Nordic Psoriasis Debate 2011: Managing Psoriasis – How Can I Improve Care for my Patients? An Interactive Debate on New Treatment Options for Psoriasis

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Following a successful inaugural meeting in 2010, the second Nordic Psoriasis Debate took place in Copenhagen in September 2011 and was coordinated by a faculty of distinguished Nordic and international experts. The meeting was co-chaired by *Professor Knud Kragballe* (Arhus University Hospital, Denmark) and *Professor Mona Ståhle* (Karolinska Institutet, Stockholm, Sweden). The Scientific Committee, responsible for the programme development, included, in addition to Professor Kragballe and Professor Ståhle, *Professor Robert Gniadecki* (Copenhagen University, Bispebjerg Hospital, Copenhagen, Denmark), *Dr Nils-Jørgen Mørk* (University Hospital Oslo, Norway) and *Dr Tapio Rantanen* (Tampere, Finland). The following speakers contributed to the meeting: *Professor Wolf-Henning Boehncke* (Johann Wolfgang Goethe University, Frankfurt, Germany), *Dr Ole Ahlehoff* (Copenhagen University Hospital Gentofte, Copenhagen University Hospital Roskilde, Denmark), *Professor Philip Helliwell* (University of Leeds, Bradford Hospitals NHS Trust, UK), *Professor Kristian Reich* (Dermatologikum Hamburg, Germany) and *Professor Frank Nestle* (St John's Institute of Dermatology, King's College London and Guy's and St Thomas' Hospitals, London, UK).

The objective of the meeting was to review and discuss treatment options in psoriasis, including established and novel agents, and to discuss how best to incorporate these into current management strategies. In addition, the link between psoriasis and cardiovascular (CV) risk was examined. The meeting also included a review of screening and assessment strategies for psoriatic arthritis. Finally, an overview of ongoing research activities provided a look into the future of psoriasis management. During the meeting, interactive workshops coordinated by the Scientific Committee, were held, during which specific patient case scenarios were reviewed and discussed.

Investigating the link between psoriasis and cardiovascular risk

Professor Boehncke and *Dr Ahlehoff* examined the link between psoriasis and CV risk, from the dermatologist's and cardiologist's view, respectively. Both noted that there is a compelling body of evidence indicating that psoriasis is an independent risk factor for CV disease, which is linked to the underlying mechanism of the disorder, its inflammatory nature (1, 2). Professor Boehncke explained the so-called "psoriatic march", which outlines a pathogenetic concept of how psoriasis may drive CV disease (1, 3). Based on the known relationship between psoriasis and obesity, with obesity being a recognized risk factor for psoriasis, the concept of the psoriatic march postulates that the systemic inflammation caused by psoriasis and obesity triggers insulin resistance and endothelial dysfunction, which in turn result in atherosclerosis and myocardial infarction.

Dr Ahlehoff reviewed a number of publications that demonstrate a clear association between psoriasis and CV disease. He explained that psoriasis is associated with an increased risk of arterial and venous thrombosis, atrial fibrillation, and CV and all-cause mortality (4–6). In addition, psoriasis as a clinically relevant cardiovascular risk factor is comparable to the risk posed by diabetes mellitus. Furthermore, Dr Ahlehoff outlined that the prognosis following myocardial infarction and percutaneous coronary intervention is impaired in patients with psoriasis compared with patients without psoriasis (7).

Professor Boehncke and Dr Ahlehoff noted that because of the known association between psoriasis, metabolic syndrome and CV risk, which contributes substantially to reduced life expectancy, there are clear intervention strategies that can be proposed to halt or prevent the development of CV disease. These interventions should encompass, on the one hand, close monitoring of pulse, blood pressure, body mass index (BMI), fasting blood lipids and fasting blood glucose, as well as pharmacological intervention to treat hypertension and dyslipidaemia, as well as lifestyle modifications to combat obesity. On the other hand, continuous effective systemic therapy may be beneficial to treat insulin resistance and endothelial dysfunction. Both Professor Boehncke and Dr Ahlehoff stressed that an increased awareness of CV risk in patients with psoriasis is needed. They highlighted that early CV risk factor management would be valuable and that, particularly

in patients with severe psoriasis, an aggressive approach to CV risk factor management should be considered to improve the outlook for these patients.

The presentations generated a lively discussion surrounding the optimal management of patients regarding CV risk. There was consensus that there is currently a large number of psoriatic patients with uncontrolled CV risk factors. It was suggested that patients should be screened for risk factors with the aim of initiating interventions, encompassing lifestyle changes, as well as pharmacological treatment, earlier, in order to prevent the development of severe CV comorbidity. Obesity was noted as the major known factor and it was highlighted that even a relatively modest reduction in body weight may have beneficial effects.

Screening and assessment of psoriatic arthritis

Professor Helliwell started his presentation by noting that the impact of psoriatic arthritis equals that of rheumatoid arthritis and that there is therefore a strong need to identify affected patients. A recent publication reported an annual incidence of 1.87% for psoriatic arthritis in patients with psoriasis (8). A number of factors are thought to be associated with its development, including both psoriasis-related factors, such as nail disease, scalp disease and natal cleft psoriasis, as well as environmental factors, including infection and lifting, while smoking appears to be protective. Psoriatic arthritis is a heterogeneous disease with diverse clinical features (9), resulting in a number of domains that require investigation in trials (10).

One of the key questions concerns the prediction of those patients with psoriasis who will go on to develop psoriatic arthritis, for which the application of biomarkers may provide a promising approach. A number of biomarkers are currently being investigated, including osteoprotegerin (OPG), soluble interleukin-2 receptor (sIL-2R), osteocalcin, crosslaps and osteoclast precursors, and results from these studies are awaited. Professor Helliwell went on to note that the presence of unrecognized psoriatic arthritis in a proportion of patients with psoriasis is a well-known fact, and outlined screening tools available to identify those patients. These various screening tools, including the PAQ (1997), modified PAQ (2002), PASE (2007), ToPAS (2008), PEST (2008) and PASQ (2009), mainly consist of questionnaires, some of which include pictures. The optimal tool remains to be determined, and an ongoing study (CONTEST) is comparing three tools in a head-to-head design, with final results expected in 2012 (11).

Next, Professor Helliwell summarized the results of a study aimed at investigating the reproducibility of skin and joint assessments in patients with psoriatic arthritis by rheumatologists and dermatologists. The study showed that there was agreement on most measures, with only dactylitis showing a significant discrepancy (12). Such an assessment of reliability is an important step in evaluating the utility of clinical measurements with a view to devising training programmes to further improve the assessment of patients.

Professor Helliwell stated that a shared care approach in the assessment and management of patients, involving both dermatologists and rheumatologists, would be optimal, but may not always be practical. Finally, he outlined an ongoing project aimed at developing a tool for the assessment and screening of psoriatic disease for dermatology clinics on the one hand and rheumatology clinics on the other hand, which will provide recommendations for the management of patients in each setting and should contribute substantially to improving the care of patients.

In the discussion following Professor Helliwell's presentation, it was noted that many dermatologists may perceive current screening tools as overly complex. The PASE tool was mentioned as the one that may be most feasible in a dermatology setting. There was consensus that dermatologists play a vital role in identifying patients with psoriatic arthritis and should therefore be aware of and vigilant to its symptoms. It was also stressed that all patients who have been identified as having psoriatic arthritis should have access to a rheumatologist.

Methotrexate revisited

Professor Reich remarked that methotrexate (MTX) currently remains the therapy of choice in the first-line treatment of psoriasis in Europe, which is backed by current guidelines. Three recent studies have provided valuable insights into the optimal use of the agent, and the results of these were summarized by Professor Reich.

In one study, MTX was compared with briakinumab (M10-255 trial) (13), while in the RESTORE and CHAMPION trials, the comparator arms consisted of infliximab and adalimumab, respectively (14, 15). In all three studies, MTX resulted in a response (PASI 75) in 35–40% of patients, providing consistent results regarding the expected efficacy of the agent. In addition, all trials showed that there is a certain percentage of loss of response beyond week 16. Professor Reich highlighted that these recent studies have demonstrated a good safety profile for MTX and that the large drop-out rates due to increases in liver enzymes that were seen in earlier studies were not observed, irrespective of the dosing schemes used in the different studies. He explained further that the co-administration of low-dose folic acid (5 mg) has been shown to result in a better safety profile and is therefore recommended.

Next, Professor Reich addressed the topic of dosing schemes. A question directed at the delegates revealed that approximately 50% start MTX at 15 mg/week, while 50% start with a lower dose. Professor Reich noted that, despite the different dosing schemes used in the three studies mentioned above, the safety and efficacy profiles were largely similar, leading him to suggest that the current practice of uptitration should no longer be applied and that starting treatment with 15 mg/week is appropriate. Furthermore, Professor Reich outlined that a subanalysis of the CHAMPION study has provided an answer regarding the question of when to uptitrate to 20 mg/week (16). The trial showed that following a PASI 50 response at week 8, the likelihood of achieving a PASI 75 response with continued treatment at 15 mg/week is high. For patients without a response (PASI 50) at week 8, uptitration to 20 mg/week will result in a PASI 75 in approximately 40% of patients, suggesting that uptitration to 20 mg/week is beneficial. However, in the absence of a response to 20 mg/week, the trial suggests that uptitration to 25 mg/week is not beneficial, as it will result in a PASI 75 response in only a small number of patients. Professor Reich stressed that these data strongly suggest that treatment should be initiated at a dose of 15 mg/week, that uptitration to 20 mg/week from week 8 is beneficial in non-responders and, furthermore, that treatment with MTX should be discontinued in those patients whose disease does not respond to the higher dose.

Professor Reich explained that basing the decision for uptitration on the response at week 8 is due to the metabolism of the drug. He elaborated that MTX is a prodrug and coupling to glutamate is required for pharmacological activity, a process that takes place mainly in erythrocytes. Interestingly, there are data suggesting a correlation between polyglutamation and response. From week 8, a stable pool of glutamation is seen (17), providing the rationale for initiating uptitration for non-responders only beyond week 8.

Regarding the question on the route of administration of MTX, Professor Reich explained that the subcutaneous administration of the agent has been shown to be better tolerated, particularly regarding nausea. Furthermore, in approximately 20% of patients, a better response is observed, which may be explained by a higher glutamation seen with the subcutaneous administration. MTX is effective in nail disease; however, efficacy is not as high as seen with biologics. Similarly, while MTX improves quality of life, this is not to the same extent as is seen with biological agents.

Professor Reich outlined an interesting aspect regarding the mode of action of MTX, which had been thought to be mediated through its impact on purine and pyrimidine metabolism. However, new data suggest that other mechanisms may be implicated, involving for example adenosine, which is linked with inflammatory responses. Finally, Professor Reich observed that it is now understood that genetic variations involving various processes in the uptake, metabolism and mode of action of MTX critically influence response and tolerability to the agent. This area is undergoing intense research and it can be anticipated that, in the future, genetic testing will precede the initiation of therapy, with the aim of selecting those patients who are most likely to benefit from MTX therapy.

In the subsequent discussion, Professor Reich was asked to comment on patient selection in the recent MTX trials, particularly with regard to the low incidence of hepatopathy. He explained that no particular selection had taken place, but added that these trials had taken place in Europe and Canada and that therefore the average weight of patients was lower than that typically seen in US trials.

Another question concerned the issue of acceptable levels of increases in liver enzymes. Professor Reich noted that although an increase of three times the upper limit of normal is generally considered to be acceptable, his recommendation is to screen patients and exclude those from MTX therapy who have pre-existing hepatopathy, particularly if other risk factors are present. Professor Reich added that increases in liver enzymes following MTX treatment present a greater issue than increases seen with anti-tumour necrosis factors (anti-TNFs), as MTX-associated increases can indicate future liver damage.

Regarding a delegate question on loss of response, Professor Reich noted that this is seen in 5–10% of patients per year. This loss of response can be explained by mechanisms related to the disease; for example, it may be due to the activation of other inflammatory mechanisms or the exposure to new trigger factors. Management has to be based on an individual approach and may consist of a change in therapy, an increase in dose or addition of concomitant therapy.

Targeting IL-12/IL-23 in psoriasis: current evidence on efficacy and safety

Professor Reich began by providing a brief overview of the current understanding of the pathophysiology of psoriasis, which provides an explanation for the activity of the biological agents. It is understood that the crosstalk between dendritic cells and T cells plays a key role in the development of psoriasis. The release of cytokine interleukin-23 (IL-23) by dendritic cells drives T cells towards the T helper cell 17 (Th17) subtype, which in turn produce chemokines and cytokines that are implicated in inflammation. Of interest, investigation of inflamed bone of patients with psoriatic arthritis has shown that osteoblasts are involved in the release of mediators that

are strong attractants for Th17 cells. It will therefore be of great interest to examine the activity of the new agents in psoriatic arthritis and trials are ongoing.

Next, Professor Reich summarized the results of the pivotal phase 3 trials in the development program of ustekinumab in psoriasis: PHOENIX 1 and PHOENIX 2, which are placebo-controlled trials, as well as ACCEPT, a superiority study versus etanercept (18–20). Professor Reich emphasized that, in total, over 3,000 patients have so far been treated with ustekinumab, providing a substantial experience base for the use of the agent. These trials have shown consistent efficacy results, with a PASI 75 at week 12 of approximately 70%, indicating that ustekinumab has at least comparable efficacy to other biologics, with the caveat that no randomized head to head comparison across all biologics is available. However, in the randomized ACCEPT trial, ustekinumab was significantly superior to etanercept at week 12 both for PASI 75 and PASI 90. Of note, ustekinumab was more effective than etanercept in patients for whom conventional systemic therapies were inappropriate due to inadequate response, intolerance or contraindications (20).

A notable observation from the phase 3 trials is that full efficacy with ustekinumab is seen at around week 24, with a PASI 75 of approximately 80%, indicating that treatment has to be administered until at least week 24 before a change to a different drug is made.

Professor Reich went on to show data for ustekinumab use in maintenance, which convincingly demonstrate the efficacy of the agent in this setting. Once treatment is discontinued, there is a loss of response; however, patients can be retreated successfully and a PASI 75 of almost 86% to retreatment can be expected.

New 4-year data of the long-term extension period of the PHOENIX 2 study show that responses are maintained long-term with a PASI 75 of 78–79% and a PASI 90 of approximately 53%. In approximately 50% of patients, the drug dose was escalated during the study; however, in a substantial proportion of patients the reason was not a suboptimal response (i.e. not achieving PASI 75), but that both physicians and patients felt that more treatment was needed, suggesting that treatment goals may require revision.

A retrospective analysis of the impact of patient weight in the phase 3 trials showed that there is no difference regarding efficacy between the two doses of ustekinumab (45 and 90 mg) in patients who weigh less than 100 kg. However, in patients weighing more than 100 kg, ustekinumab at 90 mg was found to lead to a significantly greater activity than the 45 mg dose, leading to the addition of a statement to the label that, for patients who weigh more than 100 kg, a starting dose of ustekinumab of 90 mg should be considered. However, Professor Reich pointed out that, in his experience, a substantial proportion of patients who weigh more than 100 kg will also respond to the lower dose of ustekinumab, while some patients who weigh less than 100 kg will not respond well to the lower dose. He noted that the possibility of greater flexibility in the dosing of the drug would be desirable.

Professor Reich added that ustekinumab is also effective in nail disease, and that important improvements are seen in quality of life.

In the next part of his presentation, Professor Reich addressed the safety profile of ustekinumab, and highlighted that, because all patients included in the ustekinumab clinical trials are enrolled in a 5-year open-label extension programme, more than 600 patients had been continuously treated with ustekinumab at the 4-year point (21). The size of the ustekinumab data-set in psoriasis is therefore comparable to that of adalimumab, suggesting that reliable results can be derived regarding the tolerability of the agent.

Regarding the rates of serious infections, as well as the incidence of non-melanoma skin cancer, there was no difference compared with placebo and no increase with long-term treatment (21). In addition, rates were similar to those seen with adalimumab.

Professor Reich went on to summarize the data obtained with ustekinumab regarding major cardiovascular events (MACE), which are comprised of myocardial infarction, stroke and death due to myocardial infarction or stroke. He explained that in the first 12 weeks a numerical imbalance in the incidence of MACE was seen in the placebo versus the ustekinumab group (no MACE with placebo, while 5 MACE were observed with ustekinumab); however, this did not lead to a statistically significant difference in the incidence of MACE between placebo and ustekinumab (22). In addition, the rate of MACE with long-term follow-up is low and comparable to adalimumab (23). An analysis of the ustekinumab trials regarding patients who developed MACE ($n = 19$) compared with those who did not ($n = 3{,}098$) revealed a higher presence of classical CV risk factors in the MACE group, such as diabetes, hypertension and hyperlipidaemia (24). Moreover, no patient in the MACE group had received combination treatment with aspirin and statin, while approximately 20% of patients in the group without MACE had received such treatment. Professor Reich emphasized that this clearly indicates a high prevalence of uncontrolled CV risk factors in patients with psoriasis, which should be addressed urgently.

Professor Reich ended by summarizing that ustekinumab presents an innovative treatment modality with a novel mode of action based on a new cytokine target. The agent has demonstrated an excellent efficacy profile in induction and maintenance therapy, as well as a favourable risk-benefit profile with no increase in safety signals of interest over time, even with long-term follow-up (4 years).

Future perspectives on psoriasis

The final presentation of the day was a keynote lecture by *Professor Nestle*, who provided an outlook into the future of psoriasis management. He noted that substantial advances have been made in elucidating the molecular mechanisms of psoriasis, most notably with the advent of whole genome association scans. These have revealed a number of genes that are associated with psoriasis. In particular, it has led to the discovery of the association between psoriasis and the interleukin 23 (IL-23) pathway genes. IL-23 is a key pro-inflammatory cytokine that drives autoimmunity in animal models and human diseases. It plays a critical role in the T helper cell 17 (Th17) response, as IL-23/IL-23R signalling is involved in the terminal differentiation and effector functions of Th17 (25). Genome-wide association studies have shown that a variant of the IL23R carrying a single amino acid substitution, the IL23R R381Q variant, protects against psoriasis, Crohn's disease and ankylosing spondylitis. A recent study found that IL23R R381Q exerts its protective effects through the selective attenuation of IL-23-induced Th17 cell effector function without interfering with Th17 differentiation (25).

Professor Nestle presented results of a recent genome-wide association study, which has identified new psoriasis susceptibility loci. The findings of the study implicate pathways that integrate epidermal barrier dysfunction with innate and adaptive immune dysregulation in psoriasis pathogenesis, thus providing a better understanding of the disease pathobiology (26). This, in turn, provides the rationale for the development of new targeted therapies (27).

Professor Nestle noted that a 2009 publication showed that topical treatments still dominated the therapeutic modalities employed in psoriasis (28). However, he went on to point out that a large number of ongoing clinical trials are now investigating biological therapies, including anti-cytokine and anti-T cell antibodies, as well as kinase inhibitors and broad spectrum immunomodulators. In addition, there are studies focussed on the identification of biomarkers, as well as clinical subtypes of the disorder. The following cytokine inhibitors are currently undergoing investigation: anti-IL23, anti-IL22, anti-IFN-α, anti-IL17/anti-IL17R, as well as broad spectrum cytokine inhibitors (e.g. anti-PDE4). Professor Nestle went on to explain that protein kinase signalling plays an important role in inflammation, providing the rationale for the investigation of kinase inhibitors directed against Janus kinases (Jak) and p38 mitogen-activated protein kinases (MAPK) in psoriasis.

Professor Nestle noted that the complex interactions and interrelationships between different signalling molecules provide a significant challenge for the development of targeted agents. He outlined how the generation of an interactome network (a network of inter-connected genes based on similar expression profiles) has enabled the generation of a framework to assess cytokines as therapeutic targets in human disease. Based on the integration of clinical and genomic data, a cytokine with a potential role in disease pathogenesis is identified and an interactome is generated from gene expression data pooled from patient samples. This interactome is used to map gene expression data from the experimental steps that are carried out to assess the role of the cytokine in disease pathology, as well as the efficacy of anti-cytokine therapy. Using this approach, promising potential targets can be identified for further study.

Professor Nestle concluded that the approach to the development of treatments for psoriasis has progressed substantially, from an initial reliance on the serendipitous discovery of effective agents to an approach based on the development of targeted, smart drugs resulting from an increased understanding of the pathogenesis aided by the application of modelling systems (29).

Conclusion

At the end of the meeting, *Professor Kragballe* and *Professor Ståhle* summarized that the interactive debate had provided an excellent overview of current data and management strategies in psoriasis. In addition to providing the data to make evidence-based treatment decisions, a number of other important aspects in psoriasis were addressed, such as comorbidities, as well as appropriate screening and assessment modalities. Importantly, advances in the understanding of the pathogenesis of psoriasis are making it possible to offer targeted treatments, and a number of potential agents are undergoing investigation, providing a positive outlook for patients with a disorder that is associated with significant morbidity and a detrimental impact on quality of life.

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