Management of pemphigus
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Chapter V

Robust staging of disease activity for pemphigus vulgaris

Abstract

In this study a robust and simple classification into different stages of pemphigus, based on a set of therapeutic benchmarks including a definition of disease activity, is proposed. This staging method was validated against ELISA titres for autoantibodies against desmoglein-1 and -3.

The proposed staging method was applied a priori to five newly diagnosed pemphigus patients in the course of their disease. The ELISA titres for desmoglein-1 and -3, as well as the indirect immunofluorescence titres were cross tabulated against the a priori defined disease stages. ELISA titres of desmogleins seemed to show a good correlation with our proposed staging system, better than the indirect immunofluorescence titres. However, due to the small sample size, we could not perform a statistical test. We conclude that the proposed staging system for disease activity in pemphigus vulgaris is useful for international uniform monitoring pemphigus vulgaris.
Introduction

Pemphigus is a rare intraepidermal autoimmune bullous disease affecting skin and mucous membranes. Several studies propose definitions for treatment outcome such as initial control, remission, and complete remission (1-6). However, some definitions are complicated to perform, some are even conflicting with each other. A consensus for staging of disease activity in pemphigus never has been reached. Proposals for monitoring pemphigus are based on clinical parameters, such as a time-consuming counting of all blisters (1), which may be redundant for a therapeutical strategy or a scientific study. There is a need for an unambiguous easy-to-use scoring system with a small interobserver bias. Such a scoring system could be used in pemphigus trials, which often require a multicentered approach due to the low incidence of approximately 0.1-0.42 per 100,000 (7-9).

In this study such a classification into different stages of the disease, based on a set of therapeutic benchmarks including a definition of disease activity, is proposed. IgG autoantibodies to desmoglein 1 (dsg 1) and desmoglein 3 (dsg 3) were determined retrospectively by ELISA at four specific clinical therapeutic benchmarks, and compared to the indirect immunofluorescence (IF) serum titres.

Patients and methods

The medical records of 5 newly diagnosed pemphigus vulgaris patients in the Groningen University Hospital were reviewed. Diagnosis was based on clinical presentation, histological, and immunofluorescense characteristics. Patients were all on the same treatment schedule: monthly 3-days courses of 300 mg dexamethasone per os (dexamethasone-pulse = DP-therapy), or intravenous equivalent, in combination with maintenance schedule oral prednisolone, and adjuvant azathioprine 3 mg/kg/day. During the first week 80 mg prednisolone was given daily and adjuvant DP-therapy on three consecutive days. If no initial control (defined in table I) was reached after one week, daily dosage of prednisolone was increased to 120 mg during the second week, and if necessary increased to 240 mg during the third week according to Lever (10). After initial control prednisolone was tapered to 30 mg/day within 3 weeks and subsequently in 13 weeks further tapered to zero (11).
For staging pemphigus vulgaris we scored disease activity by the clinical definitions explained in table I.

**Table I: Definitions for clinical staging disease activity in pemphigus vulgaris**

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (exacerbation)</td>
<td>• &gt;1 new skin lesion per week or oral lesions &gt; 5 mm</td>
</tr>
<tr>
<td></td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>• positive Nikolsky sign type I</td>
</tr>
<tr>
<td>Negative (remission)</td>
<td>• ≤1 new skin lesion per week or presence of oral lesions ≤ 5 mm</td>
</tr>
<tr>
<td></td>
<td>and</td>
</tr>
<tr>
<td></td>
<td>• negative Nikolsky sign type I</td>
</tr>
</tbody>
</table>

**Therapeutic Benchmarks**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>Start of DP-therapy</td>
</tr>
<tr>
<td>Initial Control (IC)</td>
<td>First remission after diagnosis and (subsequent) therapy</td>
</tr>
<tr>
<td>Complete Remission (CR)</td>
<td>Remission without prednisolone treatment</td>
</tr>
<tr>
<td>Relapse</td>
<td>Re-occurrence of positive disease activity after CR</td>
</tr>
</tbody>
</table>

The Nikolsky sign plays a key-role in scoring disease activity (12,13). Only Nikolsky sign type I is used: rubbing non-affected skin, at least 2 cm outside an area of a pemphigus lesion. Nikolsky sign type II, e.g. on erythematous skin, is important for making the diagnosis pemphigus, but not considered relevant for monitoring disease activity. In the definition of disease activity the development of new skin lesions and oral involvement were also included. Positive disease activity means *exacerbation*, whereas no disease activity means *remission*.

Based on the combination of disease activity and subsequent therapy, we defined four therapeutic benchmarks: start therapy, initial control, complete remission and
relapse. At these specific therapeutic benchmarks, for each patient matching sera were retrieved from our serum bank, where sera are stored at -80°C until analysis. For these sera both indirect IF serum titres (IIF) on monkey esophagus, and anti-dsg ELISA index values (MBL, Nagoya, Japan) were determined.

Results

Patient demographics and therapy in the last months prior to admission are illustrated in table II. All patients showed erosions on both skin and oral mucosa at time of admission.

Follow-up varied from 9 to 14 months. Time to initial control varied from 1 to 4 months (median 2.6 months). Median duration of remission was 5.2 months (varying from 2 to 8 months). All patients reached complete remission. Relapse occurred in three patients respectively 2, 5, and 8 months after complete remission.

### Table II: Patient demographics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at onset</th>
<th>Mucosa / Skin Involvement</th>
<th>Previous treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>32</td>
<td>+/-</td>
<td>pred 4 days 120 mg/day</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>46</td>
<td>+/-</td>
<td>doxycycline 200 mg/day</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>28</td>
<td>+/-</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>44</td>
<td>+/-</td>
<td>pred</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>55</td>
<td>+/-</td>
<td>pred, aza 1.5mg/kg/day</td>
</tr>
</tbody>
</table>

Legend: pred = prednisolone, aza = azathioprine

A total of 20 serum samples were reviewed. Table III illustrates the relationship between the clinical benchmarks, IIF, and anti-dsg 1 & 3 ELISA values. Although wide ranges, an objective trend in titre change for each parameter is observed between consecutive benchmarks. However, there were some remarkable findings. Skin involvement in patient 4 at admission was not be accompanied by anti-dsg 1 antibodies. Initial control in patient 2 was not accompanied by decrease in indirect IF titre, however ELISA values showed a marked decrease in anti dsg 3 autoantibodies. The relapse in patient 3 was not followed by a raise of the indirect IF titre, however ELISA values showed increase for anti dsg 3 antibodies. The difference between initial control and complete remission could not be confirmed by indirect IF, nor by ELISA values in patient...
5. Due to the small sample size, however, we could not perform a statistical test and thus the data are viewed only in a descriptive way.

Table III: Indirect IF (IIF) and ELISA-values (anti-dsg1 and anti-dsg3)

<table>
<thead>
<tr>
<th>Patient</th>
<th>IIF</th>
<th>dsg1 index value</th>
<th>dsg3 index value</th>
<th>IIF</th>
<th>dsg1 index value</th>
<th>dsg3 index value</th>
<th>IIF</th>
<th>dsg1 index value</th>
<th>dsg3 index value</th>
<th>IIF</th>
<th>dsg1 index value</th>
<th>dsg3 index value</th>
<th>IIF</th>
<th>dsg1 index value</th>
<th>dsg3 index value</th>
</tr>
</thead>
<tbody>
<tr>
<td>start</td>
<td>640</td>
<td>179</td>
<td>194</td>
<td>160</td>
<td>82</td>
<td>124</td>
<td>320</td>
<td>129</td>
<td>171</td>
<td>640</td>
<td>2</td>
<td>161</td>
<td>640</td>
<td>106</td>
<td>150</td>
</tr>
<tr>
<td>IC</td>
<td>320</td>
<td>95</td>
<td>148</td>
<td>160</td>
<td>116</td>
<td>15</td>
<td>160</td>
<td>110</td>
<td>158</td>
<td>160</td>
<td>0</td>
<td>7</td>
<td>80</td>
<td>47</td>
<td>84</td>
</tr>
<tr>
<td>CR</td>
<td>40</td>
<td>18</td>
<td>29</td>
<td>40</td>
<td>0</td>
<td>1</td>
<td>80</td>
<td>0</td>
<td>86</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>8</td>
<td>96</td>
</tr>
<tr>
<td>relapse</td>
<td>320</td>
<td>117</td>
<td>134</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>80</td>
<td>1</td>
<td>101</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>160</td>
<td>44</td>
<td>186</td>
</tr>
</tbody>
</table>

Legend: IIF=indirect immunofluorescence titres, IC=initial control, CR=complete remission, -= no relapse occurred, dsg = desmoglein

Index values were calculated as indicated by the manufacturer of ELISA-essay kit (MBL, Nagoya, Japan). Sera are considered positive if the index-value is above 7 (dsg 3 ELISA-kit) or 14 (dsg 1 ELISA-kit).

Discussion

This study, in spite of the limited number of patients, underscores the usefulness of a simple scoring method for staging the course of the disease: ask for new lesions, look in the mouth and perform the Nikolsky sign type I. At four consecutive therapeutic benchmarks the changes in indirect IF-, and ELISA values for anti-dsg 1 & 3 were monitored. IIF did not detect a titre-change between consecutive benchmarks in some patients, whereas a change in anti-dsg (by ELISA) was obvious (table III). This confirms the higher accuracy of the ELISA technique above indirect IF in measuring the pemphigus antibody titres (14-16).

Indirect IF is used widely since the 1960s for monitoring disease activity, but IIF pemphigus antibody titres do not always correlate well with actual disease activity (17). Indirect IF is a semi quantitative technique which is time-consuming, and these pemphigus
titres may not be available when therapeutic intervention is required. Therefore the value of indirect IF is limited for monitoring pemphigus.

Since 1997 specific autoantibodies against the ectodomains of desmoglein 1 and 3 transmembrane desmosomal adhesion proteins, can be detected by ELISA (14). Blister formation in mucous membranes involves autoantibodies against desmoglein 3 in PV, whereas blister formation in skin is currently attributed to the concomitant presence of autoantibodies against dsg 1 (18). ELISA can differentiate between these subtypes and is more time-efficient than IIF. It was demonstrated that ELISA values parallel disease activity in pemphigus (14;15). However, there are examples of a positive ELISA result, but inactive disease. Therefore therapeutic intervention based on shifts of this immunochemical assay seems to be an attractive possibility.

A positive correlation between indirect IF titres and ELISA titers was shown in 11 PV patients by Lenz et al (16). Aoyama et al. suggested using the ELISA titre of anti-dsg 1 IgG for determining the initial therapy for pemphigus foliaceus (PF) (19). PF patients with low ELISA titre may be treated with topical steroids, whereas those with high titres with glucocorticoid pulse therapy.

In this study, we demonstrate the value of a simple scoring method for staging the course of pemphigus vulgaris supported by pemphigus antibody titres as demonstrated by IIF and ELISA. The ELISA appeared to be more exact. Our simple and robust staging system may be less prone to interobserver bias, although further validation studies are needed. The staging system is easy to use and does not require time-consuming counting of the number of blisters. This staging system is currently used in a European multicenter placebo controlled trial in which the efficacy of oral high-dose dexamethasone pulse therapy is studied.
Robust staging of disease activity for pemphigus vulgaris

References