A Retrospective Analysis of Patients With Bullous Pemphigoid Treated With Methotrexate

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Objectives: To evaluate treatment with methotrexate in patients with bullous pemphigoid and to elucidate the reduced adverse effects compared with standard treatment with prednisone.

Design: Retrospective study (January 1, 1999-December 31, 2003).

Setting: The Department of Dermatology and Venerology, Karolinska University Hospital.

Patients: A total of 138 consecutive patients with bullous pemphigoid were included and were grouped according to the treatment they received: methotrexate, prednisone, a combination of both, or topical glucocorticoids (for mild disease).

Result: Methotrexate was the most effective treatment, with only a few adverse effects and a tendency toward better survival rates in patients with moderate to severe disease.

Conclusion: Methotrexate is an effective and safe drug and provides an excellent treatment option in patients with bullous pemphigoid.

Bullous pemphigoid (BP) is the most common acquired autoimmune blistering disease. It usually occurs in elderly individuals, with onset after 60 years of age, and it seems to predominate in men. Although several clinical variants have been recognized, BP usually presents with tense blisters arising on healthy or erythematous skin, typically involving the flexor surfaces. Autoantibodies against 2 well-characterized autoantigens, BP180 and BP230, are believed to play a crucial role in the pathogenesis of BP. These autoantigens are components of the hemidesmosomes, which promote epithelial-stromal adhesion in various tissues, such as the skin. The binding of autoantibodies to the antigens results in a cascade of events, including the recruitment of inflammatory cells (neutrophils and eosinophils) and the liberation of proteases. The ensuing proteolytic degradation of extracellular matrix proteins and the destruction of the anchoring hemidesmosomes lead to the formation of subepidermal blisters.

Left untreated, the disease lasts a few months to several years. However, patients with BP have significant morbidity owing to an often intractable pruritus and the presence of bullous eroded skin. In addition, the mortality is considerable, with reported 1-year mortality varying from 10% to 41%. The prognosis of BP has been studied by several research groups, but the results of the studies have been inconsistent. Some researchers suggest that old age and the poor general condition of the patient are risk factors for a poorer prognosis, whereas others report low serum albumin levels and the requirement for a higher dosage of oral glucocorticoids as independent risk factors for death in the first year after diagnosis.

With the intention of inhibiting the inflammatory response, glucocorticoids have been the mainstay of treatment for BP. To minimize the adverse effects of systemic glucocorticoids, other immunosuppressants, such as methotrexate, azathioprine, cyclophosphamide, and cyclosporine, are sometimes used as corticosteroid-sparing agents. However, the only controlled study published to date, to our knowledge, did not demonstrate a benefit from the addition of azathioprine to glucocorticoid therapy. In another controlled study, patients with extensive BP treated with a potent topical glucocorticoid showed sig-
methionine. Furthermore, methotrexate inhibits dihydrofolate reductase, an enzyme that catalyzes reactions that produce cofactors necessary for the DNA synthesis machinery. Without dihydrofolate reductase, DNA synthesis ceases. Methotrexate was first used in the treatment of BP 4 decades ago. Further studies suggest that treatment with low-dose oral methotrexate alone or combined with systemic glucocorticoids is a well-tolerated and effective therapeutic alternative in patients with BP. At the Department of Dermatology and Venerology, Karolinska University Hospital, during the past decade we have preferentially treated patients with BP with low doses of methotrexate administered once weekly. In the present retrospective study, we investigate the medical records of all patients diagnosed as having BP at the Department of Dermatology and Venerology, Karolinska University Hospital, during a 5-year period to evaluate the efficacy and safety of this treatment regimen.

METHODS

All patients diagnosed as having BP for the first time between January 1, 1999, and December 31, 2003, were included in this study. The diagnosis of BP was based on a characteristic clinical picture suggestive of BP, which was confirmed in all cases by the finding of subepidermal blisters on routine histopathologic analysis together with direct immunofluorescence (linear deposits of IgG or complement 3 along the basement membrane zone) or indirect immunofluorescence (circulating anti–basement membrane IgG autoantibodies). Medical records from all patients were reviewed, and patient characteristics were recorded together with treatment and follow-up data. At diagnosis, patients were classified as having mild disease (<10 blisters), moderate disease (10-50 blisters), or severe disease (>50 blisters).

In patients treated with methotrexate, the initial dosage was 5 mg/wk. On the remaining 6 days, 1 tablet of folacin (5 mg) was administered. Concomitant topical betamethasone dipropionate (Diprolene; Schering-Plough Corp, Kenilworth, New Jersey) was applied twice daily until the disease was controlled (defined as the absence of new blisters for 3 consecutive days). In the case of insufficient response to treatment, the methotrexate dose was increased by 2.5 mg/wk. On disease control, methotrexate treatment was gradually tapered, and patients who experienced relapses during this time had their dosages increased to the previous level that had allowed disease control. In patients with symptoms of BP despite methotrexate treatment, low-dose prednisone (10-20 mg/d) was added until the disease was restrained. If methotrexate treatment was not suitable, owing to suspected or manifest anemia, liver disease, or renal failure or to the physician’s or patient’s preference, prednisone alone, usually 40 to 80 mg/d, was given. Patients with mild signs of BP who responded to topical betamethasone treatment within a week were not given systemic therapy. Remission was defined as the absence of new blisters after the discontinuation of all medications.

Analyses of survival and remission were performed using the Wilcoxon-Gehan test. Continuous factors were analyzed using the Cox regression analysis. Differences between groups were analyzed using the 1-way analysis of variance and the paired t test. This study was approved by the ethics committee of Karolinska University Hospital.

RESULTS

Between January 1, 1999, and December 31, 2003, a total of 145 patients were diagnosed as having BP at the Karolinska University Hospital. Seven of these patients were lost to follow-up and were excluded from the study. Of the 138 patients included, 79 (57.2%) were women and 59 (42.8%) were men. The mean patient age was 81 years (range, 43-103 years). Most patients (50.7%) had mild disease, 38.4% had moderate disease, and 10.9% had severe disease. The concentration of blood eosinophils before the start of any treatment was determined in 108 patients. Of these patients, 49.1% had normal eosinophil levels (0-500/µL [to convert to ×109 per liter, multiply by 0.001]), and in 50.9% eosinophilia was detected, with a median eosinophil value of 1300/µL (range, 600-8300/µL). The number of hospital admission days during the first year after diagnosis ranged from 0 to 81 days (median, 10 days). Patient data and significant differences among the patient groups are summarized in the Table.

TREATMENT

Of the 138 patients included, 98 (71.0%) began methotrexate treatment with a median weekly dosage of 5 mg (range, 2.5-10 mg). Of these 98 patients, 61 continued with methotrexate as monotherapy (group 1), with a median weekly dosage of 5 mg (range, 2.5-17.5 mg). The median cumulative dose in this group was 280 mg (range, 15-3280 mg). The remaining 37 patients were given prednisone in addition to methotrexate (group 2). The median weekly dosage of methotrexate in this group was 6 mg (range, 2.5-15 mg), and the median cumulative dose was 440 mg (range, 30-2250 mg). Of all the patients treated with methotrexate, only 3 received a median dosage exceeding 10 mg/wk (ie, 12.5, 15, and 17.5 mg/wk). In 19 patients, prednisone treatment was started before the diagnosis of BP was established and then was successively tapered on the administration of methotrexate, whereas in 18 patients, prednisone was periodically added owing to symptoms of BP despite methotrexate treatment.

Forty patients did not receive methotrexate. Fifteen of these patients were treated with high doses of prednisone alone (group 3). In 4 patients, this was owing to...
the presence of anemia or renal insufficiency before the start of any treatment; 1 patient was already taking cytotoxic drugs for breast cancer; and 5 patients were treated with prednisone owing to their own or their physician's preference. In 5 patients, methotrexate was initially administered but its administration was discontinued owing to adverse effects. Two patients experienced gastrointestinal tract symptoms after taking the first dose of methotrexate and did not want to continue, 1 developed anemia (hemoglobin value decreased from 12.7 to 8.5 g/dL [to convert to grams per liter, multiply by 10.0]) after 3 weeks of treatment, and in 1 patient increasing levels of liver enzymes were detected (aspartate aminotransferase, 59 U/L; alanine aminotransferase, 82 U/L [to convert either value to microkatal per liter, multiply by 0.0167]) after the third dose. In both these patients, the values returned to normal within 3 months. One patient developed alopecia after taking the third dose of methotrexate (5 mg/wk); methotrexate treatment was immediately discontinued, and a radiographic investigation 6 months later showed regress of the interstitial infiltrates. The patient had no lung symptoms and was thereafter followed up only at the Department of Dermatology and Venerology, Karolinska University Hospital; she has no lung problems but is still taking immunosuppressive drugs for BP. The median daily dosage of prednisone in this group was 12 mg (range, 6-40 mg), and the median cumulative dose was 4000 mg (range, 15-17 000 mg). The remaining 25 patients were using topical treatment with betamethasone gel only (group 4) because of mild disease and satisfying regress of symptoms with this therapy (Table).

### REMISSION AND SURVIVAL

The patients were followed up during a median of 26 months (range, 0.5-77 months). After 24 months, the remission rate (life-table estimates) was 43% in group 1, 33% in group 2, 0% in group 3, and 83% in group 4 ($P < .001$). Remission occurred after a median treatment time of 11, 20, and 2 months in groups 1, 2, and 4, respectively ($P < .001$). The median cumulative methotrexate dose to achieve remission was 210 mg (range, 20-1350 mg). Patients with mild disease went into remission after a median treatment time of 6 months compared with those with moderate to severe disease, who had a median treatment time of 17 months to obtain remission ($P = .09$). There was no association between age, sex, or eosinophilia and time to remission. The level of blood eosinophils could not be correlated with disease activity. The mean number of hospital admission days due to BP during the first year after diagnosis was similar between groups 1 and 3 (13 and 14 days, respectively). In group 2, the mean number of hospital admission days was 25, which was significantly higher than that in groups 1 and 3 ($P < .001$). In group 4, 52.0% of the patients were never admitted to the hospital, resulting in 3 days as the mean number of hospital admission days.

Increasing age was significantly associated with decreased survival ($P < .001$). Two-year survival (life-table estimates) was 65% in group 1, 67% in group 2, 47% in group 3, and 52% in group 4; none of these differences was significant ($P = .22$). When patients treated with methotrexate (groups 1 and 2) were compared with those who received treatments other than methotrexate (groups 3 and 4), there was a tendency toward a better survival rate for the methotrexate-treated group (median survival time, 38 and 24 months, respectively; $P = .06$). This difference remained borderline significant after correction for age. There were no associations

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**Table.** Patient Data and Significant Differences Between Treatment Groups in 138 Patients Diagnosed as Having Bullous Pemphigoid, 1999-2003

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Methotrexate Only) ($n=61$)</th>
<th>Group 2 (Methotrexate Plus Prednisone) ($n=37$)</th>
<th>Group 3 (Prednisone Only) ($n=15$)</th>
<th>Group 4 (Topical Betamethasone Gel) ($n=25$)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male to female ratio</td>
<td>23.38</td>
<td>16.21</td>
<td>8.7</td>
<td>12.13</td>
<td>.66</td>
</tr>
<tr>
<td>Age, median, y</td>
<td>83</td>
<td>83</td>
<td>79</td>
<td>83</td>
<td>.33</td>
</tr>
<tr>
<td>Patients with mild disease, %</td>
<td>50.8</td>
<td>32.4</td>
<td>46.7</td>
<td>80.0</td>
<td>.003</td>
</tr>
<tr>
<td>Patients with eosinophilia, %</td>
<td>56.0</td>
<td>51.5</td>
<td>33.3</td>
<td>46.1</td>
<td>.55</td>
</tr>
<tr>
<td>Hospital admission, median, d</td>
<td>10</td>
<td>18</td>
<td>9</td>
<td>0</td>
<td>.001</td>
</tr>
<tr>
<td>2-y Remission, %</td>
<td>43</td>
<td>35</td>
<td>0</td>
<td>83</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2-y Survival, %</td>
<td>65</td>
<td>67</td>
<td>47</td>
<td>52</td>
<td>.22</td>
</tr>
</tbody>
</table>

**Figure 1.** Wilcoxon-Gehan analysis of remission in 4 different treatment groups: topical betamethasone gel, methotrexate monotherapy, methotrexate and prednisone, and prednisone monotherapy.
among sex, disease activity, and survival. An increasing number of eosinophils seemed to be associated with decreased survival ($P = .05$).

In the present retrospective study, we show that in patients with generalized BP, low-dose methotrexate combined with topical betamethasone seems to be a safe and effective treatment option. Topical treatment alone can work sufficiently in mild cases. Bullous pemphigoid is the most common autoimmune blistering dermatosis, with an estimated annual incidence of approximately 7 to 10 new cases per million population. At the Department of Dermatology and Venerology, Karolinska University Hospital, which is the referral clinic for the entire Stockholm area (2 million people), we see approximately 20 to 25 new cases a year.

Today, it is well-known that many chronic immunologic diseases (eg, psoriasis, rheumatoid arthritis, and eosinophilic dermatitis) benefit from methotrexate treatment either alone or combined with other drugs. Methotrexate is an inexpensive drug, and it has been in clinical use for decades with only rare adverse effects. Methotrexate is easy to administer: tablets are ingested only once a week. However, gastrointestinal absorption varies from 20% to 80%. It is also possible to give methotrexate as an intramuscular injection.

We showed that few patients had to discontinue their methotrexate treatment owing to adverse effects and that most of these adverse effects were mild. In addition, methotrexate did not reduce the expected life span; instead, patients receiving low-dose methotrexate seemed to have a better survival rate compared with those receiving other treatment forms. The adverse effects observed in the present study, which resulted in the termination of methotrexate treatment, were gastrointestinal tract irritation (2 patients after the first dose), transient alveolitis (1 patient after 3 weeks of treatment), anemia (1 patient), and increasing liver enzyme levels (1 patient).

To exclude the development of severe anemia and renal insufficiency, all the patients are carefully monitored by means of blood sampling once weekly for the first 4 weeks and then 4 times a year. We frequently observe a decrease in hemoglobin levels during the first weeks of treatment; however, in most patients these return to pretreatment levels after a few weeks of therapy without changing the methotrexate dose. In addition, folinic acid treatment (5 mg/d, 6 days a week) is given to all patients to avoid anemia. Regarding liver function, we sometimes notice elevated levels of aspartate aminotransferase and alanine aminotransferase during the first weeks, which usually normalize again within the next 4 to 6 weeks. We never perform any pretreatment liver biopsies. A history of alcohol abuse is not an absolute contraindication; instead, those patients are individually assessed to determine whether methotrexate can be used, depending on the duration and to what extent they used alcohol. However, patients with current alcohol use are not treated with methotrexate. Patients are recommended not to drink more than 2 glasses of wine weekly.

Because photosensitivity has been noted in up to 5% of the patients, they are told to be careful with sunbathing but not to completely avoid it unless there are negative reactions. Concomitant treatment with aspirin should be taken into account and avoided if possible.

During the past 50 years, the mainstay of treatment for BP has been systemic glucocorticoids. However, the high doses needed to obtain clinical response are generally poorly tolerated, especially in elderly patients, and are associated with many adverse effects and a high mortality rate. Frequently occurring severe adverse effects are sepsis, pneumonia, gastrointestinal tract bleeding, high blood glucose levels or diabetes mellitus requiring insulin treatment, osteoporosis, heart failure, and severe skin atrophy. In a German multicenter study of 369 patients with BP, there was a considerable case fatality rate and oral glucocorticoid treatment was identified as a major risk factor for death within the first year after diagnosis. Similar results were obtained in a French study.

In the present study, the median time to remission in patients treated with methotrexate monotherapy was 11 months. Owing to our growing clinical experience regarding the safety of methotrexate treatment in patients with generalized BP, today we usually increase the methotrexate dosage (maximum, 12.5 mg/wk) or treat with intramuscular injection for better absorption instead of adding prednisone in those with insufficient clinical response to the standard methotrexate dosage of 5 mg/wk. Similar to a French study, we observed that this routine generates higher remission rates with shorter treatment periods; however, this needs to be confirmed in a randomized prospective study.

What role do eosinophils play in BP? In 1 study, blood eosinophilia was a severity marker for BP. On the contrary, the level of blood eosinophils could not be correlated with disease severity in the present patients. Apart from eosinophils, various cytokines seem to be involved in the pathogenesis of BP, which may also explain the fact that blood eosinophilia is detected only in approximately 50% of patients with BP. However, after methotrexate treatment, a reduction in the endothelial...
cellular expression of cellular adhesion molecules, which are necessary for the recruitment of eosinophils to the tissues, has been reported. These mechanisms may underlie the rapid reduction in the number of tissue eosinophils and the quick clinical response seen after the start of methotrexate treatment.

Surprisingly, none of the patients receiving only prednisone (group 3) reached complete remission (the absence of blisters after the discontinuation of all medications), but the remission rate was good among those treated with methotrexate, especially monotherapy (group 1). There was a clear relation between the severity of the disease and time to remission, although the patient group was too small for this to be proved significant. The comparatively high number of hospital admission days for patients in group 2 (those treated with methotrexate and prednisone) may reflect the relatively low number of patients with mild disease in this group.

In the present retrospective study, we included all patients diagnosed as having BP between January 1, 1999, and December 31, 2003, and compared the outcomes of different treatment options. To further evaluate the benefit of methotrexate treatment, we are now developing a BP quality register and a biobank to be able to follow up these patients more carefully and to conduct a prospective study that will give further information. In conclusion, methotrexate is a safe and effective drug that is inexpensive and easy to administer. We considered methotrexate to be an excellent treatment option in patients with BP.

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Author Contributions: All the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Kjellman and Eriksson. Acquisition of data: Kjellman and Eriksson. Analysis and interpretation of data: Kjellman, Eriksson, and Berg. Drafting of the manuscript: Kjellman and Eriksson. Critical revision of the manuscript for important intellectual content: Kjellman and Berg. Administrative, technical, and material support: Kjellman and Eriksson. Study supervision: Kjellman and Berg.

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