Nordic Psoriasis Debate: Am I Doing the Right Thing For My Patient?

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The first Nordic Psoriasis Debate, an interactive debate on new treatment options for psoriasis, was held in Copenhagen, Denmark, in August 2010. The debate meeting was coordinated by a group of Nordic and international dermatology experts, and was attended by more than 70 delegates from Denmark, Norway, Sweden and Finland.

Professor Knud Kragballe from the University of Århus, Denmark and *Professor Mona Ståhle* from the Karolinska Institute, Sweden, were co-chairs of the meeting (Fig. 1). Professor Ståhle gave a presentation on comorbidities in psoriasis, reviewing the data that highlight an increased risk of metabolic syndrome and cardiovascular mortality associated with severe psoriasis. Professor Kragballe gave the keynote lecture on the risk of infection, malignancies and cardiovascular disease associated with immunomodulating therapies, presenting data from both clinical trials and registries. *Dr Ulrich Mrowietz* from the University of Kiel, Germany, gave a comprehensive overview of the recently updated European treatment guidelines highlighting the difference between evidence-based and eminence-based treatment recommendations (1). *Professor Lluis Puig* from Hospital De La Santa Creu I Sant Pau, Barcelona, Spain, provided an overview of his experience in combining conventional and immunomodulatory therapies, presenting a series of patient cases from his clinical practice. *Professor Robert Gniadecki* from Bispebjerg Hospital, Copenhagen, Denmark, presented the Danish experience of IL12/IL23 inhibition, reviewing data from clinical trials and selected patient cases from his clinical practice.

In addition to the presentations, the meeting also included a series of interactive breakout groups, which provided delegates with an opportunity to discuss some of the key issues in psoriasis with the international faculty (Fig. 2). This article provides a summary of the key topics discussed during the debate, which included treatment guidelines, biologic treatment regimens, physician assessment of patients, treatment goals in psoriasis, and psoriasis induced by tumour necrosis factor alpha (TNF-α) inhibitors.

Fig. 1. Co-chairs of the meeting, Professors Mona Ståhle and Knud Kragballe, initiating the panel discussion during the Nordic Psoriasis Debate.

Treatment guidelines: How useful are they?

Among the subjects discussed by the breakout groups, the usefulness of guidelines for making treatment decisions when treating patients with psoriasis was a key topic. It was generally agreed that guidelines provide an overview of evidence-based medicine and provide recommendations for best treatment practices based on available clinical data. The primary focus of guidelines is to provide a robust review of the efficacy and safety of currently available therapies. When developing treatment recommendations, cost and practical considerations are considered, but efficacy and safety remain the primary considerations. However, guidelines are only guidelines, and should not be followed without consideration for the individual patient. Professor Mrowietz highlighted that by reading treatment guidelines dermatologists can stay up to date with the latest developments and ensure that patients receive the best evidence-based care. He also added that guidelines are "good, but even better when followed", as this ensures that individual patients receive the most suitable treatment that is both tolerable and effective in treating psoriasis.

Delegates questioned whether it was appropriate to treat children experiencing psoriasis with biologics and whether any guidelines existed. The faculty confirmed that no specific treatment guidelines have been published for psoriasis in children. Marji et al. (2) have reviewed the clinical evidence for the use of biologics in children. Etanercept is the only biologic licensed to treat children aged 8 years based on clinical trial and registry data (3). Few other treatments are suitable for administration in children, due to toxicities or adverse events.

Local treatment guidelines exist in many of the Nordic countries, and some delegates felt that it would be useful to develop working groups to review and update local guidelines based on European guidelines. However, not all delegates were as enthusiastic about treatment guidelines, as in some instances they may be used as a political tool. For example, in Norway biologic therapies are reimbursed only when they are prescribed in line with guideline recommendations, although exceptions may be made on a case-by-case basis. Overall, it was generally agreed that evidence-based treatment guidelines that are regularly updated are an excellent tool for making robust treatment decisions.

Biologic treatment regimens

When prescribing therapy for treatment of psoriasis, dermatologists aim to balance the risks of adverse events with efficacy in treating the condition. Modifying the dose and dosing interval of administration is a common way to balance the efficacy and toxicities of a given therapy better. However, such modifications in the biologic treatment regimen could result in a lower concentration of the antibody in plasma, increasing the risk of developing antibodies against the drug. The prevalence of immunogenicity reactions in patients treated with infliximab varies from 12% to 44%, and it has been suggested that this is inversely proportional to serum levels of infliximab (4). Immunogenicity reactions have been reported to be reduced by an induction regimen followed by maintenance treatment compared with a single dose followed by episodic retreatment with infliximab (5). The faculty sug-

Fig. 2. Participants raising questions during interactive discussions at the Nordic Psoriasis Debate.

gested that, when prescribing infliximab, the dosage should not be reduced below 3 mg/kg. An increase in infusion reactions has also been reported following modifications to the dosage of adalimumab (4). Interestingly, concomitant use of methotrexate or other immunosuppressive drugs may reduce the formation of antibodies and immunogenicity reactions (4). At the debate meeting, the faculty suggested that TNF-α inhibitor treatment regimens should be modified with caution.

Many dermatologists also commented that they would prefer to use biologics in the first-line setting, but that the price of these agents makes this prohibitive. Currently, patients must fail to respond to therapy with methotrexate before a biologic can be prescribed. However, delegates highlighted that methotrexate is indicated for use in "severe, uncontrolled psoriasis" and therefore in many European countries methotrexate is prescribed off-label (6).

Treatment outcomes for psoriasis: The future?

Following Professor Ståhle's presentation, the subject of comorbidities was a hot topic in the discussions. A study by Gelfand et al. (7) reported that patients with psoriasis had an increased adjusted relative risk (RR) for myocardial infarction (MI). A 30-year-old patient with mild or severe psoriasis has an adjusted RR of 1.29 (95% confidence interval (CI) 1.14–1.46) and 3.10 (95% CI 1.98–4.86) for having an MI, respectively. Whereas, for a 60-year-old patient with mild or severe psoriasis, the adjusted RR of having an MI is 1.08 (95% CI 1.03–1.13) and 1.36 (95% CI 1.13–1.64), respectively. There is increasing evidence that cardiovascular disease (CVD) is more prevalent among patients with psoriasis than among control populations (8–10). Given that patients with severe psoriasis have an increased risk of developing comorbidities, delegates questioned whether a satisfied patient is sufficient when considering treatment outcomes. For example, a patient with psoriasis may experience a 50% reduction in disease following therapy and be satisfied with this improvement. However, the patient still has a 15–30% inflammatory burden in the skin and is at increased risk of developing CVD. Delegates all agreed that it is important to educate patients and other stakeholders about the increased risk of CVD and metabolic syndrome associated with severe psoriasis. However, it is unclear which healthcare provider, general practitioner or dermatologist, is responsible for educating patients. Preliminary evidence suggests that preventative care and screening programmes are not currently fully implemented (11, 12). The faculty commented that, in Denmark, some healthcare providers refer patients with arthritis who have increased risk factors for CVD for further testing.

Overall, delegates generally agreed that a multidisciplinary approach would ensure that patients are given the appropriate information to help them take better care of their health and make lifestyle changes. It is important that patients receive treatment to ensure that their risk of comorbidities is reduced. In other medical specialties treatment outcomes are assessed using specific measures. For example, in dermatology treatment may be continued until the patient is satisfied with their skin, whereas in controlling hypertension it is usual to ensure that blood pressure is within a range between 120/80 and 140/90 mmHg to stop treatment, rather than when the patient is satisfied. Development of treatment outcomes that assess a patient's inflammatory burden, risk of comorbidities and response to therapy would be a new way of thinking in dermatology. Faculty and delegates emphasized that the goal of treatment was to control for morbidities that can affect patient wellbeing, morbidity and mortality, not to please the patient. A tool to measure specific treatment outcomes may therefore be the future in dermatology, but it would take time to develop and gain acceptance among dermatologists.

Physician assessments: how can we improve our assessments?

Delegates attending the meeting agreed that there was an unmet need to improve the Psoriasis Area Severity Score Index (PASI). Despite many attempts no improvements have been made in the PASI. The major criticism of the PASI score was that it is imprecise, with low response distribution, no consensus on interpretability, and low responsiveness in mild disease (13). In addition, not all physicians use the PASI on a routine basis. Many of the delegates confirmed that they either do not use the PASI or that they assess the patient using the Physician's Global Assessment (PGA) and then calculate the PASI. Overall, among the participants, use of the PASI scores varies from country to country but the faculty cautioned that numbers are typically higher among physicians attending meetings on psoriasis. The faculty and delegates agreed that the ideal tool to assess severity of psoriasis would be easy to use, precise and reproducible.

Psoriasis induced by biologics: Are patients at risk?

Delegates raised some concerns regarding the occurrence of psoriasis among patients with autoimmune disorders, such as rheumatoid arthritis, treated with biologics (14). However, the faculty reassured delegates that treatment-induced psoriasis can be treated with topical steroids administered in combination with current TNF-α inhibitors. Wollina et al. (15) reported the results of 120 patient cases experiencing a variety of autoimmune conditions, in which the patients developed pustular lesions during therapy with TNF-α inhibi-

tors. A total of 47 patients discontinued therapy with TNF-α inhibitors (in some cases anti-psoriatic topical treatments were administered) and 47 continued treatment with anti-psoriatic adjuvant therapy (also mostly topical therapy), and 93.2% and 95.9%, respectively, of the patients experienced resolution of the pustular lesions (15). The faculty suggested that patients who develop psoriasis when receiving TNF-α inhibitors could be treated with topical treatments and monitored until the flare clears.

Summary

In the concluding remarks, Professor Kragballe commented that the timing of this meeting was welcomed. However, physicians need time to adjust to the new data emerging in the field of psoriasis. Treatment goals need to be better defined to ensure that patients receive the most effective care. Satisfied patients are not sufficient in terms of treatment outcomes as there is a significant risk of CVD associated with inflammation in severe psoriasis. The psoriasis field has a lot of indirect evidence on the risk of comorbidities, and although this knowledge needs to be expanded, it must also be implemented appropriately. Patients must be counselled on possible improvements in lifestyle and cut-off values must be defined for cholesterol, blood sugar, blood pressure and other measures. Professor Kragballe also agreed that European guidelines can act as umbrella guidelines on which to base local guidelines. He stressed the importance of ensuring that guidelines are regularly updated, as they provide a useful tool for keeping up to date with developments in treatment practice even though they may not have any legal implications. Finally, it is important that patients, as the main stakeholder in psoriasis care, are included in future discussions.

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References

1. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2009; 23 Suppl 2: 1–70.
2. Marji JS, Marcus R, Moennich J, Kay-Wiggan J. Use of biologic agents in pediatric psoriasis. J Drugs Dermatol 2010; 9: 975–986.
3. Wyeth. Enbrel: summary of product characteristics. Cited Nov 2010. http://www.enbrel.eu/Enbrel-SPC/tabid/1021/Default.aspx.
4. Emi AN, de Carvalho JF, Artur Almeida SC, Bonfa E. Immunogenicity of Anti-TNF-alpha agents in autoimmune diseases. Clin Rev Allergy Immunol 2010; 38: 82–89.
5. Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004; 2: 542–553.
6. Hospira. Methotrexate: summary of product characteristics. Cited Nov 2010. Available at http://www.medicines.org.uk/emc/medicine/12034.
7. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006; 296: 1735–1741.
8. Kimball AB, Wu Y. Cardiovascular disease and classic cardiovascular risk factors in patients with psoriasis. Int J Dermatol 2009; 48: 1147–1156.
9. Kim N, Thrash B, Menter A. Comorbidities in psoriasis patients. Semin Cutan Med Surg 2010; 29: 10–15.
10. Davidovici BB, Sattar N, Prinz JC, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol 2010; 130: 1785–1796.
11. Feldman SR, Ravis S, Moran WP, Fleischer AB, Jr. Patients seen in a dermatology clinic have unmet preventive health care needs. J Am Acad Dermatol 2001; 44: 706–709.
12. Kimball AB, Szapary P, Li S. High prevalence and under-diagnosis of cardiovascular risk factors among psoriasis patients in a clinical trial population. Program and abstracts of the American Academy of Dermatology Summer Meeting; July 30–August 3, 2008; Chicago, Illinois.
13. Spuls PI, Lecluse LL, Poulsen ML, Bos JD, Stern RS, Nijsten T. How good are clinical severity and outcome measures for psoriasis? Quantitative evaluation in a systematic review. J Invest Dermatol 2010; 130: 933–943.
14. Harrison MJ, Dixon WG, Watson KD, King Y, Groves R, Hyrich KL, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009; 68: 209–215.
15. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol 2008; 9: 1–14.