted cancer therapies have a lot of specific dermatological side-effects.

The most common dermatological side-effect of the EGFR-inhibitors erlotinib (Tarceva®), gefitinib (Iressa®), panitumumab (Vectibix®), cetuximab (Erbix®) and lapatinib (Tyverb®) is an acneiform papulopustular eruption, which can be managed with tetracyclines, local antibiotics, hydrocortisone and emollients. The eruption has an early start and it usually fades away in a few months, leaving hyperpigmentation and telangiectasias. New studies show that a prophylactic treatment with tetracyclines, hydrocortisone and sunscreen use is much more effective than reactive use of the same medications. Cetuximab and panitumumab cause the most severe rash and when using those medications prophylactic treatment is advised.

B-RAF inhibitors vemurafenib (Zelboraf®) and dabrafenib (Tafinlar®) used for advanced melanoma are known to cause squamous cell carcinomas and keratoacanthomas. They also