Chapter 5
Ocular Cicatricial Pemphigoid

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Abstract Ocular cicatricial pemphigoid is a result of immune dysfunction leading to deposition of immunoglobulins and complement at the conjunctival basement membrane zone. This can lead to irreversible scarring. Patients are treated with suitable systemic immunomodulatory treatments which are usually individualized to the patient depending on the patient's age, disease stage, and presence of non-ocular symptoms. The approach to choosing the proper chemotherapy is through a stepladder algorithm. The ultimate goal of therapy is to treat the patient with corticosteroid-sparing systemic agent. The focus of this chapter will be the medical treatment strategies available for OCP based upon clinical severity, extent and progression of the disease.

Keywords Ocular cicatricial pemphigoid • Dapsone • Azathioprine • Mycophenolate mofetil • Cyclophosphamide • Methotrexate • Plasmapheresis • Rituximab • Intravenous Immunoglobulin

Introduction

Mucous membrane pemphigoid (MMP) encompasses a group of autoimmune inflammatory subepithelial blistering diseases affecting primarily various mucous membranes. Ocular complications seen in 60 % of MMP cases, known as ocular

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cicatricial pemphigoid (OCP), is the second most-commonly involved mucous membrane affecting conjunctival tissue [1, 2]. OCP is a rare, vision-threatening disorder, affecting approximately 1 in 12,000–1 in 60,000, with an average age of 65 years. It is more commonly seen in females, with a ratio of 2–3:1 [3].

OCP is a result of immune dysfunction leading to deposition of immunoglobulins and complement at the conjunctival basement membrane zone (BMZ). The most commonly identified immunoreactants are IgG, IgA and C3, deposited in a linear fashion unique to OCP [4]. The disease can initially present unilaterally or bilaterally; in patients with unilateral involvement, the other eye is typically affected within 2 years [4, 5]. The typical sequence of OCP progression begins with subepithelial fibrosis leading to foreshortening of fornices, followed by the formation of symblepharon from palpebral to the bulbar conjunctiva. Later stages of the disease present with extensive conjunctival scarring, ankyloblepharon, trichiasis, and distichiasis. The disease also causes loss of goblet cells, along with the occlusion of lacrimal and accessory lacrimal glands leading to dry eye and ocular surface pathology [1, 4]. Combination of clinical findings and immunohistopathology of biopsied conjunctiva leads to the diagnosis of OCP.

The First International Consensus on MMP categorized patients into "low-risk" and "high-risk" groups based upon the site(s) of involvement. Ocular involvement falls into the "high-risk" group, therefore requiring aggressive systemic therapy [1, 2]. The focus of this chapter will be the medical treatment strategies available for OCP based upon clinical severity, extent and progression of the disease.

Staging

OCP may present as symmetric or asymmetric disease; therefore each eye must be graded separately. The Foster classification categorizes OCP into four stages, depending on clinical features. Stage 1 findings consist of conjunctival inflammation, mucous discharge, small-patched rose bengal-staining conjunctival epithelium, and conjunctival subepithelial fibrosis (Fig. 5.1). Stage 2 exhibits foreshortening of the conjunctival fornix . Stage 2 is further subdivided (a) through (d) depending on the degree of fornix shortening: (a) 0–25 % (b) 25–50 % (c) 50–75 % (d) >75 % fornix shortening (Fig. 5.3b). Stage 3 includes symblepharon formation and is also further subdivided (a) through (d) depending on the percentage of horizontal involvement of symblephara, (a) 0–25 % (b) 25–50 % (c) 50–75 % (d) >75 % involvement of symblephra (Fig. 5.2a,b, and 5.3a. Stage 4 or end-stage OCP is characterized by severe sicca syndrome, ocular surface keratinization, and ankyloblepharon [4–6] (Figs. 5.1, 5.2, and 5.3).

OCP is a systemic autoimmune disease as a result of dysregulation of the immune system [7, 8]; therefore, the treatment is targeted towards both systemic and local immune processes and their subsequent sequelae. The goal of therapy is to abolish inflammation, prevent further cicatrization and promote healing.

It is important to emphasize that systemic, not topical treatment is required to adequately control OCP. Previous attempts of controlling OCP's activity with

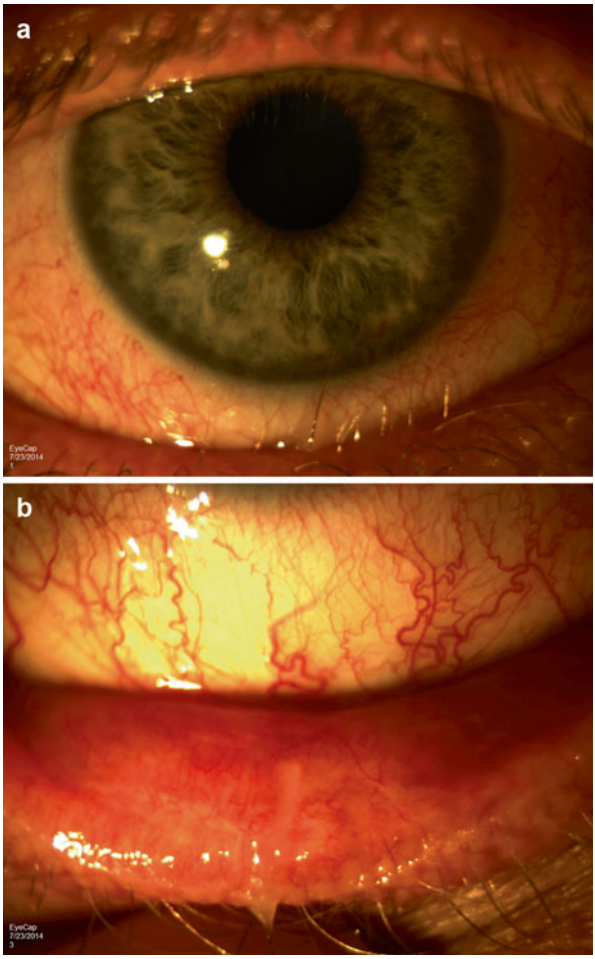


Fig. 5.1 (**a**, **b**) External photos of the same patient with biopsy proven OCP, showing extensive blepharitis, fornix foreshortening, lash-cornea touch, cicatricial changes to lower eyelid

topical corticosteroids, cyclosporine, mitomycin-C, and retinoids have failed. Furthermore, although oral prednisone may control ocular inflammation acutely, it does not suffice for long-term immunosuppression to control disease activity and therefore it is an inappropriate treatment regimen to accomplish sustainable remission [4, 5, 9, 10].

Deciding on the most suitable systemic immunomodulatory treatment is dependent on the patient's age, disease stage, and presence of non-ocular symptoms. Prior to initiating therapy, the patient should undergo a formal assessment of disease stage. Checking the following is crucial to allow for proper drug monitoring: baseline renal and liver function tests, and complete blood count (CBC). Discussion about various treatment options, potential side effects and

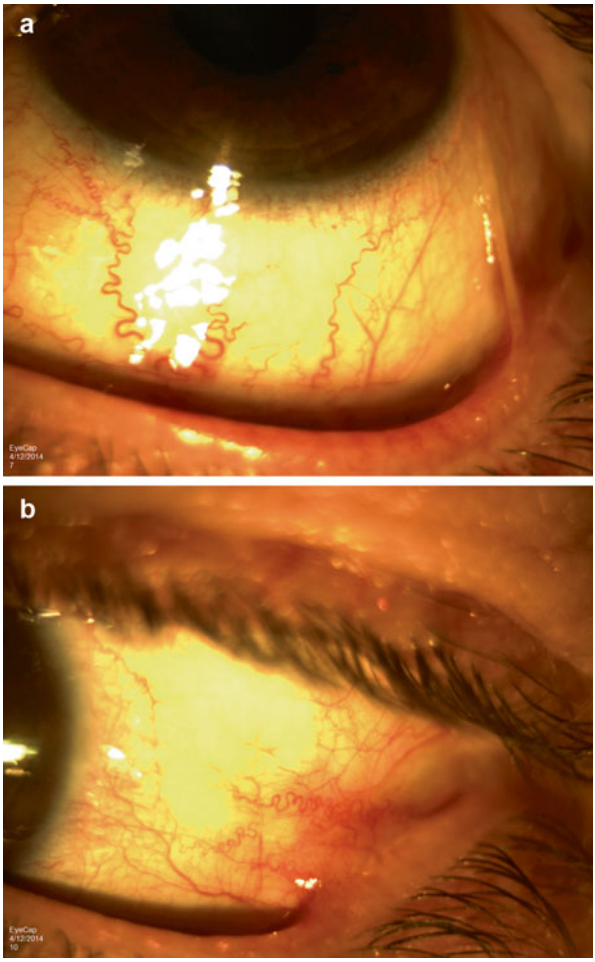


Fig. 5.2 (**a**, **b**) External photos of the same patient depicting stage 3 OCP. Patient is currently on immunomodulatory therapy, in remission

the willingness to commit to frequent follow-up visits is important for patient awareness and compliance [3, 4]. Systemic immunosuppressive therapy is appropriate in patients with active, progressive OCP (not in end-stage "burned out" disease); therapy can prevent further scarring, but cannot reverse previous damage [4]. The approach to choosing the proper chemotherapy is through a stepladder algorithm. Patients with mild to moderate disease are started on the least potent therapeutic options and if they fail to respond, continue to progress or are intolerant to side effects, patients are treated with addition of or

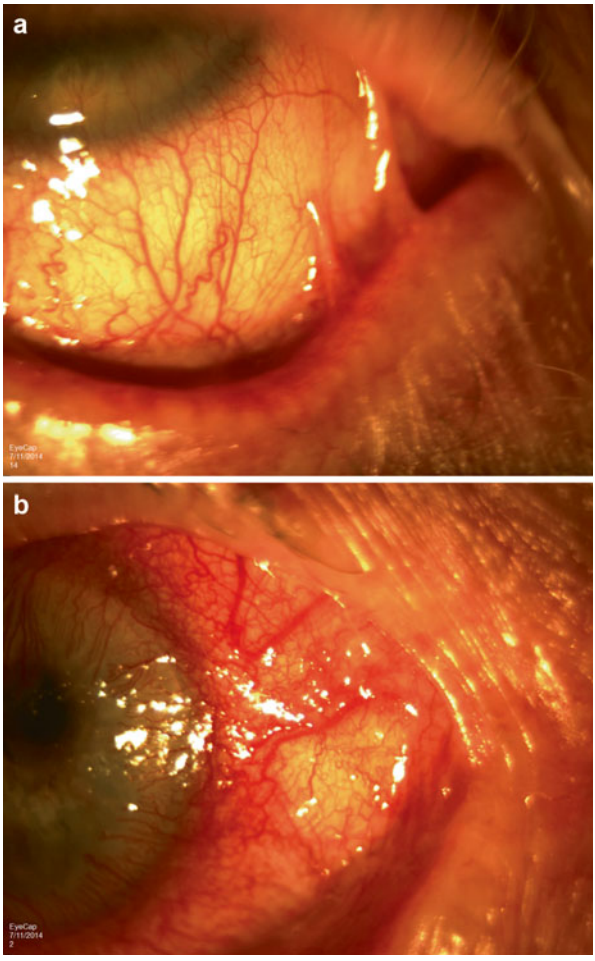
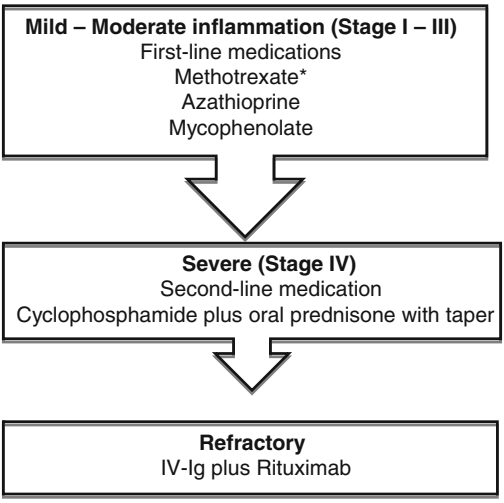


Fig. 5.3 (**a**, **b**) Photos of actively inflamed, rapidly progressing OCP. Patient failed methotrexate and is awaiting insurance approval for IV-Ig and rituximab infusions

substitution with more potent therapeutic options. The ultimate goal of therapy is to treat the patient with corticosteroid-sparing systemic therapy successfully keeping them in steroid-free remission for 2 years. Once the patient has reached the 2-year milestone, medication is slowly tapered. During tapering of medication, close monitoring is continued to observe for relapses [4]. After discontinuing medication, patients have a 30 % risk of recurrence; therefore, lifelong follow-up is recommended [5, 11]. The specific immunomodulatory therapies in the treatment of OCP are discussed in detail in the following sections.

OCP Stepladder Immunosuppressive Therapy Algorithm



*Most commonly used first-line medication because of the long track record of its application among ocular diseases for over four decades and well-known side effect profile.

Tetracycline

Tetracyclines were discovered as the natural fermentation product of the soil bacterium Streptomyces aureofaciens in 1948 and were chemically purified for the first time in 1952 [12]. They have shown efficacy on inflammation, immunomodulation, cell proliferation, angiogenesis, metal chelation, ionophoresis, and bone metabolism [13].

Tetracycline has a direct and indirect anti-inflammatory effect [14, 15]. Tetracycline or minocycline, alone or in combination with nicotinamide, were shown to be effective in cicatricial pemphigoid diseases [16, 17]. Kohler et al., in 1980, showed the synergic anti-neutrophil effect of tetracycline and nicotinamide combination in treatment of erythema elevatum diutinum [18]. Tetracycline (500–2000 mg/day) therapy alone as monotherapy or in combination with nicotinamide (500–2500 mg/day) is also effective in treating pemphigoid [19–21]. Tetracyclines are usually well-tolerated drugs. Common side effects include cutaneous side effects and gastrointestinal upset. Rash, purpura and photosensitivity are reported with both minocycline and doxycycline. Dizziness is reported in almost 10 % of the patients [22].

However, tetracycline's efficacy to achieve durable remission in OCP has not shown encouraging results. Therefore, the use of tetracycline as monotherapy or in combination with immunosuppressive agents is not administered in the treatment of OCP.

Dapsone

Dapsone is a sulfone derivative (4–4′ diaminodiphenylsulfone) [5] with antibacterial and anti-inflammatory properties. In the early twentieth century, theories on selective toxicity based on the ability of certain dyes to kill microbes developed, eventually leading to the discovery of dapsone by Ernest Fourneau and Gladwin Buttle [23]. Dapsone was originally utilized in the treatment of leprosy. Later, in 1953, Rook et al. reported 11 of 17 patients with bullous pemphigoid responded to treatment with sulfapyridine [24]. Person et al. in 1977 and Foster et al. in 1986 confirmed these results, noting the efficacy of dapsone in treating dermatitis herpetiformis and bullous pemphigoid [5, 25].

Dapsone's applicability in OCP is due to its anti-inflammatory (immunomodulating) effects [26]. The anti-inflammatory mode of action of dapsone is through inhibiting the migration of neutrophilic polymorphonuclear leukocytes [27] and suppressing effects on peroxidase enzyme systems present in monocytes, neutrophils, eosinophils, and mast cells. However, the specific cellular and molecular events involved in the anti-inflammatory effect of dapsone are unknown [5].

Foster et al. studied the efficacy of dapsone in patients with OCP, finding 88 % (14 out of 16) with mild-to-modest inflammatory activity responded to dapsone. Treatment failures in this study were in patients with 3–4+ conjunctival inflammation prior to therapy [5] indicating that dapsone is one drug of choice as first line therapy in mild to moderate OCP [5, 26].

The initial dose of dapsone employed is 2 mg/kg/day with a maximum dose of 200 mg/day. Dosage adjustments are based on therapeutic response and drug tolerance. Patients are monitored every 4–6 weeks; monitoring parameters include CBC emphasized attention on hemoglobin, hematocrit, and reticulocyte count [5].

The most common potential side effects are hemolysis and methaemoglobinemia [5, 27]. Doses greater than 50 mg/day inevitably produce some degree of hemolysis, usually well tolerated [27]. Low-grade hemolysis is acceptable under the circumstances of desired therapeutic response and adequate compensation by reticulocytosis. However, a progressive drop in hematocrit may require discontinuation [5, 26]. Wetheim et al. reported up to 33 % of patients treated with dapsone for OCP with a daily dose of 50 mg twice daily taken orally with clinically significant hemolytic anemia and a persistent fall in hemoglobin from baseline [26]. Previously published reports note approximately 10 % of patients with hemolysis required discontinuation of therapy [5, 28]. Glucose-6-phosphate hydrogenase deficient patients are at a higher risk of developing hemolytic anemia when treated with dapsone [26].

Fern et al. also confirmed dapsone was effective in treating mild to moderate OCP, however, all the patients relapsed after discontinuing therapy [27]. Foster et al. reported 41 % of patients treated with dapsone relapsed within 6 months of discontinuing therapy. Relapsed inflammation responds to either restarting dapsone or starting immunosuppressive agent: azathioprine, 2 mg/kg initial dose [5, 27].

Although dapsone is a relatively safe medication [27], its primary deficiencies are the high rate of recurrence after discontinuation and its inability to control the disease as a monotherapy [5, 27]. Thus, dapsone is not commonly utilized in the treatment of OCP.

Methotrexate

In 1948, methotrexate (MTX) was introduced as an anti-neoplastic agent [29]. In 1965, MTX was employed in the treatment of ocular diseases [30], and since then, multiple series have reported its effectiveness in managing ocular inflammation [31–36]. MTX, an anti-metabolite, functions as an immunosuppressive agent through lowering cell proliferation, increasing CD95 sensitivity of activated T-cells leading to an accelerated rate of T-cell apoptosis, inhibiting enzymes involved in purine metabolism and subsequently increasing endogenous adenosine concentrations, and altering cytokine production and humoral responses [37].

Gangaputra et al. retrospectively studied the outcome of noninfectious ocular inflammation when treated with methotrexate as a single, non-corticosteroid immunosuppressive agent. A total of 639 eyes were assessed, affected by multiple etiologies of ocular inflammation and 109 of the included eyes were diagnosed with OCP. Results demonstrated 39.5 % of patients with OCP reached complete suppression of inflammation sustained for ≥28 days within 6 months of treatment. Furthermore, 65 % of the patients with complete control of OCP continued to improve between 6 and 12 months of therapy and reached complete control of inflammation by 12 months of MTX therapy. Corticosteroid-sparing success defined as completely inactive inflammation at ≥2 visits spanning ≥28 days after tapering oral prednisone dose to ≤10 mg/day was observed in 36.5 % of patients with OCP within 6 months of treatment. Moreover, corticosteroid-sparing success continued to improve to 66.9 % within 12 months of treatment. Durable control of inflammation after tapering oral prednisone to ≤5 mg/day was achieved in 60.7 % of patients with OCP [38].

MTX is indicated for mild to moderate OCP; it is administered as one of the first-line medications. Although MTX is available in oral, subcutaneous (SC) and intravenous routes, it is initially employed orally and at once a week dosage, which reduces the potential risk of occult side effects [4, 39]. Patients are observed closely, monitoring CBC, renal panel, and liver function testing every 6 weeks. MTX is initiated at a dose of 15 mg once a week and increased according to the patients' response and tolerability to treatment, with maximum dose of 40 mg weekly. Folic acid is administered concomitantly at a dose of 1 mg daily.

Patients may develop side effects within the first year of therapy. Gangaputra et al. reported up to 18 % of patients discontinued MTX due to side effects within the first year [38]. The commonly reported side effects are fatigue, GI related: nausea, vomiting and anorexia, and transaminitis [1, 4, 32, 34, 38, 40]. Switching to subcutaneous administration may alleviate gastrointestinal side effect. Other potential side effects include cytopenia, stomatitis [41–44], and pneumonitis [1, 45–48]. Serious and rare adverse effects are bone marrow suppression (0.02 cases/person-year), liver cirrhosis (0.002 cases/person-year), and malignancy [1, 38, 49]. Miserocchi et al. reviewed treatment related side effects in 61 patients with MMP and concluded that MTX exhibited the fewest number of adverse effects, as compared to azathioprine, cyclophosphamide, and dapsone [50]. Baker et al. had similar findings, stating that within the first year of therapy, the portion of patients discontinuing treatment because of side effects was the same among MTX and mycophenolate mofetil (0.09) and significantly higher for azathioprine (0.24) [51]. MTX is a non-dose dependent teratogen, exposure leading to miscarriages and fetal malformations [52, 53]. Therefore, prior to initiating therapy, proper birth control measures should be discussed and recommended, and substitution of therapy should occur ≥3 months before attempting conception [38].

Overall, systemic use of MTX therapy for ocular inflammation is moderately effective in adequately controlling inflammation and decreasing dependency on corticosteroids MTX is tolerated relatively well and carries low risk of serious side effects when patients are closely monitored [38].

Azathioprine

In 1957, George Herbert Hitching and Gertrude Elion developed an anti-metabolite medication, azathioprine (Imuran®), which interferes with DNA and RNA synthesis [54], thus acting as an immunosuppressive drug. The first usage of azathioprine was in combination with glucocorticoids to immune suppress post kidney allotransplantation recipients [54–59].

Azathioprine's first use in the treatment of OCP came after a study by Dantzig in 1974, publishing results of azathioprine in the treatment of OCP [9]. The efficacy of azathioprine in treating OCP was further confirmed by Dave et al., who reported success in the treatment of four patients with mucous membrane pemphigoid with ocular involvement [60]. Currently, azathioprine holds the US Food and Drug Administration approval for the treatment of rheumatoid arthritis [61], organ transplantation [62] and various dermatologic [63], gastrointestinal [64] and rheumatologic diseases [65]. Azathioprine's pertinence among ophthalmalmic diseases is preventing corneal graft rejections and treating non-infectious ocular inflammatory conditions.

Pasadhika et al. evaluated outcomes of ocular inflammation patients managed on azathioprine as the sole immunosuppressive agent. One hundred forty-five patients were included in the data analysis and of the 145 patients, 33 patients

(23 %) had MMP. Each patient was followed from the initiation of azathioprine until therapy was discontinued. Treatment success was evaluated by the time-to-successful tapering of prednisone to ≤10 mg, ≤5 mg, and 0 mg daily while maintaining control of inflammation over at least two visits spanning at least 28 days. Approximately 43 % of MMP patients had control of their ocular inflammation within 6 months of treatment. Corticosteroid-sparing success by 6 months was second highest in MMP (39 %). Patients with intermediate uveitis and mucous membrane pemphigoid (MMP) were most likely to achieve both control of inflammation and corticosteroid-tapering success compared to other ocular inflammatory sites involved in this study [54].

Azathioprine is one of the first-line medications in treating OCP. The recommended dose based on TPMT levels up to 3 mg/kg/day, as the maximum dose [4]. The most common adverse effects leading to discontinuation of azathioprine are gastrointestinal upset, followed by bone marrow suppression, elevated liver enzymes, infection, allergic reaction and arthralgia [4, 54]. Pasadhika et al. estimated 24 % of patients would discontinue azathioprine due to side effects within 1 year [54]. Its main advantages are a lower cost compared to most alternative agents and some evidence of safety during pregnancy [66, 67]. Also, this medication has been used for ocular inflammatory diseases for the past forty decades, thus unknown long-term toxicities of therapy are less likely [54]. Similar to MTX monitoring, patients are evaluated every 6 weeks, each time with a complete examination and blood work to assess CBC with differential, aspartate transaminase, alanine transaminase, blood urea nitrogen (BUN) and creatinine.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF; CellCept®) was originally introduced in the 1950s as an antifungal medication and in the process was discovered to have antineoplastic and immunosuppressive properties [68]. In 1995, the U.S. Food and Drug Administration approved MMF as an immunosuppressive agent to reduce acute renal graft rejection and prolonging renal graft survival [69]. Since then, it has been utilized as a corticosteroid-sparing therapy for solid organ transplant rejection and multiple autoimmune diseases and systemic disorders [70–76]. Ocular application of MMF was first conducted in rats with experimental autoimmune uveitis showing encouraging results [77] and then preliminary studies were performed in humans with OCP [70]. Results revealed MMF to be effective in 9 of 10 eyes (five patients) during 1-year follow-up.

MMF is a morpholinoethyl ester of mycophenolic acid, with an immunosuppressive action by reversible inhibition of inosine-5′ monophosphate dehydrogenase in the de novo pathway of purine synthesis without affecting the salvage pathway of purine synthesis. Therefore, MMF selectively inhibits T- and B- lymphocyte replication [78, 79] and may be the reason for fewer side effects compared to other antimetabolites [75, 78].

Thorne et al. retrospectively evaluated treatment outcomes of MMF in 84 patients with various inflammatory eye diseases, 11 % of these patients were diagnosed with OCP. Treatment success was based on ability to control ocular inflammation and taper oral prednisone to ≤10 mg daily. Treatment success was achieved in 82 % of the patients with median time of 3.5 months with majority of the patients reaching this goal in the first 6 months of treatment. Of the patients to reach treatment success, 70 % were able to taper to ≤5 mg oral prednisone daily successfully, and 40 % were able to discontinue oral prednisone without relapse of their disease. The rate of treatment success among patients who previously had not received IMT was 0.27 per person-month with median time to treatment success of 2.4 months. The rate of treatment success among patients who received IMT previously was 0.09 per person-month with median time to treatment success of 4.7 months. Even then, treatment success was >60 % among patients previously treated with IMT. In conclusion, MMF is not only an effective corticosteroid-sparing agent to treat OCP but also among patients resistant to other IMTs [80].

Doycheva et al. were the first to report long-term efficacy and tolerability of MMF in the therapy of OCP. The study consisted of retrospectively assessing 19 eyes with OCP diagnosis that were treated with MMF with follow-up of at least 4 years. At the time of MMF treatment initiation, 17 of 19 eyes (89 %) had active inflammation. During the therapy, 11 eyes (58 %) had complete resolution of inflammation and 8 eyes (11 %) had mild inflammation. Rate of relapse was 0.09 per patient-year with a mean time of 42 months after the initiation of MMP. Also during treatment, progression of conjunctival cicatrization was prevented in 9 eyes (47 %), mild progression of cicatrization was reported in 8 eyes (42 %) and conjunctival cicatrization progressed to stage IV in 2 eyes (11 %). Overall, the results from this study suggest MMF is an adequate immunosuppressive agent with the capacity to maintain long-term inflammatory control and recommending it as first-line therapy for patients with OCP [81].

Nottage et al. retrospectively studied the outcomes of inflammatory control and rate of discontinuation of MMF in the treatment of OCP. The study consisted of 23 OCP patients that were treated with MMF. All of the patients had disease process of Foster stage 2 or greater. Eight out of the 23 patients (34.8 %) had failed IMT previously. Fifteen of the 23 patients (65.2 %) were treated with MMF as initial therapy. Overall, 19 patients achieved control of inflammation, and 16 out of the 19 patients (82.4 %) were treated with MMF as monotherapy. Of all the patients who achieved inflammatory suppression (19 patients), 3.27 months was the median length of time to disease control. The patients who had failed IMT previously, 4.10 months was the median length of time to disease control and 3.85 months for those who were IMT naïve prior to starting MMF. In 5 of the total 23 patients, MMF was discontinued due to response failure (4 patients) and allergic reaction (1 patient). Based on these observations, MMF was concluded to be an appropriate monotherapy and initial systemic immunosuppressive agent for controlling active OCP [82].

Side effect profile of MMF is found to be minimal and overall well tolerated [68, 70, 80, 83–86]. Nottage et al. observed 3 out of 23 patients to have developed side effects. One of the three patients (4.3 %) developed a rash leading to cessation of

MMF. Another patient had mild thrombocytopenia, which resolved with a decrease in MMF dose. Third patient had hypokalemia, myalgia, insomnia, and anorexia, which also resolved with lowering the dose and switching to mycophenolate sodium [82]. Saw et al. and Doycheva et al. both reported mild and transient side effects of MMF while evaluating the effectiveness and toxicity of different IMT in OCP management [81, 84]. Saw et al. went on to conclude MMF having the lowest risk of side effects when compared to other IMT [84]. The most common potential side effects observed with the use of MMF are gastrointestinal upset (diarrhea, vomiting), increased liver enzymes, and fatigue [68, 71, 80, 81] which are typically reversible and resolve with dose reduction. MMF has not been associated with causing any major organ toxicity, infection or malignancy [71, 81, 82].

MMF is employed as an orally administered medication, initially at a dose of 500 mg twice a day and titrated depending on disease control and tolerability with a maximum dose of 3 g/day. Similar to other IMT monitoring, patients are evaluated every 6 weeks and blood work is obtained to assess CBC with differential, renal panel, and liver function testing. The most appropriate application of MMF is to utilize it as a corticosteroid-sparing, first-line, monotherapy or as an adjunctive immunosuppressive agent for active OCP [68, 70, 80–82, 87].

Cyclophosphamide

Cyclophosphamide (Cytoxan®), a nitrogen mustard derived alkylating agent, became the eighth cytotoxic anticancer medication to be approved by the United States Food and Drug Administration [88, 89]. The first use of cyclophosphamide in ocular conditions was in 1952 to treat idiopathic uveitis [90] and since then it has been used to treat various ocular inflammatory diseases [91, 92]. Cyclophosphamide generates immunomodulatory effects on rapidly proliferating cells, by alkylating nucleophilic groups on DNA bases leading to cross-linking of DNA bases, abnormal base pairing, or DNA strand breakage. The end result is damage to cells undergoing mitosis and consequently suppression of lymphocyte function (B cells more than T cells) [1, 92, 93].

Pujari et al. assessed the outcomes of cyclophosphamide therapy as a single immunosuppressive agent during follow-up, with or without local or systemic corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs), for treating non-infectious ocular inflammation. Of the 215 patients in this study, 45.6 % had OCP, being the most common diagnosis in affected eyes. Results revealed that within 6 months, 43 % of patients with OCP had complete control of inflammation, sustained over at least two visits spanning at least 28 days. Success continued to improve, complete inactivity was observed in 68.7 % patients with OCP by 12 months. Disease remission leading to discontinuation of the medication occurred at the rate of 0.32/person-year and 63.1 % of patients achieved remission at or prior to 2 years [92]. Overall, cyclophosphamide achieved beneficial effects with sustained control of inflammation among non-infectious ocular inflammatory cases in 49 and 76 % by 6 and 12 months respectively [92].

Elder et al. conducted a prospective study among 19 eyes of ten patients diagnosed with either severe OCP or marked OCP who previously failed other systemic immunosuppressive therapy. They were treated with cyclophosphamide and short-term high dose oral prednisolone. All patients were treated with oral cyclophosphamide at an initial dose of 1.5–2.0 mg/kg/day and oral prednisolone 60 mg/day or 80 mg/day and other oral immunosuppressive agents were discontinued. All but one patient were treated with cyclophosphamide for longer than 6 months. The reason for discontinuing treatment in one patient was due to unpleasant feelings of being distant from the world, 'like being on [recreational] drugs'. The goal lymphocyte count was $0.5–1.0 \times 10^9$/l, which was accomplished on a maintenance dose ranging from 50 to 150 mg/day. When clinical response was observed, prednisolone was reduced and when ocular and systemic features were clinically stable, prednisolone was stopped completely. The duration of prednisolone ranged from 4 to 8 months. The results of this study revealed ocular inflammation resolved in 15 eyes in a mean time of 2.4 months. During this study two eyes perforated; one from acute microbial keratitis and the other from progressive corneal thinning. Throughout the study, systemic infections requiring antibiotics did not develop in any of the patients. Progressive cicatrization was observed in 21 % of inflamed eyes (4 out of 19 eyes). Overall, these results suggest cyclophosphamide plus short term high dose oral prednisolone effectively controls severe ocular inflammation seen in OCP, although progression of ocular cicatrization might be inevitable in some cases [89]. Mondino et al. [10, 94] and Foster et al. [5, 95] reported findings confirming Elder et al.'s work, describing oral cyclophosphamide and short-term high dose prednisolone to be the most reasonable therapeutic regimen for adequate control of ocular inflammation and prevention of cicatrization among OCP patients.

Intravenously (IV) administered cyclophosphamide is used for rapid ocular inflammatory arrest, specifically prior to ocular surface surgery. High dose oral prednisone is also initiated simultaneously; dosed 1 mg/kg/day with a maximum dose of 60 mg/day and tapered weekly. Inflammation that has failed to respond to less potent immunomodulatory therapy is also treated with pulse IV cyclophosphamide therapy [96, 97]. IV cyclophosphamide is dosed at 1 g/m^2 body surface area every 2 weeks. The dose is adjusted depending on the patients' response and tolerability to treatment, and white blood count (WBC) with an optimal range of 3.0 $\times 10^3$/μL to 4.5 $\times 10^3$/μL. Oral dosing given in 100–150 mg/day range ("full" doses) appear more likely to succeed (controlling inflammation compared to doses of <100 mg but more likely to lead to dose-limiting toxicity) than lower doses [92]. Good hydration is encouraged, 8–10 cups of non-caffeinated fluid daily to prevent bladder toxicity especially with oral cyclophosphamide and hydration is supplemented with infusions for IV cyclophosphamide [91].

Careful consideration is exercised before starting cyclophosphamide; it is reserved for vision-threatening ocular diseases which have previously failed less potent immunomodulatory therapy or non-infectious ocular inflammatory cases associated with systemic disease. After treatment with cyclophosphamide, a higher rate of medication-free remission has been reported compared to methotrexate [38], azathioprine [54], mycophenolate mofetil [83] and cyclosporine [98]. However,

given the side effect profile of the medication, diligent monitoring by an ophthalmologist and commitment to compliance by the patient are fundamental to achieve optimal results.

Pujari et al. found that the most common side effects leading to discontinuation of cyclophosphamide are leukopenia and cystitis/blood in the urine, seen in 18.1 and 7.7 % respectively within the first year of therapy. The most common opportunistic infection leading to discontinuation is *Pneumocystis carinii*, reported in 3.0 % of the patients in the first year [92]. Cyclophosphamide increases the risk of malignancy, especially bladder carcinoma [9, 89, 99] and increases overall cancer mortality [49, 100–103]. Therefore, the use of cylcophosphamide is limited to 1 year due to the increased risk of developing cancer [91]. Also, it crosses the placental blood barrier and is excreted in breast milk, thus is classified as a teratogenic medication and contraindicated if a patient is breastfeeding [104, 105]. Although the potential side effects of cyclophosphamide are greater than alternative immunosuppressive agents, its application should not be deferred or delayed under appropriate circumstances when this medication is indicated given its success rates of remission and vision-saving capacity [92].

Close monitoring is especially emphasized with the use of cyclophosphamide. CBC with differential is required every other week for IV cyclophosphamide to ensure the WBC is within the optimal range. For both IV and oral cyclophosphamide, monitoring CBC, renal panel, liver function enzymes, and urine analysis every 6 weeks is endorsed. Being that cyclophosphamide is recommended to be employed for no longer than 1 year, patients are transitioned to other IMT (i.e., MTX, azathioprine, mycophenolate) to achieve 2 full years of corticosteroid-free remission.

Plasmapheresis

Plasmapheresis refers to extracorporeal separation of blood components resulting in filtered plasma. Methods used in plasmapheresis to achieve filtered plasma are centrifugation, double filtration plasmapheresis (DFPF) and a combination of both techniques [106, 107]. It has been proven to be effective in the variety of the diseases, especially in those in which circulating antibodies are the main pathogenesis factor. Clinical indications are broad and include more than 60 diseases [108]. Although there is no formal recommendation in using plasmapheresis in treatment of bolus pemphigoid, several reports advocated its beneficial application in conjunction with immunosuppressive therapy in controlling severe or refractory cases, specifically with persistent ocular involvement [109–112].

Clinical indications of plasmapheresis in mucus membrane pemphigoid include rapid control of severe active disease when corticosteroids and immunosuppressive dosage reduction is needed, especially in patients with multiple comorbidities such as diabetes, or when above treatments are contraindicated and in resistant drug therapy diseases [113, 114].

The most effective method is 40–60 ml/kg plasma exchanges as often as every other day. In each cycle, five to ten plasma exchanges usually are performed. Automated centrifuge-based technology is the simplest, easiest and most used technique in the U.S. [115]. However, due to subsequent FFP or human albumin infusion, the risk of disease contraction such as hepatitis and AIDS is present. Other adverse complications include allergic reaction with fever, chills, hypotension and procedure complications including vein puncture, thrombosis and pneumothorax [116].

To avoid rebound phenomena, plasmapheresis should be accompanied by an immunosuppressive therapy. Turner et al. reported complete remission in four out of seven patients with pemphigus vulgaris with five series of plasma exchanges over an average of 8 days. In all cases, intravenous cyclophosphamide was administered immediately after plasmapheresis to prevent rebound flare [117]. There are also two reports on combination apheresis and cyclophosphamide in patients with mucus membrane pemphigoid [118, 119]. Hashimoto reported a 73-year-old man with anti-epiligrin cicatricial pemphigoid and ocular lesions resistant to conventional therapy successfully controlled with plasmapheresis. These cases suggested a possible role of plasma exchange treatment of otherwise refractory cases.

However, clinical trials evaluating plasmapheresis' efficacy among OCP patients are absent. The current data available is based on case reports or its effectiveness in other autoimmune diseases. Therefore, given the life threatening side effect profile and lack of evidence of its efficacy in OCP, plasmapheresis is not a recommended therapy to treat OCP.

Intravenous Immunoglobulins and Rituximab

Intravenous immunoglobulins' (IV-Ig) applicability among ocular autoimmune diseases originates from its efficacy in re-regulation of the immune system through, among other mechanisms, idiotypic anti-idiotypic regulatory network manipulations. IV-Igs are retrieved from pooled human plasma from multiple donors [120]. The precise mechanism of action of IV-Ig as an anti-inflammatory and immunomodulating agent is yet to be elucidated. However, some of the proposed effects it has on the immune system are the following: (1) modulation and blockage of Fc receptors on the surface of macrophages; (2) modulation of the complement system; (3) reduction in titers of pathogenic autoantibody; (4) induction or suppression of the production of cytokines; (5) neutralization of toxins; (6) modulation of cell proliferation, apoptosis, and demyelination; (7) alteration in sensitivity to corticosteroids [121–123].

Systemic immunosuppressive therapy is the mainstay treatment for OCP. Nonetheless, multiple studies have shown some cases progressing while treated with IMT [50, 95, 124, 125] and a risk of advancing to end-stage OCP [126]. Therefore, when conventional approach fails to adequately control disease activity, achieve clinical remission or is intolerable to IMT side effects, IV-Ig is an appropriate alternative treatment option.

Foster et al. in a preliminary, uncontrolled study were the first to assess the safety and effectiveness of IV-Ig for treating OCP among ten patients, who were otherwise resistant to conventional IMT. IV-Ig infusions were administered at a dose of 2–3 g/kg/cycle, divided over 3 days and repeated every 2–6 weeks. The duration of therapy ranged from 16 to 23 months (mean of 19.3 months) without medication induced side effects. Results revealed termination of clinical progression and resolution of chronic conjunctivitis in all of the ten patients [127].

Letko et al. evaluated the clinical outcomes of IV-Ig therapy to conventional IMT among patients with OCP. Patients were enrolled in the study when ocular involvement of MMP was noted and confirmed by biopsy. At the time of enrollment into this study, all patients were diagnosed with stage 2 OCP. They were placed into two groups, group A and group B, each consisted of eight patients. Both of these groups were studied at the same time. Group A patients were treated with IV-Ig as monotherapy while group B patients were treated with conventional IMT or in combination with systemic corticosteroids. All of the patients were followed for a minimum of 18 months after diagnosis of OCP. The mean length of therapy was 24 months (range 16–30) for group A and 45 months (range 21–90) for group B. The median time from initiation of therapy to achieving clinical remission was 4 and 8.5 months in group A and B, respectively, with a statistically significant difference ($P < 0.01$). Recurrence of ocular inflammation was not observed in any of the patients in group A. On the other hand, in group B, recurrence was noted in five patients. All of the eight patients in group A, at the last follow up visit, revealed no progression of their ocular inflammation and both eyes in each patient were quiescent. On the contrary, at the last follow up visit, four of the eight patients in group B progressed from stage 2 to stage 3 and some level of conjunctival inflammation was observed in five patients. The findings of this study demonstrate encouraging outcomes for IV-Ig application to halt disease progression and achieve remission, making it a favorable alternative to conventional IMT among patients with OCP [126].

Sami et al. studied 15 patients with severe MMP refractory to systemic corticosteroids and IMT who then were treated with IV-Ig therapy. These patients' quality of life during this study was evaluated: first, before starting IV-Ig therapy, and second, at the last visit. A numeric scoring system was used, assigning a score based on the symptoms of the disease and the side effects of treatment affecting their lifestyle. The scoring system was as follows: (1), poor; (2), unsatisfactory; (3), livable; (4), reasonably good; (5), high quality of life. Among the 15 patients, the average score at the last visit was 4.7 [128].

RTX is a monoclonal antibody against CD20 protein, mainly targeting B-cells [129]. Combination treatment regimen with rituximab (RTX) plus IV-Ig is an effective modality to treat OCP, stage 3 or 4, moderate to severe inflammation, rapidly progressive, or recalcitrant to conventional IMT. Foster et al. conducted a preliminary report studying the efficacy and safety of combination therapy of RTX and IV-Ig compared to other IMT among OCP patients. A total of 12 OCP patients were evaluated. Six patients were in study group and six patients were in

control group. The study group patients received RTX plus IV-Ig while control group received more aggressive IMT but not RTX and IV-Ig. Prior to each infusion, complete blood count and complete metabolic profile were checked. Dosing for IV-Ig was 2 g/kg divided over three consecutive days and this is repeated at a monthly interval. Rituximab dosing is 375 mg/m^2 body surface area once a week for 8 weeks and then switched to once a month interval. The average follow up was 57.5 and 55.5 months in the control group and the study group, respectively. Results showed all patients in the study group did not have progression of their OCP and visual acuity was stable. Patients in the control group all had progression of their OCP and deterioration of their vision. Immediate or delayed side effects were not observed in any of the patients in the study group. Employing combination regimen of RTX and IV-Ig successfully arrested progression of the disease and as a result restored the patients' quality of life [129]. The combination therapy of IV-Ig plus rituximab has shown to be very effective in attaining durable remission. Therefore, this combination therapy is favored for refractory cases of OCP.

Prior to the study conducted by Foster et al., reports of RTX application in treating OCP were based on case reports. Ross et al. reported a patient with severe OCP who failed oral prednisone, dapsone, and cyclophosphamide but showed response to RTX infusions. However, adjuvant therapy with oral prednisone and MMF was required to achieve remission [130]. Schumann et al. described a patient with OCP who was unresponsive to dapsone and cyclophosphamide who then showed positive outcomes after receiving four RTX infusions [131]. Concomitant therapy was administered in this patient with intravenous and oral corticosteroids. Schmidt et al. observed partial response in a MMP patient after four infusions of RTX with accompanying therapy of pulse dexamethasone and cyclophosphamide therapy. When RTX is utilized as monotherapy or in combination with other immunosuppressive therapy, the primary concern is a high risk of systemic infections potentially leading to lethal septicemia [132, 133]. Employing RTX in combination with IV-Ig, an immunomodulating agent without immunosuppressing, as adjuvant therapy, has shown to be an appropriate and safe therapeutic regimen under indicated circumstances. The study conducted by Foster et al. reported no deaths or infections in any of the patients treated with RTX.

Conclusions and Future Directions

The treatment of OCP has certainly evolved over several decades when ophthalmologists have encountered refractory disease. The majority of patients will initially require conventional immune suppression for control of their OCP. However, biologic treatments are more target specific, and treatments such as rituximab and IVIg have the potential to improve clinical outcomes and quality of life. These results could provide a basis for the earlier usage of targeted therapies in the treatment algorithm of OCP.

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