Use of Biological Response Modifiers in Dermatology – Preliminary Recommendations for the Treatment of Psoriasis

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Biological response modifiers ("biologics") for psoriasis: from the bench to the clinic

Decades of intensive research in psoriasis changed our views on the pathogenesis of this common skin disease. What initially appeared to be a disorder of epidermal proliferation and differentiation is nowadays viewed as an autoimmune disease in which the major pathogenic role is ascribed to T- and NK lymphocytes attacking the yet unknown antigen in the skin. This paradigm shift has been one of the most consequential in dermatology. Powerful methods of modern molecular immunology have been applied to get further insight into the pathogenesis of psoriasis and pinpoint potential targets for therapy. The emerging picture points to the CD8+ and NK lymphocytes as the major effector cells in psoriasis. These cells mediate the so-called type I immune reaction in which the inflammatory process is promoted by the cytokines, including but not limited to interferon (IFN)-γ, and tumor necrosis factor (TNF)α, and by interleukins (IL) 12, 15 and 20. In contrast, IL-10 is described to inhibit type I immune reactions and thus inhibits the extensive inflammatory process seen in psoriasis.

Nowadays we have drugs that can target the above-mentioned cells and cytokines and change the natural history of psoriasis. Some of them have already proven their efficacy in large clinical trials and are available for clinical use. Others are still in phase II/III trials. In this review we will only deal with the drugs that have already been accepted or are likely to be registered in the very near future for use in treatment of dermatological disorders. For a more extensive description of available biologics a few recent key original papers and overview papers are listed at the end of this article.

Structure and nomenclature of biologic therapeutics

Biologics are modified proteins or recombinant cytokines produced artificially with the aid of genetic engineering technology. Special nomenclature has been introduced for the biological response modifiers (Table I). The final part of the name indicates whether the protein represents an antibody or fusion protein or whether the antibody is chimeric, humanized or fully human (Fig. 1).

How the biologics work?

Many strategies are available for biological response modifying therapy in psoriasis but two approaches have shown most promise (Fig. 2).

Table I: Nomenclature for biological therapeutics

Suffix	Description	Example
-ximab	chimeric antibody	Infli**ximab**
-zumab	humanized antibody	Efali**zumab**
-umab	fully human antibody	Adalim**umab**
-cept	receptor/fusion protein	Etaner**cept**

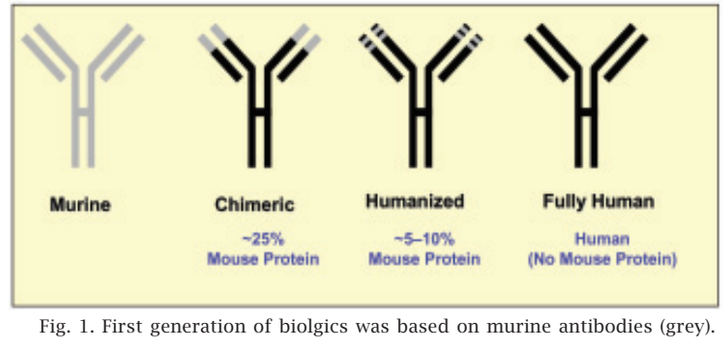

Fig. 1. First generation of biolgics was based on murine antibodies (grey). Later, new techniques made it possible to insert human sequences (black) leading the generation of chimeric (less than 25% mouse protein) and humanized (less than 5–10% mouse protein) molecules. Today, a technique exists to produce human molecules (antibodies or receptor/fusion proteins).

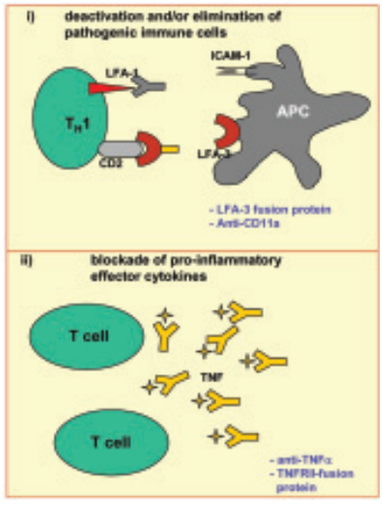

Fig. 2. Strategies for biological treatment. Alefacept (LFA-3 fusion protein) and efalizumab (anti CD11a) are examples on strategy i) involving immune deactivation/ elimination of immune cells. Inflimab (anti TNFα) and etanercept (TNF receptor II fusion protein) are exaples of straty ii), both molecules are blocking the pro-inflammatory cytokine TNFα.

These include:

i) deactivation and/or elimination of pathogenic immune cells
ii) blockade of pro-inflammatory effector cytokines

Amevive, (alefacept) and Raptiva, (efalizumab) are examples of the first approach (i) whereas Enbrel, (etanercept) and Remicade, (infliximab) inhibit the pro-inflammatory cytokine TNFa, and thus represent examples of the second approach (ii).

How effective are the biological response modifiers for use in psoriasis?

PASI (psoriasis activity and severity index) is a validated scoring system for the assessment of psoriasis activity and has been recommended by American (FDA) and European (EMEA) agencies as the endpoint measurement of the response to the drug. Earlier trials reported the mean change in PASI in the studied population. However, the recent trend is to show the so-called PASI 75 and PASI 50 values. This is a much more informative approach which tells how many percent of patients obtains a 75% or 50% reduction in PASI score during the treatment. The most efficacious systemic treatments in the pre-biologic era, cyclosporine and methotrexate (MTX), have the PASI 75 values of 71% and 60%, respectively.

Amevive® (alefacept)

The use of alefacept for psoriasis has been approved by FDA but the European application has been rejected by EMEA who required more clinical data comparing the efficacy of alefacept with other available therapies.

Structure and mechanism for action

Alefacept is a fully human fusion protein that contains the external domain of lymphocyte function antigen (LFA)-3 coupled to the Fc-domain of human IgG1 molecule. Alefacept specifically binds to CD2 on T- and NK cells and thus blocks their activation. Furthermore, some reports have suggested that alefacept causes selective elimination of autoimmune cells by apoptosis. Interestingly, the autoreactive lymphocytes in psoriasis have an increased expression of CD2 and thereby are probably more sensitive to alefacept than resting circulating lymphocytes.

Table II. Data from clinical trials – advantages and disadvantages of treatment regimens

Drug	PASI 75	Advantages	Disadvantages
Alefacept	~20% at wk 14	Safe. No rebound	Slow onset
	~40% at wk 24	Some patients have long-lasting remission	Low efficacy
Efalizumab	~30% at wk12	Safe	
		Quicker onset than alefacept.	Moderate efficacy
			Rebound after treatment
Infliximab	~90% at wk 10	Quick action (days, weeks)	Side-effects
		Very potent	Require i.v. infusions
		Possibly synergistic with MTX	Allergic reactions
		Efficient against arthritis	Autoantibodies
Etanercept	~35% at wk 12 up to	Can be used for children	Slow onset of action
	~50% at wk 24	Efficient against arthritis	Require injections
		Some patients have long-lasting remissions.	twice weekly
		Marginal increase in PASI 75, if treatment regimen, using double dose (50 mg twice weekly), is introduced	

Administration

Alefacept is administered either by intramuscular (i.m.) or by intravenous (i.v.) injection, once weekly.

Clinical findings

Data are accessible from clinical trials (phase II and III). No major difference in response to the drug has been observed, whether it is given by the i.m. or i.v. route. Data from i.m. application reveals a PASI 75 in 21% of treated patients (35/166) when the highest dosage was used (15 mg/week). In addition, if alefacept was given i.v., for a 12 week course, 14% (53/367) achieved a PASI 75, and this number increased to 40% (73/183) if a second course was introduced (i.e. a total of 24 week treatment regimen (Table II). Of particular interest, the treatment was generally well tolerated, and no serious adverse effects or infections were reported. Furthermore, no rebound was seen following termination of treatment. Finally, a recent follow-up study has shown that in patients that originally achieved response towards treatment ("clear or almost clear"), a sustained response was seen with a median value of 10 months.

Cost

Alefacept is given as a fixed dose regimen, once weekly. One treatment course, consisting of 12 treatments cost approximately 110,000 DKr (14,500 Euro). If two courses are applied, the total cost is 220,000 DKr (29,000 Euro).

Raptiva® (Efalizumab)

The registration status is the same as for Amevive.

Structure and mechanism for action

Efalizumab is a humanized monoclonal antibody against CD11a, a subunit of LFA-1. LFA-1 is a transmembrane molecule present on e.g. T cells, where it functions both as a cell adhesion molecule and a co-stimulatory molecule and as such is involved in T-cell activation and migration into inflamed tissue. Treatment with efalizumab interferes with T-cell activation. However, in contrast to alefacept, efalizumab does not deplete pathogenic T cells.

Administration

Efalizumab is administered subcutaneously (s.c.), once weekly.

Clinical findings

Data are accessible from clinical trials (phase II and III).

Initial trials revealed that a dose of >0.3 mg/kg resulted in clinical improvement, later a clinical phase III study demonstrated effect of 1 mg/kg with no further improvement if increasing dosage was used (Table II). In one study, in which an initial conditioning dose was applied followed by weekly injections, PASI 75% was achieved in 30% (117/394) of the treated patients. Furthermore, clinical improvement has been reported following only 2 to 4 injections. In general, the drug is well tolerated and no major side effects have been reported until now.

Cost

Unknown in Scandinavia.

Remicade® (Infliximab)

Infliximab has been registered for the therapy of Crohn's disease and rheumatoid arthritis. Data are available from clinical phase II studies in psoriasis.

Structure and mechanism for action

Infliximab is a chimeric monoclonal antibody against TNFα, probably the most important pro-inflammatory cytokine in psoriasis. Infliximab completely blocks the activity of TNFα.

Administration

Infliximab is administered by i.v. infusion. Most data is obtained from a regimen in which the drug is given at weeks 0, 2 and 6.

Clinical findings

Several open label studies have demonstrated significant results of infliximab for treatment of psoriasis. Furthermore, data from a clinical phase II study has shown that 88% (87/99) of patients receiving infliximab (5 mg/kg) at week 0, 2, and 6 had a 75% or greater PASI reduction when clinically scored at week 10

(Table II). Furthermore, effect on psoriasis arthritis has been reported. A limited number of responders have been followed-up to determine long-term efficacy of treatment. These limited data suggest a prolonged effect of treatment, showing that almost 50% of responders maintained a 75% or more reduction in PASI when clinically scored after 26 weeks with no further therapy. Data from open label studies have indicated a rapid (2–4 weeks) onset of clinical response.

Of concern, however, is the amount of adverse effects reported. Especially, neutralizing antibodies, infusion reactions, and cases of serum-sickness has been reported. Furthermore, reactivating of latent tuberculosis (even with fatal outcome) has been observed. Finally, an increased number of lymphomas have been reported in patients receiving anti-TNF treatment, when compared to the general population. These data, however, are primary generated in patients with Crohn's disease and rheumatoid arthritis, patient groups predisposed to develop lymphoma. Thus, it is imperative to stress that as of today no direct cause-relationship has been established, however further epidemiological studies are crucial to evaluate this observation.

Cost

The following estimation is based on a regimen using infliximab at 5 mg/kg and a body weight of 70 kg. One course, consisting of three infusions costs approximately 64,500 DKr. (8,500 Euro). If a sustained treatment regimen is implemented, consisting of 3 initial infusions, followed by intermittent treatments every 8th week, the yearly cost is approximately 172,500 DKr (22,800 Euro).

Enbrel® (etanercept)

Etanercept has been approved by FDA for psoriasis. In Europe it is approved for the treatment of Crohn's disease and rheumatoid arthritis, but not yet registered for psoriasis.

Structure and mechanism for action

Etanercept is a fusion-protein composed of the extracellular part of TNF receptor type II and the Fc region of human IgG1. Etanercept thus binds both TNFα and TNFβ and blocks their biological activities.

Administration

Etanercept is administered s.c., twice weekly.

Clinical findings

Data are available from phase II and III studies. In general, between 1/3 and 1/2 of patients receiving etanercept obtain a 75% reduction in PASI during treatment. Data from a clinical phase III study showed that 75% reduction in PASI was achieved in 34% (55/162) and 44% (71/162) of patients receiving etanercept (25 mg/twice wk) for 12 weeks and 24 weeks, respectively (Table II). In addition, etanercept is effective for treatment of psoriasis arthritis, and as such is a good treatment alternative in patients experiencing both skin and joints symptoms. Etanercept is generally well tolerated, with primary adverse effects reported as injection-site reactions and upper respiratory infections. However, as with infliximab, reactivation of latent tuberculosis has been reported as well as occurrence of lymphoma in patients receiving etanercept. The latter, however, to lesser extent than observed with infliximab, and again, no cause-relationship has been established.

Cost

Etanercept is given as a fixed-dose treatment, regardless the patient weight. If a 12-week regimen is implemented, the price is approximately 40.100 DKr. (5.300 Euro), increasing to 80.200 DKr. (10.600 Euro) if the treatment period is prolonged to 24 weeks. If a continuous treatment using etanercept is

Table III. Clinical use of biologics at Bispebjerg Hospital (May 2004)

Drug	No of patients	Diagnosis
Amevive	19	Psoriasis vulgaris
Enbrel	12	Psoriasis vulgaris, plaque type
		Pustular psoriasis
Remicade	21	Psoriasis vulgaris, plaque type
		Erythrodermic psoriasis
		Pustular psoriasis

initiated, the yearly cost runs up to approximately 175.000 DKr (23.000 Euro). Some reports have emerged, in which double doses of etanercept (50 mg twice weekly) has been used. This will of course double the price of the treatment.

Biologics – suggestions for use in treatment for psoriasis

At Bispebjerg Hospital, we request that the candidate patients have failed at least two other systemic treatments, including but not limited to MTX, cyclosporine, acitretin, or PUVA. At present (May 2004) we have used biologics for treatment of 52 patients (Table III).

Infliximab is used at 5 mg/kg, administered as i.v. infusions, given at weeks 0, 2, and 6. All patients receive MTX in combination with infliximab to prevent the occurrence of neutralizing antibodies. Mantoux test and chest X-ray is used on routine basis to exclude patients with latent or active tuberculosis before the treatment is initiated. Infusions are given in our inpatient clinic throughout the treatment period, followed by controls on an outpatient basis. Lab tests are run before each treatment administration (haemoglobin, leukocytes, differential counts, ASAT, basic phosphatase, and creatinine). Finally, at initiation and end of the treatment regimen, anti-nuclear antibodies are measured.

Today, no final long-term treatment regimen has been implemented, but data from several groups use an initiation infusion with re-administration following 2 weeks and subsequently 4 weeks. For long-time regimen, several possibilities exist and in the following some examples are given.

i) Infliximab is given at weeks 0, 2, and 6 together with low dose MTX (level 5 to 7.5 mg/week). Following this, further administration is given "on demand" when clinical relapse is evident.
ii) Infliximab is given at weeks 0, 2, and 6 together with low dose MTX, followed by continuous administration of infliximab every 8th week
iii) Infliximab is given as a "pulse" – therapy at weeks 0, 2, and 6 together with moderate doses of MTX (15 to 20 mg weekly). Following this pulse-treatment, the patient continues with moderate doses of MTX.

Our experience with the use of infliximab confirms a very rapid onset of action with clinical beneficial effect occurring during the first weeks of treatment. Especially cases of erythrodermic and pustular psoriasis have revealed astonishing results with almost clearing following the first treatment. If no convincing clinical effect is evident following 6 weeks, the treatment should be stopped. Some reports, however, have indicated that treatment failure with one biologic, does not prevent beneficial effect when using an alternative drug, thus in therapy resistant psoriasis, the use of more than one biological response modifier can be introduced.

Long-term data are not yet available for psoriasis, but our experience is, that during elongated treatment regimens (e.g. i) or ii)), gradual decrease in the effect of the drug occurs, and some patients even experience clinical relapses during the treatment course. Thus, some concern is present, that prolonged treatment regimens may not yield the expected clinical results. Furthermore, data from Crohn's disease have indicated that regimen described in (i) results in decreased length of symptom-free periods and in an increased induction of anti-infliximab antibodies. Thus, taken in account the above-mentioned observations and the current very high price of the drug, we tend to favour the introduction of regimen iii). We strongly suggest that both clinical (PASI score) and para-clinical (blood-test) controls are effectuated before and during treatment regimen to control treatment tolerability and to gather data for long-term effect of infliximab in humans.

Our experience with etanercept is an often delayed onset of action, with clinical effect occurring following several weeks of treatment. For classical psoriasis, plaque type, we administer 25 mg twice weekly. We normally plan a 12-week treatment regimen, but if a partial result is achieved, some patients have received an extended treatment period of up to 24 weeks. We do not require

that supplemental treatment be administered together with etanercept, however, e.g. MTX can easily be given simultaneously. On a routine base, we perform both clinical examination and laboratory workup as for Remicade. In our hands, the treatment is well tolerated, and the patients that respond to treatment are very satisfied. However, if no significant clinical response is observed following 6 weeks of treatment, we tend to discontinue the drug.

At present, Amevive and Raptiva, are used only in the setting of clinical trials in our institution.

The future

The biologics have been introduced as treatment regimens in dermatology and will without doubt be an important part of the future therapeutic armamentarium. They are already today a vital supplement for traditionally treatment regimens. The important questions that cannot be resolved presently are the cost-benefit ratio and the risk of long-term side effects. Undoubtedly, the cost issues precluded a wider use of biologics and raised concerns in the approving agencies, especially in Europe where the treatment cost is defrayed by the taxpayers. Solid, post-marketing data are needed to justify the therapeutic cost. In this regard, national or Nordic database is virtually a must, if dermatologists should have a chance to implement novel treatments.

The companies seem to be unwilling to reduce the prices due to the allegedly very high developmental costs, high production cost and the need to conduct expensive clinical trials. Price reduction will undoubtedly move the biologics from the last to the first therapeutic line in psoriasis. Another interesting aspect is the market lifetime of the current products. Biotechnology evolves rapidly and it is now possible to produce fully human, high affinity antibodies without the risk of allergic reactions encountered sometimes with the chimeric or humanized antibodies. Moreover, new therapeutic targets will undoubtedly be identified. It is likely, that competitive, newer products will push the older biologics off the market and create an unprecedented, rapid flow of biologic drugs.

Selected key original papers:

1. Lebwohl M, Tyring SK, Hamilton TK et al. A novel targeted T-cell modulator, Efalizumab, for plaque psoriasis. N Engl J Med 2003: 349: 2004–2013.
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3. Krueger GG, Papp KA, Stough DB, et al. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. J Am Acad Dermatol 2002: 47: 821–833.

Selected reviews:

1. Weinberg JM. An overview of Infliximab, Etanercept, Efalizumab, and Alefacept as biological therapy for psoriasis. Clin Ther 2003: 25: 2487–2505.
2. Gottlieb AB, Bos JD. Recombinant engineered human proteins: Transforming the treatment of psoriasis. Clin Immunol 2002: 105: 105–116.
3. Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. J Am Acad Dermatol 2002: 46: 1–23.
4. Gniadecki R, Zachariae C, Calverley MJ. Trends and developments in the pharmacological treatment of psoriasis. Acta Derm Venereol 2002: 82: 401–410.