Peer Review File

Article information: https://dx.doi.org/10.21037/aes-22-41

Reviewer A:
Thank you very much for your submission. Article is well-written and easy-to-follow. Important topic.

Comment 1: -consider mentioning the risk for disease flare with biopsying the conjunctiva

Reply 1: Added to manuscript in line 302-303

Changes in Text: It is important to note that performing a conjunctival biopsy may exacerbate conjunctival inflammation

Comment 2: -consider describing the factors that can contribute to false negative DIFs (important because need therapy if high clinical suspicion)

Reply 2: Added to manuscript in line 314-317.

Changes in Text: Factors such as poor tissue handling, using incorrect tissue preservation media, delayed transport to the lab and utilizing a lab with limited experience in handling conjunctival specimens can all contribute to negative results.

Comment 3: -might be nice to have example clinical photos for stage 1-4 Foster and Mondino if not too much trouble

Reply 3: I was able to obtain images from my own patient library and from a colleague (Dr. Ninani Kombo) for the Foster stages 1-4 as shown in Figure 1 thru Figure 7B. However, I was not able to obtain clinical photos for the Mondino stages.

Comment 4: -consider adding some evidence for MTX for advanced disease (and also may help to more explicitly distinguish mild-moderate-severely actively inflamed eyes vs advanced staged scarring in the context of selecting appropriate therapy) PMID: 30235689

Reply 4:
- Agree on adding further details in regards distinguishing mild to moderate to severely actively inflamed eyes as outlined in line 185 – 189.
- In regards to selecting appropriate therapy it is outlined in Table 4 based on Foster staging.

- Added an additional paragraph describing the use of low dose MTX for patients with advanced disease (Stage 3 & 4) by Shi et al. (PMID30235689) – Line 452-456.

Changes to Text:

Line 185-189
Conjunctival inflammation is characterized by the degree of conjunctival injection and chemosis ranging from mild to severe states. It is also important to tease apart contributing factors such as trichiasis and ocular surface dryness that can contribute to conjunctival injection. Degree of cicatrization is demonstrated by subepithelial fibrosis, symblepharon, and forniceal shortening

Line 273-274- The natural clinical course of OCP has been characterized by early conjunctival injection typically attributed to allergic conjunctivitis or dry eyes. It is followed by chronic conjunctival scarring and shrinkage that progresses to symblepharon, trichiasis, corneal neovascularization and keratinization. Without treatment or in aggressive recalcitrant cases it can lead to bilateral blindness.

Line 452-456 - In comparison, Shi et. al conducted a retrospective case series, where low dose methotrexate was used in patients with advanced disease with 4 patients at Foster stage 3 and 7 patients at stage 4. Conjunctival inflammation was noted to improve in 5 patients with improvement in ocular surface keratinization, however, 3 patients noted no improvement (68)

Comment 5: -consider mentioning the steroid-sparing capacities of some of the immunosuppressives, which may help maintain disease control after it is achieved with steroids and facilitate tapers. PMID: 34929217 PMID: 23132447

Reply 5: Added to manuscript in line 372-376.

Change in Text: Line 372-376- The various immunomodulatory therapies outlined in this review are used not only for OCP but also for other ocular inflammatory diseases for their steroid-sparing properties, maintaining disease control and facilitating systemic steroid tapering. Close monitoring for side effects and blood monitoring labs are recommended for all patients taking immunomodulatory agents.

Comment 6: -I would mention lab monitoring is prudent for mycophenolate- related to the above, consider comparing the costs of various drugs and also expected time to response even if just qualitatively described based on what we know about the medications (for instance steroids and IVIG being much faster acting than say MTX). PMID: 31356420

Reply 6: Added comment about blood monitoring for all patients taking immunomodulatory agents in line 374-376. Added comment for blood monitoring for blood monitoring for patients on MMF in line 471- 472 in the MMF section.

Change in Text:

Line 374 - 376- Close monitoring for side effects and blood monitoring labs are recommended for all patients taking immunomodulatory agents.

Line 471- 472- Blood monitoring with complete blood cell count, liver functions tests and basic metabolic panel is also indicated.

-- Discussed the impact of cost in choosing therapy and in generic terms how anti-metabolite therapies may be more affordable compared to recently developed biologics in lines 266- 271. The exact cost of therapy is ultimately determined by pt's insurance or lack of coverage, so I did not include exact values.

Change in Text: Line 392-397

Cost of therapy is another factor to consider since insurance coverage will determine the cost to the patient with many of these agents needing prior authorization. Anti-metabolite therapies such as methotrexate, mycophenolate and azathioprine tend to be more affordable given their long-standing and generic availability compared to more recent biologic therapies such adalimumab, rituximab and infliximab that tend to be more expensive.

--Added expected times of response to:
Methotrexate- **Line 447**- Expected onset of action ranges from 3 to 6 weeks (66).
Mycophenolate mofetil- **Line 464-465**- Its onset of action can range from 2 weeks to 3 months (66).
Azathioprine – **Line 483-484**- Response to therapy can occur from 1 to 3 months.
Cyclosphosphamide- **Line 513-514**- while the response to cyclophosphamide takes effect in 6 to 8 weeks.

Rituximab – **Line 560-561**- Onset of action can occur in about 12 weeks (66).

Comment 7: -can you elaborate on why methotrexate considered before mycophenolate?

Reply 7: Added comment on line 442-44

Change in Text: Line 442-444- Its weekly dosing can facilitate patient compliance and facilitate its use as first line therapy compared to other agents such as mycophenolate or azathioprine that need to be taken on a daily basis.

Comment 8: -good job using generic names but would double check (eg. Rituxan -> rituximab, ln 263)

Reply 8: Modified to Rituximab in line 402.

Comment 9: -not sure about the sentence "corticosteroids do not provide enough immunosuppression for disease control", recommend sticking with unfavorable long term due to side effects and flares upon tapers

Reply 9: Modified sentence to the following in Line 494-496

Change in Text: Line 494-496- However, corticosteroids should not be used as monotherapy for long-term management due to unfavorable side effect profile and high risk of disease recurrence after tapering and discontinuation.

Comment 10: -make it clear in the conclusion that treatment ladder is still not well defined due to the uncontrolled nature of the studies and small sample sizes we have from which to draw conclusions from

Reply 10: Agree on clarifying this point as follows in Line 649-652

Change in Text: Line 649-652- Current treatment protocols may vary given the rare nature of this disease, small sample sizes and uncontrolled nature of published studies.

Comment 11: -would also describe the types of studies and sample sizes to improve clarity regarding strength of evidence

Reply 11: Please refer to new Table 5 (in supplemental materials) that summarizes types of studies discussing therapies that were included in this review, # patients, immunomodulators studied and response rates.

Comment 12: -also would make it clear in the conclusion that cicatrization can progress despite control of inflammation

Reply 12: Agree on this point and the following has been added in Line 651-652.

Change in Text: Line 651-652-Even despite immunosuppressive therapy and control of conjunctival inflammation, cicatrization may still progress

Reviewer B:

After carefully reading this article, I think that some aspects have to be explained once again:

Comment 1: lines 97-98 please add percentage value for young adult and pediatric patients. Also, please define "young adult"

Reply 1: I have added the number of cases reported as of 2019 of pediatric patients (2-18 yrs of age). I do not have a percentage value for younger adults. Younger adults being defined as <60 yrs of age as noted in the study by Rauz et al. comparing patients <60 yrs vs pts >70 yrs.

Changes in Text: Line 101- 104 - However, younger adults (age <60 years) have also been observed to present with severe ocular and systemic disease, including mucocutaneous involvement (13). It is a rare condition in the pediatric population, with about 20 cases reported in the age range of 2 months to 18 years manifestations (14, 15).

Comment 2: lines 104 please add the aim of the review, precise a "gap in knowledge about this disease"

Reply 2: Agree on clearly stating the aim for this review and included the following pararaphs in Lines 125- 138.

Change in Text: Line 125-138: Multiple review articles discussing OCP, its diagnosis and treatment modalities have been published in the past to assess emerging therapies that can be effective and serve as additional tools in the efforts to halt the progression of this sight-threatening disease. However, most reported data on current treatments are from case reports, case series and uncontrolled clinical trials. There is a lack of randomized, controlled double-blind studies comparing the response to these agents. As a result, treatment algorithms continue to be primarily influenced by the expertise of the treating clinicians.

This review aims to thoroughly discuss the immunopathogenesis, clinical features, and diagnosis of patients with OCP. It will focus on the current immunomodulators utilized for disease management and proposed stepladder strategies. This review will discuss and provide an update on the role of combination therapy, novel use of biologics as well as the recent use of adrenocorticotropic hormone analog in severe recalcitrant cases. The importance of a multidisciplinary approach will be emphasized to optimize clinical care, outcomes and quality of life of patients with ocular cicatricial pemphigoid.

Comment 3: I think that number of references and their date were chosen correctly. However, I suggest adding the table (perhaps in supplementary materials) to

summarize the impact of studies used in this review paper. The table should include information: Type of Study Authors Number of Cases (n) Results (95% Confidence Interval)

Reply 3: Please refer to new Table 5 (in supplemental materials) that summarizes types of studies discussing therapies that were included in this review, # patients, immunomodulators studied and response rates.

Comment 4: I wonder if the authors considered the systematic -review

Reply 4: I primarily focused on Clinical practice review.

Comment 5: Please clearly describe in which aspects this review is different from other one about this disease.

Reply 5: I provide an updated and thorough discussion including the current immunomodulators utilized for OCP as wells as the role for combination therapy (such as IVIG/ Rituximab), novel use biologics and recent use of adrenocorticotropic hormone analog as reported by Sharon et al. as recently as 2022.

Changes in Text: Line 132-138- This review aims to thoroughly discuss the immunopathogenesis, clinical features, and diagnosis of patients with OCP. It will focus on the current immunomodulators utilized for disease management and proposed stepladder strategies. This review will discuss and provide an update on the role of combination therapy, novel use of biologics as well as the recent use of adrenocorticotropic hormone analog in severe recalcitrant cases. The importance of a multidisciplinary approach will be emphasized to optimize clinical care, outcomes and quality of life of patients with ocular cicatricial pemphigoid.
.

Comment 6: The graphical abstract should be very useful to better understand this topic.

Reply 6: Please see attached graphical abstract

Editorial Comments

1. Abstract
Comment 1: We suggest the authors make a statement about the primary objectives of this review in the Abstract.

Reply 1: Agree on clarifying primary objects as included in line 56- 60.

Changes in Text: Line 56- 60- This review will address the immunopathogenesis, clinical features, keys to diagnosis and staging of patients with OCP. It will highlight the current immunomodulators utilized for disease management and proposed stepladder strategies. This review will discuss the updated roles of combination therapy, novel use of biologics as well as the recent use of adrenocorticotropic hormone analog in severe recalcitrant cases.

2. Introduction

Comment 2: (1) In the Introduction, also specify existing REVIEWS on the same topic. Based on this, highlight what unique information THIS REVIEW adds compared to the existing reviews.

Reply 2: I included the following paragraphs discussing other reviews and included Table 6 summarizing other review articles recently published on this topic.

Changes in Text: Line 125-138: Multiple review articles discussing OCP, its diagnosis and treatment modalities have been published in the past to assess emerging therapies that can be effective and serve as additional tools in the efforts to halt the progression of this sight-threatening disease. However, most reported data on current treatments are from case reports, case series and uncontrolled clinical trials. There is a lack of randomized, controlled double-blind studies comparing the response to these agents. As a result, treatment algorithms continue to be primarily influenced by the expertise of the treating clinicians.

This review aims to thoroughly discuss the immunopathogenesis, clinical features, and diagnosis of patients with OCP. It will focus on the current immunomodulators utilized for disease management and proposed stepladder strategies. This review will discuss and provide an update on the role of combination therapy, novel use of biologics as well as the recent use of adrenocorticotropic hormone analog in severe recalcitrant cases. The importance of a multidisciplinary approach will be emphasized to optimize clinical care, outcomes and quality of life of patients with ocular cicatricial pemphigoid.

Comment 3: (2) Please also specify the key question(s) identified for the review topic in the Introduction.

Reply 3: I have updated the Abstract and Introduction to include this.
Overall, the goal of the review is to highlight previously used agents such as MTX, MMF but also more recent emphasis on combination therapy (with IVIG/RTX), the role of biologics (etarnecept, infliximab) and most recently reports of using adrenocorticotropic hormone analog. May refer to Line 125-138.

Comment 4: 3. L. 152: Please consider change “Stage 2” and “Stage 3” to “Stage II” and “Stage III” to make the statement consistent.

Reply 4: Modified all stages to the number values (Stage 1,2, 3, 4) for consistency rather than using roman numerals.

Comment 5: 4. L. 263: When terms appear for the first time, the full English and abbreviation shall be used. Then, the abbreviation shall be used. Please add the full name of “IVIG”.

Reply 5: Intravenous immunoglobulin was added, now on line 402- 403.

Comment 6: Don’t forget to cite references for the sentences.

Comment 6 - (1) L. 276: “Dapsone has been noted to have the highest number of complications leading to its discontinuation in 3 different studies”.

Reply 6- (1): Added references 54, 63 and changed line text to various studies rather than 3 different studies

Comment 6 - (2) L. 281: “Sulfasalazine has been reported to inhibit T lymphocyte proliferation, reduce production of immunoglobulins and cytokines and inhibit neutrophil chemotaxis”.

Reply 6- (2): Added reference 63, and modified sentence to the following:

Change in Text: Line 423-424 - Sulfasalazine has been reported to inhibit proliferation of T-lymphocytes, decrease production of immunoglobulins and cytokines and hinder neutrophil chemotaxis

Comment 6 - (3) L. 430-433: “Adrenocorticotropic hormone (ACTH) is a melanocortin produced…refractory ocular inflammation”.

Reply 6- (3): Added references 108 and 109.

Comment 7 : 6. L. 418: Please consider cite more references for the sentence “Studies have shown elevated TNF-□ levels in the serum of patients…” to be consistent with the “Studies”.

Reply 7: Added reference 101

Comment 8: 7. Table 4

We suggest the authors make a statement about the information in the Table 4 in the footnote, especially what's the meaning of the arrow. For the authors' kind reference, Methotrexate can be an alternative if a patient has an incomplete response to Dapsone or is unable to tolerate it.

Reply 8: Table 4 has been modified according to the AES guidelines for sample tables. It is supposed to show a proposed algorithm for the different stages of the disease. The arrow indicates the next step that could be taken. This has been described in the footnote as requested.

Change in Text: Footnote added to Table 4 (line 604-610)
The systematic approach outlined indicates that for mild disease defined as Foster stage 1 to 3, initial therapy options include dapsone, however, methotrexate can be an alternative if a patient has an incomplete response or is unable to tolerate it. If methotrexate is not a viable option, then mycophenolate or azathioprine can be alternatives. The arrows indicate the possible next step in management. For severe disease defined as Stage 4, then combination therapy can be an option using cyclophosphamide with corticosteroids or rituximab with IVIG. Newer agents such as TNF-α inhibitors and adrenocorticotropic hormone analog can have a role for recalcitrant cases.

Comment 9: 8. Table formatting and copyright
Please pay attention to the Tables' formatting. Normally, researchers choose to use the trilinear table to present experimental data. It's also necessary to confirm the copyright of the Tables. Are the Tables original? Or, from an article in a journal (may require permission to use)?

Reply 9: The tables have been modified to trilinear format according to the AES guidelines provided for sample tables. The information presented on these tables is based on multiple sources (textbook, articles, lectures) and have been adapted for this review. See attached file with Tables only. I also reference the sources as for example for Table 3 on line 286.

Comment 10: 9. References formatting
Please kindly revise the references formatting as indicated
(https://aes.amegroups.com/pages/view/guidelines-for-authors#content-3-8) .

Reply 10: Reference formatting was modified according to AES guidelines with EndNote reference style download for AME journals

Changes in Text: All references were modified as noted on Reference table.

Comment 11: 10. Title Page

The title page should also include a running title of no more than 60 characters (including spaces); disclaimers (if applicable); word count; number of figures and tables.

Reply 11: Running title has been added in header as well as word count, # of figures and tables.

Changes in Text: Running title: OCP DIAGNOSIS AND MANAGEMENT