

July 26, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4243-Review.doc).

Title: Topical Biological Agents Targeting Cytokines for the Treatment of Dry Eye Disease

Author: Kyung Chul Yoon

Name of Journal: *World Journal of Ophthalmology*

ESPS Manuscript NO: 4243

The manuscript has been improved according to the suggestions of reviewers. Please refer to the following pages.

1 Format has been updated.

2 Revision has been made according to the suggestions of the reviewer

- (1) The number of words in the Abstract was changed to be more than 200.
- (2) Titles for the text were added.
- (3) The number of references was changed to be more than 50

3. The manuscript was edited by a professional English language editing company, American Journal Experts: <http://www.journalexperts.com>

Thank you again for publishing our manuscript in the *World Journal of Ophthalmology*.

Sincerely yours,



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RESPONSE TO REVIEWER #1 COMMENTS:

This is an interesting editorial that focuses on TNF alpha and B cell related treatment for dry eye and Sjogren's syndrome. This is an important area of ocular surface science and treatment. I think there is enough material in this writeup to make this a novel and meaningful writeup but I suspect that the title can be more specific and accurate, or alternatively, mention a few other types of upcoming biological treatment that may be relevant to dry eye. If the editorial is about biologics in general in dry eye, consider including some of these to make the writeup more balanced: 1.

Biologics in the targeting of cell adhesion or leukocyte trafficking (integrins). 2. Biologics in the targeting of cytokine signaling such as JAK inhibitors. 3. Role of meibomian gland dysfunction in Sjogren's syndrome. Some biologics can target that, for example topical vitamins that target keratinization. 4. The author correctly mentioned autologous serum. It should be mentioned that variants of plasma and serum are also forms of biologics. 5. Biologics in the protection of the ocular surface against ocular surface stress in dry eye. How about carnitine and osmoprotectants that reduce MAPK signaling? (Even though these may not be true biologics) 6. How SNPs of TNF alpha affects the systemic TNF alpha response to omega3 lipid intake. Pharmaforte even has a topical omega3 preparation.

→ Thank you for your important comments. In this manuscript, I wanted to describe future possibility of application of topical biological agents mainly targeting cytokines (Not in general in dry eye) which has been known as key molecules in the pathogenesis of dry eye disease. Therefore, instead of mentioning other types of upcoming biological treatment (from 1 to 6), the title and content in the manuscript was made more specific as follows: "Topical biological agents targeting cytokines for the treatment of dry eye". In addition, in consideration of the reviewer's comment, some of other biological agents were additionally described in the text as follows: "As biological products, variants of serum and plasma, such as autologous serum, umbilical cord serum, and platelet-rich plasma, can also be used topically in severe dry eye.", "Among many targets including cytokines, cytokine signaling pathways, and cell adhesion or leukocyte trafficking, cytokines are the most commonly used therapeutic target for Sjögren's syndrome and inflammatory dry eye."

Specific comments:

1. Third paragraph line 3 'Infusion of topical...' is not good English as infusions normally refer to intravenous and such forms of treatment. Perhaps "Administration of..." is better?

→ I am sorry for the mistake. It meant infusions of intravenous form of the agent, not topical form. The words "infusions of a topical TNF- α agent" was changed to "application of a TNF- α agent."

2. Fourth paragraph line 1 'By contrast' is not as good as 'In contrast'

→ The words "By contrast" was changed to "In contrast".

3. Fourth paragraph line 3 Please specify what are ocular test results or rephrase

→ The test result was specified as follows: "ocular surface staining by lissamine green"

4. Fourth paragraph line 5 A short sentence to explain the relative importance of role of B cell versus T cell may be appropriate here.

→ A sentence was added as follows: "Although the marked inflammatory infiltrate in the affected glands includes a high percentage of T cell, there is abundant evidence that B cell hyperactivity is a main pathogenic factor in Sjögren's syndrome^[41]."

5. Sixth paragraph line 3 Adiponectin is structurally similar to TNF alpha. Please indicate if adiponectin is an antagonist of TNF alpha?

→ The sentence "Adiponectin can inhibit TNF- α and TNF- α -mediated activation of nuclear factor- κ B^[51,52]." was added.

6. Sixth paragraph line 6 The sentence on IFN induced apoptosis may benefit from one sentence explaining the role of IFN induced apoptosis in Sjogren's.

→ A sentence was added as follows: "CD4+ T-cell-produced IFN- γ plays a pivotal role in Sjögren's syndrome-like conjunctival epithelial apoptosis via activation of the extrinsic apoptotic pathway^[54]."

RESPONSE TO REVIEWER #2 COMMENTS:

This is a good and interesting editorial manuscript that focuses on TNF alpha and B cell related treatment for dry eye and Sjogren's syndrome.

→ Thank you.