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Optimizing Treatment Outcomes for Ocular Mucous Membrane Pemphigoid

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Abstract

Purpose: To evaluate the change in best corrected visual acuity over time for patients with ocular mucous membrane pemphigoid (MMP) and to compare the effectiveness of various immunosuppressive treatments in preserving vision.

Design: Retrospective chart review.

Outcome measures: The principal outcome measures assessed were: improvement in vision, no change in vision or a decrease in vision.

Methods: All patients diagnosed with ocular cicatricial pemphigoid or mucous membrane pemphigoid at UT Southwestern Medical Center in Dallas, Texas from 2003 to 2012 were identified and their charts reviewed

Results: 29 patients and 57 eyes were included in the study. 22 of the patients had positive biopsies. The average age of the patients was 67 years old. The average follow-up was 49 months (range 6–143 months). More than half (15 of 29 patients) required a change in therapy and one patient had their treatment changed seven times. When used as first drug therapy, the percent of eyes that had either no change or an actual improvement in vision over the course of that treatment was 83% (10 of 12 eyes) for Mycophenolate, 69% (22 of 32 eyes) for Dapsone, and 60% (6 of 10 eyes) for Cyclophosphamide. When second drug therapy was necessary, the percent of eyes that had either no change or an improvement in vision over the course of that treatment was 75% (3 of 4 eyes) for Rituximab, 64% (9 of 14 eyes) for Azathioprine, 50% (4 of 8 eyes) for Mycophenolate, and 25% (1 of 4 eyes) for Dapsone. Looking at all outcomes without regard to the stage of treatment, 90% of eyes (9 of 10) treated with Rituximab had either no change or an improvement in vision over the course of their treatment.

Conclusions: MMP is a blinding disease which can respond to aggressive and compliant long-term treatment. Newer therapies show promise; in this series Rituximab was found to provide the best results in preserving vision.

Background

Mucous membrane pemphigoid (MMP) is a rare (from 1 in 12,000 to 1 in 60,000), chronic, autoimmune systemic blistering disease that can affect any or all of the mucous membranes and the skin. MMP has been known by many names, most commonly ocular cicatricial pemphigoid, but in 2002 a panel of experts agreed on the term mucous membrane pemphigoid [1]. Oral lesions are most common, occurring in around 90% of patients. Ocular involvement is also common, occurring in up to 66% of patients [2]. Life-threatening laryngeal or esophageal involvement is also possible, occurring in up to 9% of patients [3]. The likelihood of extraocular disease in those with ocular MMP is about 82% [4].

Ocular involvement is in the form of a chronic cicatrizing conjunctivitis. Early on there is a chronic, non-specific conjunctivitis, usually bilateral. As the disease progresses there is subepithelial fibrosis and scarring which eventually leads to forniceal shortening and symblephara formation. Scarring involving the eyelids can cause lagophthalmos, entropion and trichiasis. There is also loss of goblet cells and lacrimal gland ductules. This all leads to a progressive keratopathy with neovascularization and opacification of the cornea which left uncontrolled can lead to painful bilateral blindness.

The immunopathogenesis of MMP involves deposition of immunoglobulins (IgA, IgG) at the epithelial basement membrane [5]. Mucous membranes can also be affected in the mouth, eye, nose, pharynx, larynx, trachea, esophagus, genitalia, anus and skin [6]. Tests may also show antibodies in the serum of some patients [7]. Biopsy with direct immunofluorescent testing is the gold standard for diagnosis.

MMP is a systemic disease requiring systemic treatment. Various topical therapies have been tried but have been ineffective. Immunosuppressive therapies have been used since the 1970's [8], and evidence supporting such use has been shown in a number of studies [9-13]. Despite this, there is still no universally accepted treatment protocol and patients are often treated with several different therapies before successfully quieting the ocular surface inflammation. Some institutions use a step-ladder approach similar to that described by Saw et al. [11]. Dapsone is typically reserved for mild disease, followed by mycophenolate [14], azathioprine [15], cyclophosphamide [16], IVIG [17] and rituximab [18] for progressively more severe cases. Systemic steroids are often used for a time in conjunction with the listed therapies. Typically, treatment with immunosuppressants is continued until the disease has been in remission for 2-3 years before an attempt at reducing therapy is made.

The purpose of this study was to compare the various treatment modalities in preserving vision. Most of the previous studies on this

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topic have defined success or failure of treatment based on control of ocular inflammation. However, studies have shown that progression of the disease can occur even in the absence of clinically detectable inflammation [19]. Given that the ultimate untreated outcome of this disease process is permanent vision loss, our goal was to compare differences in visual outcomes based on treatment modalities.

Methods

A retrospective chart review was performed of all patients diagnosed with ocular cicatricial pemphigoid or mucous membrane pemphigoid at UT Southwestern Medical Center in Dallas, Texas from 2003 to 2012. The records of 29 patients were included. Inclusion criteria included patients with a clinical diagnosis of MMP who had at least two follow-up visits after initiating therapy. We preferred to have a biopsy for diagnosis but this was not required. A clinical diagnosis was made based on characteristic clinical findings after excluding other causes of cicatrizing conjunctivitis and after ruling out the use of medications which have been shown to cause a cicatrizing conjunctivitis. If present, glaucoma was treated and controlled in study patients.

Outcome measures included date of diagnosis, biopsy results if available, other mucosal involvement, bilateral or unilateral involvement, dates and types of therapy initiation, dates of changes in therapy, and best corrected visual acuity recorded in snellen notation at diagnosis and each follow-up visit. The snellen fractions were then converted to both LogMar and ETDRS notation for statistical comparison.

Drug therapy was tailored to each patient but followed a step-ladder approach according to initial severity of the disease and subsequent response to therapy. Dapsone was previously the most commonly prescribed initial treatment and cyclophosphamide was used in recalcitrant cases. These are still being used in some of our patients but today many patients are initially started on mycophenolate or azathioprine, and rituximab is reserved for more severe or unresponsive cases.

Results

Twenty nine patients were treated and results were obtained on 57 eyes. Average age at diagnosis was 67 years. There were 16 males and 13 females. Positive biopsy results were available for 22 of the 29 patients. Fourteen of the patients had evidence of other mucosal involvement at the time of diagnosis. All of the patients had bilateral ocular disease. One patient had NLP vision in one eye from a different cause and was not included in the study. Eight patients had glaucoma. Average follow-up period was 49 months (range 6–143 months). Many of our patients had side effects from treatment requiring a change in therapy. None of our patients died from treatment side effects, and we saw no episodes of secondary cancers related to treatment.

A total of 53 treatment episodes occurred. The total number of drugs given to any patient is listed in Table 1. Fourteen patients were given only one drug and one patient changed treatments seven times. For the fourteen patients treated with only one drug, the drug used is listed in Table 2.

A survival curve showing the likelihood of having to switch therapies based on the initial treatment chosen is shown in Figure 1. Our sample size only allowed Dapsone, Mycophenolate and Cyclophosphamide to be included in this analysis, but it shows that patients that are initially treated with Dapsone are less likely to need a change in therapy.

The visual outcome comparisons are shown in Tables 3 and 4. Table 3 shows the number of eyes that had improved vision, no change in vision or decreased vision based only on the initial drug therapy used. Table 4 shows the same outcomes but it is based on the second drug used if a change in therapy was required. Figure 2 shows the outcomes for all patients treated with Rituximab regardless of any previous treatments. For example, one of the patients included in Figure 2 was treated with Rituximab as the second therapy and another

Total number of drugs given	Number of Patients
1	14
2	11
3	3
7	1
Total	29

Table 1: Number of drugs given to each patient.

	Number of Patients
Dapsone	8
Mycophenolate	4
Cyclophosphamide	1
Azathioprine	1
Total	14

Table 2: Drug used for patients not requiring a change in therapy.

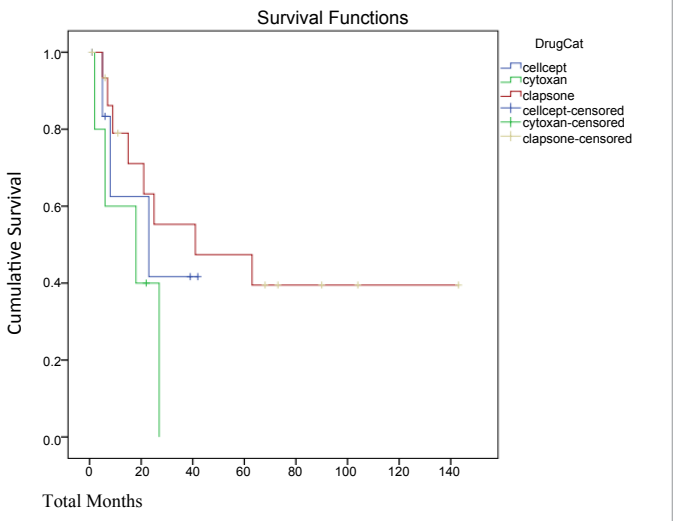

Figure 1: Likelihood of having to change therapy based on the initial treatment.

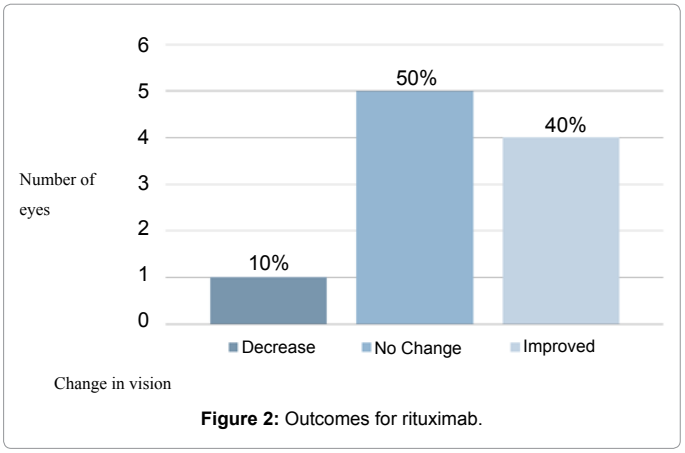

Figure 2: Outcomes for rituximab.

	% of eyes with no change or an improvement in visual acuity	Number of Eyes with a Decrease in acuity (average change in LogMar value)	Number of Eyes with no change in visual acuity	Number of Eyes with an Improvement in acuity (average change in LogMar value)	Total
Mycophenolate	83%	2 (0.1)	2	8 (0.47)	12
Dapsone	69%	10 (0.2)	14	8 (0.17)	32
Cyclophosphamide	60%	4 (0.4)	3	3 (0.19)	10
Azathioprine	100%	0	0	2 (0.5)	2

Table 3: Outcomes for first drug treatment.

	% of eyes with no change or an improvement in visual acuity	Number of Eyes with a Decrease in acuity (average change in LogMar value)	Number of Eyes with no change in visual acuity	Number of Eyes with an Improvement in acuity (average change in LogMar value)	Total
Rituximab	75%	1 (0.4)	2	1 (0.7)	4
Azathioprine	64%	5 (0.2)	7	2 (0.22)	14
Mycophenolate	50%	4 (0.24)	3	1 (0.2)	8
Dapsone	25%	3 (0.2)	1	0	4

Table 4: Outcomes for second drug treatment.

patient included in the chart was treated with rituximab as the seventh therapy. The average change in LogMar acuity for patients treated with rituximab that lost vision was 0.4. The average change in LogMar acuity for patients treated with rituximab that gained vision was 0.47.

Discussion

Patients with ocular MMP regularly require trials on multiple therapies in order to quiet their ocular surface inflammation. In our study, more than half (15 of 29 patients) required a change in therapy and one patient had their treatment changed seven times. The frequent changes of therapy in some patients are due not only to the difficulty in controlling inflammation but also because of the various side effects of each of the drugs. Of the patients treated with only one drug for the duration of their therapy, Dapsone was the most commonly used drug (57%), followed by Mycophenolate (28%). The higher percentage for Dapsone may be a result of the fact that Dapsone is often the first drug started in more mild cases, and these cases are easier to quiet.

At our facility Dapsone is used primarily as a first line treatment and only rarely as second. Cyclophosphamide was used only as a primary treatment in this series. Mycophenolate was used frequently as primary and as secondary treatment. Azathioprine was used mostly as a second line treatment. Rituximab was used only as second line therapy.

In Figure 1 we show a survival curve comparing the length of time before patients require change to a different treatment for Dapsone, Cyclophosphamide and Mycophenolate. On average, patients on Dapsone last a longer period of time before requiring change to a different therapy. This is somewhat expected given that Dapsone is usually the initial treatment for more mild cases. Also, Cyclophosphamide is typically only used for a period of time required to quiet inflammation and then a change is made to a medicine with fewer side effects.

Table 3 shows the percentage of patients successfully treated based on the initial drug used. Successful outcomes are not straight forward when treating this disease. While an improvement in vision is obviously the best outcome, this disease is so difficult to manage that we consider suppressing the disease and preserving vision present when a patient starts treatment as a clinical success as well. 83% of eyes that were treated with Mycophenolate as initial therapy had either no change or an actual improvement in vision over the course of that treatment (10 out of 12 eyes). For eyes treated with Dapsone, 69% (22 of 32 eyes) had either no change or an improvement, and for Cyclophosphamide 60% (6 of 10 eyes) had either no change or an improvement. Only one patient in this series was started on Azathioprine as initial treatment, and that patient manifested improved vision in both eyes.

In an attempt to identify the best second line therapy we looked at visual outcomes based on the second drug used, shown in Table 4. When Rituximab was used as the second therapy 75% of eyes either had no change or an improvement in vision (3 of 4 eyes). For Azathioprine, 64% of eyes had no change or an improvement in vision (9 of 14 eyes). For Mycophenolate, 50% of eyes had no change or an improvement (4 of 8 eyes). And for Dapsone only 25% of eyes had no change or an improvement (1 of 4 eyes). Due to sample size, these differences did not reach statistical significance but they do support the manner in which these therapies are administered. Dapsone is not thought of as a second line therapy and it had the worst results when used as such. Azathioprine and Mycophenolate are commonly used as second line therapies and they managed to stabilize or improve the vision in 64% and 50% of treated eyes respectively. Rituximab is now thought of as one of the most effective treatments for aggressive and resistant MMP and it performed best when used as the second therapy. We also looked at the overall performance for rituximab, without regard to the stage of treatment (whether it was the second drug or seventh). Table 4 shows that 90% of eyes (9 of 10) treated with rituximab had either no change or an improvement in vision. These are remarkable results given that patients treated with rituximab had the most aggressive form of the disease and had failed at least one drug previously.

There are several aspects that make studying MMP difficult. It is a rare disease and it is difficult to include a large number of patients in one series. Studying the visual outcomes is difficult because MMP is not the only process responsible for potential reductions in the level of vision. Giving credit to one drug for patients visual changes is not straight forward because these patients are often treated with multiple different drugs and there is likely a carry-over period when the previous treatments are still having some effect. These drugs also have significant side effects and often the changes in therapy are due to these side effects rather than a failure of therapy. Despite these limitations, the results presented represent the current clinical paradigm for treatment of MMP. Clearly, further studies are indicated to help preserve and/or improve vision in this devastating condition.

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