All in all, the new generation of biological drugs recently made available for the treatment of psoriasis are, for several reasons, not the ideal treatment of psoriasis, but they deserve their place as visitors in time and as templates for next generation of psoriasis treatments, which are yet to come.

Biological Therapy Provides New Possibilites for Combination Therapy for Serious and Previously Therapy-resistent Psoriasis

Experiences from the Department of Dermatology at St. Olavs Hospital, Trondheim, Norway.

Morten Dalaker
Department of Dermatology, St Olavs Hospital, University Hospital Trondheim, NTNU, Norway
E-mail: Morten.Dalaker@stolav.no

In Norway, infliximab (Remicade®) and etanercept (Enbrel®) are approved for treating moderate to serious plaque psoriasis and psoriatic arthritis, while adalimumab (Humira®) is approved for psoriatic arthritis. Efalizumab (Raptiva®) is approved for severe plaque psoriasis. In Norway, the patient must apply to the National Office for Social Insurance before each separate treatment occasion in order to get a referral for treatment using biological therapy. Relatively strict indication exists: the patient must have moderate to serious plaque psoriasis, which has not responded to or is intolerant to other systemic treatment, including cyclosporine, methotrexate and/or PUVA, or where such treatment is contraindicated. Norway has about 4,5 million inhabitants. 2–3% of the population has psoriasis, and roughly 25% of the psoriasis patients are serious cases. If 10% of those with serious psoriasis have a therapy-resistant form of psoriasis and in need of biological therapy, we would have about 2500–3000 Norwegian patients in need of such treatment.

At the Department of Dermatology in Trondheim, we began biological treatment using infliximab for a patient with serious plaque psoriasis in August 2001, our first patient treated using biological therapy. He still uses infliximab (3 mg/kg) combined with methotrexate 4.5 years after starting treatment, and we have seen a continued positive effect of this treatment. Since then, we have treated 22 patients with severe plaque psoriasis using infliximab. Etanercept has now also been approved for treatment of plaque psoriasis, and we have 25 patients who have begun treatment with etanercept for psoriasis. During the last year, we have also begun treatment using efalizumab of 11 patients with widespread plaque psoriasis. Adalimumab has recently been used for 3 patients with psoriasis at our department, and for the time being, this is the therapeutical agent with which we have the least amount of experience.

Patients who come into question for treatment using biological therapeutics are often patients who have a long treatment history, and who are difficult to treat successfully. They have already tried light treatment, including PUVA, methotrexate, cyclosporine, and often also systemic retinoids. Biological therapeutics make an important addition to the treatment options available for these patients. However, that does not mean that biological treatment works equally well for all patients with severe psoriasis. We have the impression that those of our patients who come into question for this type of therapy have a more active/severe form of psoriasis than patients who have participated in large international studies. Even though our patient numbers are small, this may explain

the somewhat weaker response we have observed in monotherapy using etanercept and ezalizumab. However, I believe that biological therapeutics should to a greater extent be combined with traditional systemic treatment such as methotrexate and cyclosporin to optimise effect. I think dermatologists have much to learn from rheumatologists who are increasingly combining medicines in their treatment of patients. Combining the new therapeutics with traditional systemic treatment for maximum effect has been a positive method in our practise. Some of our experiences are reported below.

Infliximab

Until now, we have most experience of infliximab. So far, we have treated 22 patients and we consider our long-time data to be relatively good. Fourteen of our patients have used infliximab for more than one year, of which 10 have used infliximab for 2 years. Four patients have used infliximab for more than 3 years, of which 2 patients have used infliximab constantly for more than 4 years. Only 5 patients have terminated treatment. One patient terminated treatment because she developed a lung embolism after 2 infusions. Tromboembolic illness may be associated with TNFα-blockade and this is something to look out for. Only 4 of 22 patients have terminated treatment because of loss of effect. All those patients initially experienced good effect, but the effect decreased gradually. In no patients have we experienced severe reactions to infusions or other serious side effects, such as severe infections. At the Department of Dermatology in Trondheim, we wish to combine infliximab with either methotrexate or imurel. Patients receive 3 mg/kg of infliximab combined with methotrexate in doses from 7.5 to 15 mg per week. This is the standard treatment of rheumatoid arthritis and we fail to see that it would be less effective for treatment of psoriasis. It has also proved effective, as all of the 4 patients treated with infliximab for more than 3 years are treated according to this regimen. If the patient cannot be treated using methotrexate, we combine infliximab 5 mg/kg with 50 mg imurel daily. The reason for this treatment method is that we want to avoid monotherapy. The significance of development of antibodies to infliximab is not yet known. Meanwhile, we have relatively good experience of this regimen as we have quite good long-time data, and have not experienced serious reactions to infusions. Giving 3 mg/kg also has not-insignificant financial consequences for long-time treatment compared to 5 mg/kg. When the patient has reached a treatment interval of 8 weeks and has a continued high effect, we try to prolong the treatment intervals. Patients then receive infusions every 10–12 weeks combined with either imurel or methotrexate. In addition to psoriasis, we have also treated 5 patients with pyoderma gangrenosum with very good results, as well as one patient with acrodermatitis continuae suppurativa. This patient has had very high effect. She is also being treated with 3 mg/kg combined with methotrexate, and has been receiving treatment for more than 4 years. On the other hand, we have also tried treatment with Remicade in a patient with generalised pustular psoriasis without any effect. We have also recently started treatment of a 9-year-old boy with widespread psoriasis. Here we have chosen 5 mg/kg infliximab combined with 12.5 mg methotrexate to avoid infusion reactions and development of antibodies.

Etanercept

The effect of etanercept is somewhat later than infliximab. Therefore, we always start with a double dose of etanercept, i.e. 50 mg subcutaneously twice a week when we use etanercept as monotherapy. Upon noticing a response to therapy, we reduce the dosage to 25 mg s.c. twice weekly. All studies of etanercept and psoriasis have been monotherapy with etanercept. We know that rheumatologists combine etanercept with methotrexate to a large extent. In patients who tolerate methotrexate, but do not experience full effect of the medicine, I advocate that it is better to add etanercept to methotrexate, rather than to give etanercept as monotherapy. If treatment with methotrexate is withdrawn just before starting treatment with etanercept, the patient may experience a rebound of psoriasis before getting effect of the etanercept. The same principle applies to beginning treatment with efalizumab. In some patients, we find that etanercept has a very good effect on their arthritic psoriasis, but a not-satisfactory effect on skin changes. We have therefore, in some patients, combined etanercept with synthetic retinoids (Neotigason®) with very

good results. In one patient, I have even combined etanercept with efalizumab. (See Case study below.)

In our patients we have not seen any serious infections or other serious side effects of use of etanercept and only one of our patients has stopped using etanercept due to side effects. This was a patient who experienced flu-like symptoms after each injection, even after long-time usage. One patient had a slightly elevated ALT level, for which we could not find any other explanation. We have also not seen any injection-related side effects. Roughly one-third of our patients have withdrawn from treatment due to little or no effect, or because of loss of effect despite treatment with 50 mg subcutaneously twice weekly.

Efalizumab

It is well-known that all medicines used to treat psoriasis have responders and non-responders. In Norway, we are performing a longitudinal, multi-centre study, designed to find out which patients respond to efalizumab and which do not (the ROCAC study). The goal is to characterise these patients by registering a number of factors before they start treatment, while keeping in mind end points such as PASI and DLQI. This is an investigator-initiated study, led by a control group of which the author of this article is the project leader. Until now, 29 patients have been included in the study, and 11 of these were referred by the Department of Dermatology in Trondheim. Even though it might be too soon to say anything about who is a responder or non-responder to this treatment method, our experience is that efalizumab has the best effect in patients with stable plaque psoriasis. If the patient has very active inflammatory unstable psoriasis, it is better to choose another therapeutic or combine efalizumab with methotrexate or cyclosporine during the start-up phase. When the disease is under control, the methotrexate/cyclosporine can be phased out. The patient can then continue treatment with efalizumab as maintenance treatment. It is too soon to say anything about the results of this study, but one-third have interrupted treatment due to no effect or because of side effects. One of our patients developed serum sickness syndrome after 3 months of treatment. After treatment withdrawal, he was completely restored after 10 days. Otherwise, we have had no serious side effects, especially no serious infections. Some of the patients have experienced flare-ups of psoriasis during the treatment, so-called transient localized papular eruption. This is a small-papule form of psoriasis which occurs in the neck, chest, shoulders and elbows. It is usually temporary, and not a reason to interrupt treatment. It can be treated with local steroid application. However, it is important to inform patients about the possibility of this side effect. In one of our patients, such a change developed into generalised psoriasis during treatment. This is occasionally seen in non-responders, and it is therefore important to monitor the patients. Patients who have not responded within 3 months should be withdrawn from treatment and be transferred to some other type of treatment.

Case study

A 23-year-old woman who has had psoriasis with arthritic psoriasis all her life. Her entire adolescence was characterised by psoriasis treatment. In her youth, she underwent light treatment continually over long periods of time. She had considerable gastrointestinal side effects of methotrexate and had to interrupt treatment. Cyclosporine induced hypertension. She tried infliximab, but experienced infusion-related side effects to such a degree that continued treatment was not possible. She has tried adalimumab without effect. When the patient moved to Trondheim early last year, she had been receiving double doses of etanercept for 18 months. This had a very good effect on her arthritis, but she still had relatively widespread psoriasis with PASI over 12. Treatment options were very few. We continued treatment with 50 mg etanercept once a week and, in addition, gave 1 mg/kg efalizumab once weekly. After 5 weeks, effect was very good and PASI went down to 3.4. She was very satisified. Not many doctors have combined biological therapeutics, but it has been described earlier (1). This requires frequent and careful follow-up. After 6 weeks of this combination treatment, she became acutely ill with high fever, lymph gland swelling in the neck, headache and bad general condition. CRP was 114. The patient was admitted to the De-

partment of Dermatology and cared for by infectious disease specialists. The diagnosis was mononucleosis. Monospot and Epstein Barr virus PCR were positive. No liver affection was present. All immunosuppressive treatment was withdrawn, and we concluded that this was a primary infection and not a reactivation of a virus due to immunosuppressive treatment. The patient recovered relatively quickly and after three weeks she had recovered completely.

After 6 weeks, her arthritis reappeared and we restarted treatment with etanercept: 50 mg per week + local application. After another 4 weeks, her psoriasis was back to original level with a PASI of 18. We then added 1 mg/kg of efalizumab to her treatment regime of 50 mg etanercept per week. Again, effect was prompt. She has now been receiving this treatment for six months. She is checked every month through blood samples and is in a good state of health. She has been receiving disability benefits since the age of 18, but is now in a rehabilitation programme and will begin studies at the University of Trondheim in the autumn.

Reference

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Biological Drugs for Psoriasis in Stavanger University Hospital

Thomas Ternowitz
Department of Dermatology, Stavanger University Hospital, NO-4068 Stavanger, Norway.
E-mail: teth@sir.no

Over the past 3 years our department has treated 75–80 patients with biological drugs for psoriasis. This number will increase considerably as biological drugs have become an accepted tool in the dermatological treatment arsenal. Currently three approved biological drugs are available in Norway for the treatment of psoriasis: Remicade® and Enbrel®, which are approved for both psoriasis and psoriatic arthritis, and Raptiva® for psoriasis. Humira® is approved for psoriasis arthritis, but at present not for psoriasis. In addition, we have used Amevive® for psoriasis.

In our experience biologicals are highly efficacious, more specific, safer, without the broad activity and risks found in traditional systemic treatment, but definitely not unproblematic. It is important to select the right patients for the right biopharmaceutical, because these drugs differ with regards to onset of action, control of inflammation, sustainability and safety profiles. In addition to potentially serious side-effects and association with important co-morbidities, not all psoriasis patients respond to biologicals.

Clinical studies have been performed on selected patients with stable moderate to severe disease, but we have only limited knowledge of biologicals in the treatment of unstable psoriasis, erythrodermic psoriasis or pustular forms of psoriasis. In other words, treatment of the most problematic group of patients with biologicals is based on clinical experience and reports from other medical centres, but not on controlled studies.

Psoriasis is now considered as a complex autoimmune disease, which shares common inflammatory pathogenesis with other immune-mediated inflammatory diseases. TNF-α antagonists: Remicade®, Enbrel® and Humira® are also used in inflammatory bowel disease, rheumatoid arthritis and spondyloarthropathies. Raptiva® and Amevive®, which inhibit activation of T-cells, have only psoriasis as indication. The mode of action of Raptiva® and Amevive® is at an earlier step in the psoriatic