How to Judge the Clinical Utility of New Biologic Treatments for Psoriasis?

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The last several years have been an extremely exciting period for all of us involved in the treatment of patients with psoriasis. New treatments comprising the biological response modifiers ("biologics") emerged as a useful supplement to the existing therapies. Several drugs of this type, including etanercept (Enbrel®), alefacept (Amevive®) and efalizumab (Raptiva®) have been approved by the FDA (Food and Drug Administration) for the treatment of moderate to severe psoriasis in the United States. These drugs are not yet approved in Europe by the EMEA (European Agency for Evaluation of Medicinal Products). This agency raised some concerns as to efficacy and utility of these products in the clinical practice. Accompanying article in this issue of Forum by Dr Lisby briefly describes the available drugs and current experience of biologics in the hospital setting.

Taking the high price tag and unknown safety profile of the new biologics into consideration, the treatment will be offered primarily to patients who for some reason cannot be controlled by the currently existing therapies. This raises the following questions:

- How can we identify and define this group of patients (also called the "high need" population)?
- Can data from existing clinical studies predict outcome in the "high need" population?
- How to interpret the clinical efficacy from clinical trials?
- Do we need new drugs that demonstrate inferior efficacy comparing to existing therapies?

What constitutes the "high need" population?

Generally, the "high need" patients have insufficient response to therapy. The pre-requisite for being included in this group is the patient's desire to be treated, in other words a certain degree of psychological discomfort due to the disease. Closer analysis reveals at least two major categories of such patients:

- "Objective high need patients": Those who have psoriasis that objectively meets pre-defined severity criteria, such as certain cut-off of PASI (psoriasis activity and severity index) score or body surface area (BSA) involvement.
- "Subjective high-need patients": Those who despite low psoriasis activity feel unhappy and need more efficacious therapy.

Recent quantitative studies employing various parameters of psychological well-being (such as quality of life, psychological impairment, etc) have documented the existence of the latter group of patients. Objective activity of psoriasis is not always correlated with the patient's subjective perception of the disease (for further discussion see Ref. 1). For that reason some researchers feel that it is necessary to employ quality of life as a variable defining the "high need" population (discussed in Ref. 2). This approach, however, is not without problems. First, the patients may be unhappy for a variety of reasons, and blame psoriasis for low life quality. Some may feel depressed simply due to having a chronic, incurable disease or necessity for long-term, cumbersome treatment. Also, even minimal psoriasis affecting cosmetically important areas such as hands, nails or the face is likely to give a lot of distress. Secondly, new therapies are primarily designed to interfere with the pathogenic process of psoriasis, not to improve life quality. There is a risk

that even potent, expensive therapies would have minor influence on life quality in the patients in question. For these reasons, the objective assessment of psoriasis activity should remain the cornerstone in the definition of "high need" patients. The candidates for new therapies should thus be narrowed to the "objective high need" patients.

Is the "objective high need" population homogenous?

Even when defined as patients with moderate-to-severe psoriasis with insufficient response to existing treatments, the "high need" population remains a heterogenous group. It comprises at least 4 major categories of patients:

- true non-responders to available therapies
- patients in whom the treatment cannot be continued due to side effects or risks of side effects (e.g. skin cancer in PUVA patients or nephrotoxicity associated with cyclosporin A)
- patients not eligible for potent systemic therapies (children, pregnant women, interfering systemic diseases, patients who refuse therapy due to safety concerns, etc)
- low compliance

The proportion of the "high need" patients is unknown but has been estimated at the level of 5–20% of all psoriasis patients treated by dermatologists.

Can data from existing clinical studies predict outcome in the "high need" population?

Clinical studies on the efficacy of new therapies are usually made on a broad population of patients with moderate to severe plaque psoriasis who do not receive any other concomitant therapy. This is quite different from the everyday practice where the biologics are likely to be combined with other modalities (like topical steroids or methotrexate) and used selectively in the "high need" population. It is assumed, but by no means proven, that efficacy of new drugs in the "high need" population is similar to that reported in clinical studies. The reassuring finding is that some drugs (e.g. Raptiva® and Amevive®) seem to have similar efficacy in treatment-resistant patients and in those who did not receive systemic therapies earlier. The necessity for clinical trials on the prospectively defined group of "high-need" patients has been endorsed by EMEA and judged important in the registration process of the new drugs.

How to interpret the clinical efficacy data from clinical trials?

The PASI score remains the most widely used hard endpoint in clinical trials. In earlier trials the mean PASI score decrease was reported. However, recent trials adopted a much more informative approach of reporting the proportion of patients reaching a pre-determined PASI value during a given period. For example, PASI-75 of 45% means that the drug caused a 75% PASI score reduction in 45% of patients. The most widely used PASI cut-offs are PASI-50, PASI-75 and PASI-90, referred to as, "moderate improvement", "significant improvement" and "clearance or almost clearance", respectively. It is important to remember, that the PASI score system demonstrates some irregularities. For instance, a 95% reduction in psoriasis area without any change in redness, scaliness or thickness translates to only a 66% PASI score drop. The PASI score is designed to measure the biological activity of psoriasis and correlates poorly with the patient's perception of treatment effect. It is therefore important to use objective secondary efficacy parameters for the global assessment of the utility of new drugs. Some useful parameters are:

- Mean PASI score reduction and individual PASI components (area, redness, scaliness, plaque thickness) in responders and non-responders. (Gives information on the expected degree of clinical response).
- Time to PASI-50 and PASI-75 in responders. (How long the treatment should be tried before deemed ineffective?)
- Relapse rate for responders and non-responders. (When to repeat the therapy? Is there a rebound phenomenon?)
- Efficacy data for repeated treatment cycles. (Is the repeated treatment as efficacious as the first one?)

- If the drug is planned for continuous use. (Efficacy of prolonged (>1 year) treatment.)

Do we need new drugs that demonstrate inferior efficacy comparing to existing therapies?

New biologics vary tremendously with respect to clinical efficacy. The least potent Amevive® and Raptiva® have PASI-75 values of ³30% followed by Enbrel® with ³50% and Remicade® ³90%. PASI-75 for existing therapies is in the range of 30% (acitretin) to 70–90% (cyclosporin A, RePUVA). This further emphasises the notion that biologics should primarily be used in the preselected "high need" patient population. On the other hand, comparative studies with the active treated area rather than placebo, are probably superfluous. Highly efficacious drugs are certainly wanted, but therapies of lower efficacy may provide a very useful addition to the available battery of treatment. As expressed by Krueger et al. (2): "Psoriasis is a multigenic disease. Thus it is likely that responses to agents will be selective, that is, some patients will have a constant response and others will not. Any treatment that consistently leads to clearing provides a CSI [clinically significant improvement], even if it occurs in fewer than 5% of subjects, and would be a valuable clinical tool. […] Such treatments should be made available to the patients who would benefit from them. […] Approving treatments with limited but proven efficacy will permit clinicians the latitude to determine what is most effective for their patients."

Further reading

1. The burden of skin disease. J Invest Dermatol Symp Proc, 2004;9 (2).
2. Krueger GG, Feldman SR, Camisa C, Duvic M, Elder JT, Gottlieb AB, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? J Am Acad Dermatol 2000; 43: 281–285.