

Systemic Treatment for Psoriasis – a New Biologic Era

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Professor Mona Ståhle, head of the Department of Dermatology at Karolinska Institutet in Stockholm, was one of the chair persons at the symposium “Biologics – Anything Unsaid?” at the Nordic Dermatology Congress in Reykjavik. She gave this lecture on systemic treatment for psoriasis.

Abstract

Psoriasis is the most prevalent inflammatory skin disease in our part of the world. Despite considerable advances in knowledge about disease pathology, the ultimate cause of psoriasis remains elusive. Current understanding recognizes the significant clinical heterogeneity of the disease, which may result from differences in pathomechanisms and variations in the genetic background. How such differences translate into therapeutic response in the individual patient is an emerging challenge, which has become more obvious with the introduction of the novel biologic drugs. In fact, these drugs constitute powerful *in vivo* models for studying disease mechanisms and may provide important clues to pathogenesis. Even within the class of drugs antagonizing tumor necrosis factor (TNF)- α , there are differences in response among psoriasis patients and, interestingly, insufficient response to one drug does not preclude an excellent response to another. In the Nordic countries, we currently have access to four different biologicals for treatment of psoriasis: efalizumab, etanercept, infliximab and adalimumab, and additional drugs are already in clinical trials. This is a fortunate situation for patients with psoriasis and provides us with new possibilities to control even the most severe disease manifestations.

Introduction

The ultimate cause of psoriasis is unknown and the disease thus remains a challenge in dermatology. However, the challenge may be emerging from the shadows and starting to show shape and contour. Thus, the way we conceptualize psoriasis has changed dramatically during the past decade. While initially being regarded as a single disease, we now appreciate the complexity and heterogeneity of the symptoms that constitute psoriatic manifestations. We are also beginning to acknowledge significant comorbidities, particularly the risk of cardiovascular disease and metabolic syndrome, and taking them into account in clinical practice; psoriasis is certainly more than skin deep (1–4).

In global genetic studies currently underway in psoriasis, new strategies and tools are being implemented and attempts to sharpen analyses and, most importantly, to stratify for different phenotypes are major aims. Genetic approaches for studying complex diseases are improving and it is apparent that several complex immune-mediated diseases, such as psoriasis, rheumatoid arthritis, multiple sclerosis and Chron's disease share genetic susceptibility factors. We are now starting to benefit from such interdisciplinary interactions and collaborations (5, 6). During the past year we have experienced the identification of at least one novel psoriasis gene, interleukin-23 receptor (IL-23R), for which the association with psoriasis has been replicated by several groups using different populations (7–9). This pathway certainly constitutes a major drug target in psoriasis and impressive efficacy is reported from the clinical trials with monoclonal antibodies directed against the IL-12/IL-23 p40 subunit (10–12).

Novel regulatory mechanisms important for skin biology are also being explored and one of the more exciting fields that is currently evolving is the role of small regulatory RNA genes, the microRNAs. The first comprehensive profiling of microRNAs in inflammatory skin diseases was published recently and the aberrant expression of several microRNAs in psoriasis was reported. One of these microRNAs, miR-203, is highly conserved and skin-specific and significantly upregulated in psoriasis (13). The functional role for miR-203 and other microRNAs in skin biology are currently being explored and they are likely to be involved in the pathogenesis of inflammatory diseases (14). Since microRNAs act as master-switches and control the expression of multiple molecules in a network, they can effectively suppress a complete functional unit and, as such, represent attractive therapeutic targets.

Targeted systemic therapies in psoriasis

Treating severe psoriasis can be a real challenge and to achieve sustained control without substantial side-effects is the ob-

vious goal. Traditional systemic drugs, such as methotrexate, cyclosporine and acitretin, are effective in many patients, but not all. In addition, organ toxicity can be a problem and more specific therapies are needed.

The paradigm shift in acknowledging the role of T cells and the immune system in the pathogenesis of psoriasis opened up attempts to intervene specifically in such pathways (15, 16). Here, dermatology was able to benefit from the drug development already underway in rheumatology and gastroenterology, and at least one exclusive “skin drug” – efalizumab – was also put on the market. Today the focus is mainly on cytokines that drive the inflammatory process in psoriasis, such as TNF- α and on suppressing the activation of T cells (17, 18).

Today four different biologics are in clinical use in Europe, one blocking the activation of T cells, efalizumab, and the others directed against TNF- α (Table I).

Efalizumab

Efalizumab is a recombinant humanized IgG1 monoclonal antibody that blocks the CD11a subunit of LFA-1 on the surface of T cells. LFA-1 is a heterodimer consisting of CD11a and CD18. By binding to LFA-1, efalizumab blocks the inflammatory pathway at three critical points: generation of the second signal to activate memory T cells, extravasation of T cells, and subsequent activation of keratinocytes by T cells.

Efalizumab received approval in 2003 for the treatment of chronic, moderate to severe plaque psoriasis. It is particularly recommended in patients with a high risk of latent tuberculosis or demyelinating disease where anti-TNF- α treatment is contraindicated.

Table I. Nomenclature of biologics (adapted from Tzu et al. *Dermatol Ther* 2008; 21: 131–141).

Suffix	Definition	Murine vs human components
zumab	Humanized monoclonal antibody	Complementarity determining region from variable region of donor mouse mAb grafted onto acceptor human variable region
cept	Receptor-antibody fusion protein	N/A
ximab	Chimeric monoclonal antibody	Variable region from donor mouse mAb grafted onto acceptor human antibody
umab	Human monoclonal antibody	Fully human mAb

mAb: monoclonal antibody

Numerous trials have demonstrated that efalizumab is effective in treating plaque psoriasis (19–21). Sustained effect and safety has been assessed for up to 3 years and no increase in side-effects with duration of treatment has been shown. Among the side-effects noted are thrombocytopenia, exacerbation of psoriasis and re-bound, particularly in non-responders (22), and a transient papular eruption (23).

The recommended dose of efalizumab is 0.7 mg/kg subcutaneous (s.c.) injection for the first week in order to reduce frequency and severity of acute adverse events (17). The dose is then increased to 1 mg/kg every week for the next 11 weeks. If a 50% reduction in the Psoriasis Area and Severity Index score (PASI 50) response is not attained within 12 weeks, efalizumab should be discontinued, since the risk of rebound is substantial in non-responding patients (24). Clinical effect is expected between 4 and 8 weeks.

Drugs targeting TNF- α

The TNF- α inhibitors in use today include etanercept, infliximab and adalimumab. They all decrease levels of TNF- α produced by resident and migratory cells in the skin and joints and, in doing so, the psoriasis process is suppressed.

The long-term safety of TNF- α inhibitors is being monitored closely. In theory, inhibition of TNF- α may impair the body's defence against infections and tumours, as TNF- α is a key molecule in innate immunity. An increased risk of serious infections, and malignancies in rheumatoid arthritis patients treated with infliximab and adalimumab was found recently in a meta-analysis of multiple controlled trials (25). Cases of opportunistic infections, granulomatous diseases and hepatitis B reactivation have been reported with all anti-TNF- α agents (26). It appears that infection rates may be higher in patients treated with infliximab and adalimumab compared with etanercept (27). Despite the increased risk of malignancy in treated patients, it was concluded that lymphoma risk is not increased with anti-TNF- α agents, and that the increased frequency of lymphomas may reflect a higher background incidence of lymphoma in the disease population (28). Other serious adverse events associated with anti-TNF drugs include exacerbation of congestive heart failure and demyelinating disease.

Given the potential serious adverse events associated with anti-TNF- α agents, physicians are advised to exercise caution when prescribing this category of biologics, especially in patients who have predisposing risk factors. All patients should be screened for tuberculosis, demyelinating disorders including optic neuritis, and cardiac failure prior to starting treatment.

Etanercept

Etanercept is a receptor antibody fusion protein that combines the human IgG1 Fc region with two TNF type II (p75) receptors. In contrast to other anti-TNF- α agents that bind soluble and transmembrane TNF- α , etanercept binds to soluble TNF- α and TNF- β (lymphotoxin- α).

Etanercept was approved for the treatment of chronic, moderate to severe psoriasis in 2004 and recently it was also effective and approved for paediatric psoriasis (29). Etanercept is also used in rheumatoid arthritis, psoriatic arthritis, juvenile rheumatoid arthritis and ankylosing spondylitis.

Numerous clinical trials have demonstrated the efficacy of etanercept in the treatment of chronic, moderate to severe plaque psoriasis (30, 31). It is recommended that patients obtain a tuberculin (PPD) test and/or chest X-ray prior to starting therapy. The recommended dose for etanercept is 50 mg s.c. twice weekly for 12 weeks, followed by 50 mg s.c. per week. Significant clinical effects can be expected between 4 and 8 weeks. Etanercept should be discontinued if patients do not reach a PASI 50 response by week 12. The risk of rebound upon discontinuation of this biologic is minimal, and patients can be restarted on therapy as needed.

Common side-effects of etanercept therapy include injection site reactions. The reported rate of serious infections in treated patients is comparable to that of placebo. Cases of tuberculosis reactivation have been reported in rheumatoid arthritis patients treated with etanercept, although the causal relationship has not been verified (27, 32).

Infliximab

Infliximab is an anti-TNF- α chimeric monoclonal IgG1 antibody. In addition to blocking soluble TNF- α , infliximab also binds transmembrane TNF- α , resulting in antibody-mediated cytotoxicity. Unlike etanercept, which binds only trimeric TNF- α , infliximab binds to monomeric and trimeric TNF- α in more stable complexes. These differences probably explain the more rapid clinical effects observed with infliximab compared with etanercept.

Infliximab was approved in 2006 for treatment of chronic plaque psoriasis. Like etanercept, it is also used for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis. Given the rapid effect and high response rate, infliximab is recommended when rapid disease control is required in unstable conditions, such as erythrodermic or pustular psoriasis. If compliance is expected to be a problem infliximab may be the preferred therapy.

The recommended dosing regimen for infliximab is a 5 mg/kg intravenous (i.v.) infusion, to be repeated at 2, 6 and then every 8 weeks. Clinical effect is usually apparent by 1–2 weeks (19). Patients are required to undergo purified protein derivative (PPD) and chest X-ray testing for tuberculosis screening before initiating treatment.

Numerous clinical trials have demonstrated the efficacy of infliximab in treatment of chronic, plaque psoriasis and higher PASI scores were achieved with continuous than intermittent therapy during a 50-week evaluation, and a 5 mg/kg dose was more effective than a 3 mg/kg dose (27, 28).

Common side-effects associated with infliximab include headache, pruritus and sinusitis. Neutralizing antibodies against infliximab develop in more than 20% of patients (17) and appear to reduce the efficacy of treatment over time (29). Interestingly, the development of these antibodies correlates with the development of infusion reactions (22). Use of immunosuppressants, such as methotrexate, prior to treatment suppresses the formation of neutralizing antibodies.

Serious side-effects associated with infliximab include tuberculosis reactivation, exacerbation of congestive heart failure, invasive fungal infections, severe hepatic reactions, and lupus-like syndrome (31).

Adalimumab

Adalimumab is a fully human monoclonal IgG1 antibody against TNF- α . Similar to infliximab, it blocks soluble as well as transmembrane TNF- α (23).

Adalimumab recently received approval for the treatment of moderate to severe chronic plaque psoriasis. In addition it is approved for psoriatic arthritis, Crohn's disease, rheumatoid arthritis and ankylosing spondylitis. Prior to starting treatment, recommended laboratory tests include PPD and/or chest X-ray and liver function tests (32).

As with all TNF- α inhibitors, caution is advised in patients with a history of or predisposition to demyelinating disease, congestive heart failure, and malignancy. Common side-effects associated with adalimumab include injection site reactions, headache, nausea and fatigue.

Serious side-effects reported are similar to other anti-TNF agents (33). Similar to infliximab, neutralizing antibodies develop in a fraction of patients and reduce the efficacy of treatment. This effect is reduced with combination with methotrexate.

The recommended dosing for adalimumab is 80 mg s.c. loading dose followed by 40 mg s.c. every other week. Clinical trials have demonstrated the efficacy of adalimumab in the treatment of chronic plaque psoriasis (29, 33, 34).

Drugs in the pipeline

Current research indicates the importance of a new biological pathways in psoriasis, the Th17 pathway. Drugs targeting IL-23, a cytokine stimulating the proliferation of Th17 cells are in development and are very promising.

Ustekinumab and ABT-874, both targeting the p40 subunit, a component of IL-12 and of IL-23, show impressive PASI reduction in phase II and III trials.

Final remarks

In dermatology, experience of treating psoriasis patients with biological drugs is increasing by the hour and quality registries are being established for post-market surveillance. In Sweden, PsoReg has been up and running since 2007 and more than 700 patients on systemic treatment for psoriasis have been registered to date. Obviously, structural follow-up is necessary to appreciate fully the value of biologicals and, it is hoped, will help in alerting for side-effects that may not have been noticed in the clinical trials. A major challenge at this point is to identify markers, biomarkers or clinical markers that can serve as indicators for responders/non-responders.

Without doubt, the biological drugs that are currently in use constitute a major step forward in treatment of moderate-to-severe plaque psoriasis. As our understanding of the disease deepens, sharper and even more specific targets will appear. However, for all the biologicals, long-term safety issues are vital and only time will tell whether they meet safety criteria.

In conclusion, the introduction of biologicals represents the start of a new and proactive era in the treatment of psoriasis. In addition to dramatically improving quality of life for thousands of patients, these drugs also teach us about psoriasis *in vivo*. We can foresee exciting developments as, it is hoped, we will identify biomarkers for treatment response that may make even more tailored and individualized therapy possible.

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The Status of Infotech, the Internet and Telemedicine in Dermatology in the Nordic Countries

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Lars Erik Bryld chaired the session Infotech, Telemedicine and Dermatological websites at the 31st Congress of Dermato-Venereology in Reykjavik. For those of you who missed the session, he has written a short summary.



At the recent Nordic Congress of Dermato-Venereology in Reykjavik a full session was dedicated to infotech, telemedicine, and dermatological websites.

Implementation of information technology in healthcare today is ubiquitous, but in far too many cases it is locked within proprietary systems with limited potential for seamless exchange of information. This prevents optimal patient care when patients move between different healthcare providers and locations.

Furthermore, many patients situated in remote locations of the world do not receive healthcare on a par with what can be provided in more densely populated areas. The recent worldwide spread of internet access has resulted in emerging solutions that address some of these problems. The challenge of servicing remote locations such as the Faroe Islands, north-

ern Norway, and Alaska using telemedicine was addressed by *Drs Jemec, Moseng and Bocachica*, respectively, while *Drs Bryld and Bleeker* gave talks about using the internet to perform cross-site tracking of non-melanoma skin cancer and to educate health personnel, respectively.

Another session featured a talk about home care eczema counselling using telemedicine. While these systems are still under development, and many issues regarding patient confidentiality and security remain to be resolved to the satisfaction of all users and authorities, the currently presented results overall appear very promising.

Internet-driven information technology must currently be regarded as an inevitable tool when trying to provide near-equal access to high-quality healthcare knowledge with a limited number of healthcare specialists.