18 Evidence Based Medicine’s Perspective on Biologics

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18.1 What is EBM?

Since the first articles by Sackett in the 1990s (Sackett and Rosenberg 1995), evidence based medicine (EBM) has developed considerably. Defined as “the integration of the best research evidence with clinical expertise and patients’ values”, EBM is an attempt to improve the care of our patients.

There are certain misconceptions about EBM. It is not a standard recipe and there are no standard patient and individual factors that have to be taken into account for definite decisions to be made. EBM is also not an exclusive concept, neither is it a sophisticated “l’art pour l’art” for specialists. If EBM were only practiced by specialists, it would be dead – EBM should thrive in daily practice. Last but not least, EBM is not a cost regulating instrument. Often, the best documented therapies – like biologics – are the most expensive ones.

18.2 EBM Steps to Treating an Individual Patient

In order to clarify what EBM means in daily practice, it is important to bear in mind the steps of EBM in the treatment of an individual patient. First a structured and answerable set of questions based on the patient encounter needs to be generated. Next is the search for valid external evidence and then the critical appraisal of that evidence for its relevance and validity. At the end of this process the results of the appraisal of evidence should be applied to the patient, and last but not least one’s own performance should always be recorded and evaluated.

Imagine therefore a 50-year-old patient with severe plaque psoriasis in your private practice. The past history reveals recurrent hospitalisation in the previous couple of years, intolerance of fumaric acid, unsatisfactory results with oral cyclosporin and an increase in liver enzymes while under treatment with methotrexate. Based on this case history, one question would be “What is the best and safest therapy for this patient?” As this question is quite broad, it is recommended to focus the question a bit more. Therefore if biologics are being considered as a treatment choice the question could be: “What is the best and safest biologic for this patient?” Based on either question the next step will be the search for evidence. Here there are several possibilities. One step is to search the primary literature, which means going to Pubmed or Medline and making the necessary searches to retrieve the relevant literature. As this is quite an exhausting way of finding the evidence, other possibilities, such as searching the secondary literature, should be considered. Depending on the question, systematic reviews from the Cochrane library, evidence based books such as Clinical Evidence (Naldi and Rzany 2005) or Evidence-Based Dermatology (Williams et al. 2003) as well as the evidence-based guidelines (Nast et al. 2006) might be helpful in gathering the relevant evidence.

During searches of the evidence based literature for biologics, it has been quite clear that there are no systematic reviews for this group of new drugs in the Cochrane library. The Evidence-Based Dermatology book from BMJ/Blackwell does not discuss biologics either. There is a chapter in the most recent Clinical Evidence book from the BMJ group which discusses two of the four biologics used in the treatment of psoriasis.

The EBM-based secondary literature might give recommendations for the use of biologics based on the evidence for efficacy and safety but it does not usually consider other aspects such as practicability and cost. These aspects might be covered by a set of guidelines.
At the moment, two evidence based sets of guidelines for the treatment of psoriasis exist: a set of British guidelines (Smith et al. 2005), which consider only the use of the presently available biologics, and the German S3 guidelines (Nast et al. 2006), which focus on all the systemic and topical treatments of psoriasis including biologics.

### 18.3 German S3 Guidelines for the Treatment of Plaque Psoriasis

As evidence-based guidelines, the German S3 guidelines follow a structured approach. The first step in the guideline process is to nominate the people who will contribute to the guidelines. This includes the guideline project team who coordinate the guidelines, the team of experts who review the literature and last but not least the extended committee who formulate and pass the proposed recommendations. The next step is to review the literature. As the hits based on the different literature databases are not very sensitive and specific, the relevant articles need to be pre-screened and selected for the review process. In the review process itself the papers are evaluated for inclusion/exclusion criteria, quality of the methods and presentation of the results. Finally, a grade of evidence is given to each paper. As several definitions for the “grade of evidence” exist, the grade of evidence itself needs to be defined. Usually, it is based on the recommendations from the Oxford Centre of Evidence Based Medicine.

Using the Oxford classification as a basis, the German Guidelines Team developed an adapted version, ranging from systematic reviews with meta-analyses (the highest level) to expert opinions (the lowest level). As the grade of evidence is based on a single paper, a “level of evidence” was assigned to sum up the evidence of all reviewed papers for one intervention. Here again, the highest grade would be for an intervention that is based on systematic reviews or the consistent results of good clinical trials.

The final “therapeutic recommendations” are formulated considering the evaluated evidence-based literature on efficacy, as well as other aspects such as safety, practicability and costs. These therapeutic recommendations should be real consensus statements and great efforts have to be taken to make sure that the majority of the guideline group agrees on the formulation.

### 18.4 EBM and Biologics

Biologics are quite new drugs. The pre-marketing studies follow the high present standards of good clinical practice. Therefore, it is not surprising that the level of evidence is better for biologics than for many of the other older treatments of psoriasis, e.g. methotrexate. On the other hand, for most available biologics the clinical experience is limited and issues such as rare side effects and the results of long term treatment cannot be discussed conclusively.

Comparison of the published trials on the efficacy of biologics will lead to the assumption that there is nothing like “THE” biologic. The biologics differ in efficacy and safety. Based on the recommended dosages, the highest efficacy can be found for infliximab, followed by etanercept and efalizumab. The Number Needed to Treat (NNT), an established EBM tool to clarify efficacy, gives numbers from 1.22 (1.10 – 1.37) for infliximab, 3.30 (2.62 – 4.44) for etanercept at the low dose and 2.18 (1.65 – 2.66) at the higher dose, to 4.49 (3.62 – 5.91) for efalizumab (Table 18.1).

So what does it mean? For infliximab it means that if you treat approximately four patients with infliximab

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Time of evaluation/dosing</th>
<th>Number of patients needed to treat to reach a 75% PASI reduction</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>10 weeks; 5 mg/kg in weeks 0, 2, 6</td>
<td>1.22 (1.1 – 1.37)</td>
<td>Gottlieb et al. 2004</td>
</tr>
<tr>
<td>Etanercept</td>
<td>12 weeks a) 2 × 25 mg/week; b) 2 × 50 mg/week</td>
<td>a) 3.3 (2.62 – 4.44) b) 2.18 (1.65 – 2.66)</td>
<td>Leonardi et al. 2003</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>12 weeks; 1 mg/kg; 1/week</td>
<td>4.49 (3.62 – 5.91)</td>
<td>Menter et al. 2005</td>
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