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Update

Update on ocular cicatricial pemphigoid and emerging treatments

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ABSTRACT

Mucous membrane pemphigoid is a systemic disorder that primarily affects mucous membranes. When localized to the conjunctiva, it is known as ocular cicatricial pemphigoid, a potentially blinding disease. Ocular cicatricial pemphigoid is an indication for systemic immunosuppressive treatment to achieve adequate remission. Immunosuppressive agents are selected with a "stepladder" approach, commencing with medications having the fewest side effects. We provide an update of the literature on immunomodulatory agents since 2011 as additional treatment modalities have been explored in the last 4 years.

1. Introduction

Mucus membrane pemphigoid (MMP) is a multisystemic autoimmune disease that characteristically manifests as blisters on mucosal surfaces such as the oral cavity, larynx, pharynx, esophagus, eye, nasal cavity, and genitalia. MMP has lethal potential and may result in serious irreversible scarring. Some cases are isolated to the conjunctiva, and this clinical manifestation is known as ocular cicatricial pemphigoid (OCP).[25] OCP is a blinding subepithelial blistering disease that is bilateral, asymmetrical, and chronically progressive. OCP has a strong association with the human leukocyte antigen DQ. OCP may cause relapsing or chronic conjunctivitis with conjunctival cicatrization, secondary corneal vascularization, and opacification. Currently, a stepladder approach is used to control OCP and its complications. Significant advances have been made in the last 4 years with respect to the management and treatment of OCP.[10] A number of pharmaceutical trials have been conducted to improve treatment of OCP.[29]

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2. Medications

Dapsone or methotrexate has been the first line of treatment in mild-to-moderate OCP. Adverse effects include skin rash, malaise, gastrointestinal tract problems such as vomiting and diarrhea, anemia, hepatotoxicity, and leukocytopenia. Complications caused by dapsone have led to discontinuation rates of 9/9,[6] 25/51,[24] and 28/90[20] in 3 separate trials. Because of these adverse effects and poor compliance rates, alternatives sulfapyridine and sulfasalazine are used with much lower risk of adverse effects.[29]

Mycophenolate mofetil (MMF) is a more effective treatment option than dapsone and sulfapyridine. In a recent long-term study on 19 eyes of 10 patients treated with MMF, there was complete control of inflammation in 11 of the 12 eyes in 6 patients (58%). These patients were diagnosed with MMP at Mondino-Foster stage IIIa or higher with a mean follow up of 6.1 years.[8] Daniel and colleagues achieved adequate control of inflammation in12 of 18 patients (70%); however, their follow-up period was short (1 year).[5] As a result of fewer side effects of MMF, there was a lower rate of discontinuation. They concluded that MMF should be the first choice treatment in OCP patients who do not have sight-threatening complications.[29]

Methotrexate and azathioprine are viable alternatives to MMF. McCluskey and colleagues achieved complete control of conjunctival inflammation in 83% (10/12) of patients treated with MMF after administering a course of methotrexate over 15 months.[22] This study had a mean follow up of 30.2 months, leading McCluskey and colleagues to recommend methotrexate as an option for first-line treatment of OCP. Methotrexate, however, had more side effects than MMF. The most serious side effect associated with long-term therapy was hepatic and pulmonary fibrosis. Recent studies have also demonstrated the low efficacy of azathioprine, which have also led to the drug being categorized with dapsone and sulfapyridine owing to their similar side effects and discontinuation rates.[29]

There are new drug regimens for cyclophosphamide, a nonspecific alkylating agent. This is the treatment of choice in ocular inflammation secondary to a number of other inflammatory conditions and is the first choice in OCP and Behçet disease when vision loss is imminent.[1,12,15] Currently, pulsed intravenous cyclophosphamide is one of the most effective treatments in patients with severe or stubborn ocular inflammatory conditions.[9] This, however, produces adverse reactions in some patients. Trials carried out by Friedman and colleagues have shown that low-dose pulsed intravenous cyclophosphamide treatment is likely to be better tolerated in OCP, especially with elderly patients who commonly have other illnesses. This lower dose decreases the toxicity in accordance with the Euro-Lupus trials.[18,19] The dosage used was of 500 mg, with a total dose of 4 g over 8 sessions. The only adverse reaction was transient nausea. They concluded that the ideal regimen for elderly suffering from autoimmune OCP was a monthly pulse of intravenous cyclophosphamide at a fixed low dose of 500 mg.

Intravenous immunoglobulin (IVIg) therapy is, at present, only considered in patients when conventional treatment fails or is causing severe complications.[29] Another study by Sami and colleagues presented long-term results of patients with stage III OCP with multiple cycles of IVIg therapy.[27] Clinical remission was sustained in 80% (8/10) of patients, with a mean follow-up period of 35 months; however, 2 of the patients interrupted their treatment regimen, and this led to the progression of vision loss. They also reported that <1% of patients suffered from adverse effects.

There has also been a number of antitumor necrosis factor α drug trials performed in recent years.[29] El Darouti and colleagues found that OCP patients who did not respond to cyclophosphamide or IVIg were stable or improved after undergoing treatment with a biologic agent,[11] 25 mg of etanercept subcutaneously twice a week. A monotherapy was also used with infliximab 5 mg/kg intravenously. Another antitumor necrosis factor α drug, pentoxifylline, was combined with cyclophosphamide and corticosteroids. Patients showed a better clinical response, 80% versus 60%, and no relapse during the 18-month follow-up period compared to those who received only corticosteroids and cyclophosphamide. Patients who were treated with pentoxifylline had histopathologic improvement of conjunctival fibrosis and inflammatory infiltrates.

Foster and colleagues retrospectively examined the combination of rituximab and IVIg administered to patients who had a poor response to IVIg monotherapy. This was performed for a period of 1 year on 6 patients with blindness in 1 eye and persistent ocular inflammation. These patients were treated with a median of 25 IVIg infusions and 12 rituximab infusions. Improvement in visual acuity was noted 11 months later with no further deterioration.[14] Potential complications of rituximab such as infection could, however, be fatal.[2]

To better understand the disease pathophysiology, a study in 2012 by Rashid and colleagues identified the epitopes within β4 integrin to which antibodies produced in patients with OCP, MMP, or OCP plus MMP bind.[25] Sera were collected from 7 patients with active OCP and also from 8 patients who had MMP and OCP at the Center for Blistering Diseases in Boston, Massachusetts. Serologic confirmation *via* Western blot analysis highlighted the presence of antibodies bound to β4 integrin subunit proved to be a crucial diagnostic marker in the detection of OCP and MMP.[4] Autoantibody titer of integrin β4 was high during the active phase, and levels declined with improvement.[21] These tests showed that cloned fragments of the OCP and MMP sera were bound to the IC3.0. Sera of these patients with OCP and MMP involvement were bound to IC3.0 IC3.3 IC3.4 IC3.4.1 IC3.6 IC3.6.1. Therefore, the ability of the sera to bind to multiple epitopes demonstrated the principle of epitope spreading.[26] In this study, sera of patients with active OCP were seen to bind with the IC3.4.1 acting as the putative OCP antigen.[25]

Because OCP is a systemic disease, topical medications are used only as a temporary measure to relieve symptoms before systemic therapy has time to induce stable quiescence of the ocular inflammation. Topical and subconjunctival corticosteroids may offer short-term relief of symptoms but are ineffective in halting disease progression.[13] In addition to the use of topical corticosteroids, topical formulations of the calcineurin inhibitors, cyclosporine A, and tacrolimus have been used for the treatment of OCP. Holland and colleagues noted lack of a therapeutic response to topical cyclosporine in a small series.[17]