A Hidden Concern in Ocular Rosacea

Sandra Lora Cremers, MD, FACS

March 2013
THUMP!

Sensing that he was about to doze off, the air bag on Wade’s computer rapidly deployed.
Rosacea, Boring and Not Glamorous?
Objectives:

1. Describe Epidemiology, Diagnosis, Pathophysiology, and Treatment of Rosacea and Ocular Rosacea

2. Discuss Recent Research Finding of Rosacea and Ocular Rosacea

3. Discuss Ocular Rosacea's Relationship to other Angiogenesis Based Diseases
Outline:

1. Case Presentations
2. Diagnosis and Details
3. Observations & Collaborations
4. A Hidden Concern
1. Case Presentations
Case Presentation:

79 yo white male presents complaining of "poor vision in right eye after cataract surgery. Worse than before the surgery"
Case Presentation:

BCVA: 20/50 OD, 20/30 OS

External exam:
Hello,
My name is R. I am a 79 year old white male.

Some 5 or so years ago, I began to have the first signs of Rosacea on my nose, constant itching with minor visual blemishes. I had not heard of the name ‘Rosacea’ at the time.

My physician advised to use an over the counter itch cream, but did not comment on the possibility that I might be in the early stages of Rosacea.

By now, the nose Rosacea had progressed to the visual stage with whelps and some enlargement of the nose.

I had cataracts. One required removal soon, and I arranged to have the surgery.

The Ophthalmologist apparently took no notice, nor precautions for the possible Ocular Rosacea being present, and performed the surgery.

After surgery, I had (and still have) a small macular anomaly which causes anything in the dead center of my vision to be ‘scrambled’, the peripheral vision is good, and the area of the anomaly is about half an inch at arm's length, increasing with distance.

This almost completely destroys depth perception.

I have seen 4 Ophthalmologist - Optometrist, none of which has identified the problem, but have recently prescribed treatment consistent with Ocular Rosacea. Hot eye compresses, artificial tears, and a topical Erythromycin Ophthalmic Ointment to the eye margins.

My questions are:

Did the presence of Ocular Rosacea in the eye region infect the eye during cataract surgery? (theories accepted) especially since the surgeon did nothing prior to cataract removal to cleanse the eye, and no antibiotics were administered before or after. After the surgery, and the anomaly was discovered, I was treated for edema, although there was no evidence of edema in either eye. (Timed series of photographs, using an intravenous dose of Angiography, a derivative of fluorescein)?

The second Ophthalmologist did (laser?) scans of both eyes, the right eye that has the macular problem showed what he described as 'an infection'.

For the following year, I had eye scans every 2 to 4 months...the anomaly was treated with Nevanac, an antibiotic eye drop, (nepafenac ophthalmic suspension) 0.1%.

The doctor did advise this eye drop was not designed for this type of infection, but was the only medication he knew of that could help.

Over the course of one year, the anomaly did subside, but stopped short of complete healing.
Unhappy patient because he perceived a missed diagnosis of ocular rosacea as the reason for less than expected vision after cataract surgery.
A Brief Historical Perspective
2. Diagnosis and Details
A Definition of Rosacea

Rosacea is a multifactorial, hyper-reactivity, vascular and neural based disease with a broad range of facial and manifestations where normal vasodilation is greater and more persistent and involves an autoimmune component where microscopic amounts of extravasated plasma induce localized dermal inflammation where repeated external triggers lead vasodilation, telangiectasias, redness with eventual fibrosis and hypertrophic scarring of the dermis.
Subtypes of ROSACEA

**Subtype 1:** FACIAL REDNESS
(erythematotelangiectatic rosacea) Flushing and persistent redness. Visible blood vessels may also appear.

**Subtype 2:** BUMPS AND PIMPLES
(papulopustular rosacea) Persistent facial redness with bumps or pimples. Often seen following or with subtype 1.

**Subtype 3:** SKIN THICKENING
(phymatous rosacea) Skin thickening and enlargement, usually around the nose.

**Subtype 4:** EYE IRRITATION
(ocular rosacea) Watery or bloodshot appearance, irritation, burning or stinging.
## Differential Diagnosis of Rosacea

<table>
<thead>
<tr>
<th>Disease</th>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne vulgaris</td>
<td>Papules, pustules, erythema</td>
<td>Comedones</td>
</tr>
<tr>
<td>Steroid rosacea</td>
<td>Erythema, papules,</td>
<td>Related to topical application of corticosteroids, tacrolimus (Protopic,</td>
</tr>
<tr>
<td></td>
<td>pustules, telangiectasias</td>
<td>Astellas/Fujisawa), and pimecrolimus (Elidel, Novartis)</td>
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<tr>
<td></td>
<td>Central third of face</td>
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<tr>
<td>Seborrheic dermatitis</td>
<td>Blepharitis</td>
<td>Scaling, eczematous changes</td>
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<td></td>
<td>Erythema</td>
<td>Paranasal, nasolabial, extrafacial distribution</td>
</tr>
<tr>
<td>Perioral dermatitis</td>
<td>Erythema, papules</td>
<td>Perioral distribution</td>
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<tr>
<td></td>
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<td>Smaller lesions</td>
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<tr>
<td></td>
<td></td>
<td>No telangiectasia, flushing, or blushing</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Erythema, papules, pustules</td>
<td>Follows size and shape of causal agent</td>
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<tr>
<td></td>
<td>Burning, stinging</td>
<td>Scaling</td>
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<tr>
<td></td>
<td></td>
<td>Spongiosis and parakeratosis on histology</td>
</tr>
<tr>
<td>Photodermatitis</td>
<td>Erythema, papules, plaques</td>
<td>Seasonal</td>
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<tr>
<td></td>
<td></td>
<td>Usually extrafacial</td>
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<tr>
<td>Lupus</td>
<td>Erythema</td>
<td>Malar distribution</td>
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<td></td>
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<td>Photosensitivity</td>
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</tbody>
</table>
## FDA-Approved Topical and Oral Therapies for Rosacea

<table>
<thead>
<tr>
<th>Topical Antibiotics</th>
<th>Non-antibiotics</th>
<th>Oral Antibiotics</th>
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<tbody>
<tr>
<td>Metronidazole 0.25%, 0.75%, 1% cream, gel, lotion (e.g., Metrocream, MetroGel)</td>
<td>Azelaic acid 15% gel (Azelex)</td>
<td>Doxycycline, USP (Oracea Capsules) 40 mg once daily (30-mg immediate-release and 10-mg delayed-release beads)</td>
</tr>
<tr>
<td></td>
<td>Sodium sulfacetamide 10% and sulfur 5% combination, lotion, cream, pledgets, short-contact preparation, cleanser (Sulfacet)</td>
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<tr>
<td></td>
<td>Sodium sulfacetamide 10% lotion</td>
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<td></td>
<td>Sodium sulfacetamide 10%, sulfur 5%, sunblock lotion</td>
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</tbody>
</table>
## Non-FDA-Approved Oral Treatment of Rosacea

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<tr>
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<tbody>
<tr>
<td>Tetracycline 500 mg b.i.d.</td>
<td>Azithromycin 250 mg t.i.w. (Zithromax)</td>
<td>Penicillin 2.4 million units q.d.</td>
<td>Oral contraceptives (Ovosiston)</td>
<td>Ivermectin 250 μ/kg q.w. (Stromectol)</td>
</tr>
<tr>
<td>Doxycycline 50–100 mg b.i.d.</td>
<td>Clarithromycin 250–500 mg b.i.d.–q.d. (Biaxin)</td>
<td>Erythromycin 250–500 mg b.i.d.–q.i.d. (Akne-Mycin)</td>
<td>Psychiatric medications</td>
<td>Isotretinoin 0.15–2 mg/kg q.d. (Accutane)</td>
</tr>
</tbody>
</table>

- Amitriptyline 25 mg q.d. (Elavil)
- Clonidine 0.1 mg q.d.
Non-FDA-Approved Topical Treatment of Rosacea

<table>
<thead>
<tr>
<th>Topical Antibiotics</th>
<th>Topical Treatment Reportedly Used Effectively</th>
<th>Topical Treatments Theoretically Useful But Not Used Clinically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin 1% lotion, gel, solution, pledget (Cleocin)</td>
<td>Azelaic acid 20% cream (Azelex)</td>
<td>Crotamiton 10% q.d.–t.i.d. (Eurax)</td>
</tr>
<tr>
<td>Erythromycin 2% solution, ointment, pledget (Akne-Mycin)</td>
<td>Permethrin cream 5% q.d.–q.w. (Nix)</td>
<td>Lindane 1% cream q.d.</td>
</tr>
<tr>
<td>Benzoyl peroxide 5%/clindamycin 1% (BenzaClin, Benzamycin)</td>
<td>Adapalene cream, gel (Differin)</td>
<td>Benzoyl peroxide, gel, wash q.d.–b.i.d. (Benzac, Benzagel)</td>
</tr>
<tr>
<td>Sunscreen with dimethicone or cyclomethicone</td>
<td>Tacrolimus ointment q.d.–b.i.d. (Protopic)</td>
<td>Retinaldehyde 0.05% cream</td>
</tr>
<tr>
<td>Benzoyl peroxide 5% and erythromycin 1% combination cream, pledget</td>
<td>Pimecrolimus 1% Cream q.d.–b.i.d. (Elidel)</td>
<td>Tretinoïn cream, gel (Retin-A)</td>
</tr>
</tbody>
</table>
What is Ocular Rosacea and How do you make the Diagnosis?
Epidemiology of Ocular Rosacea:

1. In 3-58% of patients with Rosacea
2. M=F
3. European descent more common
4. Starts in 20's and often worsens with age
5. Can be seen in kids
Symptoms:

1. Burning
2. Foreign body sensation
3. Dry eye
4. Tearing (reflex)
5. Eye redness
6. Mattering of eyelids
1. Blepharitis & MGD
2. Lid margin telangiectasia
3. Conjunctivitis
4. Recurrent chalazia
5. Corneal pannus
6. SPK
7. Episcleritis, Scleritis (not common)
8. Interstitial keratitis & corneal scarring
Signs:

5. Corneal pannus
6. SPK
7. Episcleritis, Scleritis (not common)
8. Interstitial keratitis & residual corneal scarring
Pathophysiology
Many Theories of Ocular Rosacea

- Ingested Agents
- Climatic Exposures
- Chemicals
- Microbial
  - Demodex
  - Bacillus oleronius

Vascular

Pilosebaceous anomalies

Matrix

Degeneration
Many Theories of Ocular Rosacea

- *Demodex folliculorum* mites: Bacillus oleronius bacteria within
- Increased sulfated O-glycans in tear film
DEMODEX
Complications of Ocular Rosacea

1. Chronic Dry Eye
2. Corneal Vascularization
3. 2nd Bacterial Infections
4. Perforation
5. Increased graft failure after PK
Complications of Ocular Rosacea

Increased Graft Rejection in PK patients
Treatments
Usual Treatments of Ocular Rosacea

1. Lid hygiene: Warm Compresses Baby shampoo scrubs
2. Artificial tears, nonpreserved
3. Antibiotics po: doxycycline, tetracycline, clarithromycin, metronidazole; Erythromycin for kids
4. Erythromycin ointment
5. Topical steroids
6. Restasis: Topical cyclosporine A b.i.d. x 3 mo
Newer Ocular Rosacea Treatments:

1. Intense Pulse Light Therapy (IPL)

3. LipiFlow

4. Intraductal MG Probing, Maskin
Doxycycline Risks:

RetiredDirector
Senior Veteran (male)

Join Date: Oct 2001 Location: Washington Posts: 1,358

06-15-2005, 11:07 AM

Re: Clostridium difficile, c.diff intestinal infection anyone?

I too, was on antibiotics for a long time. I was on Doxycycline and never dreamed I'd have any problems like C-Diff, but I did. Things were really getting bad and I was to the point where I would have "accidents" at night while asleep and it even happened twice in public. Fortunately they were small and I was able to leave and go home before it was noticed by anyone.

I had gone to the doctor and had a colonoscopy when it was diagnosed from a stool culture. I spent two weeks on Vancocin, 250 mg BID, but now am on Vancocin, 125 mg one every other day. I am able to tell a huge difference already and I think when I finish the medication it should be cleared up completely. It will be just in time for our vacation trip to Hawaii.

Welcome to the boards Greenmyst, I hope things go better for you from now on and your symptoms are taken care with the medication.

Director
Prevention
Usual Prevention:

- Avoid foods, drinks, and situations that trigger outbreaks like sun
- Hat, sunglasses
- increase Omega 3s intake
<table>
<thead>
<tr>
<th>Ingested/Iatrogenic</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foods and drinks</strong></td>
<td><strong>Temperature</strong></td>
</tr>
<tr>
<td>Cheese (except cottage)</td>
<td>Sauna heat</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Overheating</td>
</tr>
<tr>
<td>Spicy food</td>
<td>Sun lamp</td>
</tr>
<tr>
<td>Soy sauce</td>
<td>Humidity</td>
</tr>
<tr>
<td>Vanilla</td>
<td>Hot baths</td>
</tr>
<tr>
<td>Dairy products</td>
<td><strong>Weather</strong></td>
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<tr>
<td>Liver</td>
<td>Sun</td>
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<tr>
<td><strong>Beverages</strong></td>
<td><strong>Emotion</strong></td>
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<tr>
<td>Red wine</td>
<td>Heat</td>
</tr>
<tr>
<td>Hot drinks</td>
<td>Strong wind</td>
</tr>
<tr>
<td>Alcohol (beer, bourbon, gin, vodka)</td>
<td>Cold</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td><strong>Activity</strong></td>
</tr>
<tr>
<td>Niacin</td>
<td>Exercise</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Menopause</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Caffeine withdrawal</td>
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<tr>
<td><strong>Topical agents</strong></td>
<td>Chronic cough</td>
</tr>
<tr>
<td>Topical corticosteroids</td>
<td>Straining</td>
</tr>
<tr>
<td>Retinoids</td>
<td></td>
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<tr>
<td>Cosmetics (sometimes)</td>
<td></td>
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<tr>
<td>Acetones</td>
<td></td>
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<tr>
<td>Alcohol</td>
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</tr>
</tbody>
</table>
4. A Hidden Concern
Years of Observations of Ocular Rosacea

1. If also had diabetes, tended to develop proliferative diabetic retinopathy

2. If they also had age related macular degeneration (ARMD), tended to develop wet ARMD

3. If they had a corneal transplant, they would tend to have a rejection more often.
A Chance Encounter at Grand Rounds
Who is this man?
Dr. Folkman's WAR

Angiogenesis and the Struggle to Defeat Cancer

ROBERT COOKE

Foreword by Dr. C. Everett Koop
ISOLATION OF A TUMOR FACTOR RESPONSIBLE FOR ANGIOGENESIS*

BY JUDAH FOLKMAN, M.D., EZIO MERLER, Ph.D., CHARLES ABERNATHY, M.D., AND GRETCHEN WILLIAMS

(From the Departments of Surgery and Pediatrics, Children's Hospital Medical Center and Harvard Medical School, Boston, Massachusetts 02115)

(Received for publication 15 September 1970)

Algire suggested that an attribute of tumor cells is their capacity to elicit continuously the growth of new capillary endothelium in vivo (1). Subsequently, Greene observed that tiny tumors implanted for more than a year in the anterior chamber of the guinea pig eye would not grow because they could not become vascularized (2). When these tumors were reimplemented in the muscle of a rabbit where they could become vascularized, they grew to a large size.

The growth of tumors which have been implanted in any one of several different organs and maintained by a long-term perfusion stops when the tumor reaches a diameter of 3–4 mm (3). Further growth of tumor tissue in in vitro organ cultures cannot be sustained without neovascularization of the tumor (4). Neovascularization does not require direct contact by tumor cells since vessels have been elicited from the hamster cheek pouch by tumors contained in a Millipore filter (5, 6). Similar outgrowth of new blood vessels was observed by us when Millipore chambers containing cells of B-16 melanoma or Walker carcinoma were implanted into the dorsal air sac of rats. In the present communication, the isolation of a soluble factor from human and animal neoplasms which is mitogenic for capillary endothelium is described. This factor induces growth of new capillaries, and it is proposed that it is responsible for tumor angiogenesis.

Materials and Methods

Isolation of Tumor-Angiogenesis Factor (TAF).—Walker 256 ascites tumor was harvested from 21-day old Sprague-Dawley rats which had been injected with $2 \times 10^6$ tumor cells 4–5 days previously. About 5 ml of bloody ascites were removed aseptically from the exposed

* This investigation was supported by U. S. Public Health Service Grants CA 08185-5-05, AI-05877, and AI-00366, and by a Grant from the Merck Company, and a gift from the Given Foundation.

A preliminary report of portions of this work has been presented (J. Clin. Invest. 1970. 49: 30a. [Abstr.]).

1 Abbreviation used in this paper: TAF, tumor-angiogenesis factor.
Down’s syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1

Kwan-Hyuck Baek1,*, Alexander Zaslavsky1,*, Ryan C. Lynch1,*, Carmella Brittl, Yoshiaki Okada2, Richard J. Siarey3, M. William Lensch4, In-Hyun Park4, Sam S. Yoon5, Takashi Minami6, Julie R. Korenberg7, Judah Folkman1, George Q. Daley4, William C. Aird4, Zygmunt Galdzicki3 & Sandra Ryeom1

The incidence of many cancer types is significantly reduced in individuals with Down’s syndrome1-4, and it is thought that this broad cancer protection is conferred by the increased expression of one or more of the 231 supernumerary genes on the extra copy of chromosome 21. One such gene is Down’s syndrome candidate region-1 (DSCR1, also known as RCAN1), which encodes a protein that suppresses vascular endothelial growth factor (VEGF)-mediated angiogenic signalling by the calcineurin pathway5-10. Here we show that DSCR1 is increased in Down’s syndrome tissues and in a mouse model of Down’s syndrome. Furthermore, we show that the modest increase in expression afforded by a single extra transgenic copy of Dscr1 is sufficient to confer significant suppression of tumour growth in mice, and that such resistance is a consequence of a deficit in tumour angiogenesis arising from suppression of the calcineurin pathway. We also provide evidence that attenuation of calcineurin activity by DSCR1, together with another chromosome 21 gene Dyrk1a, may be sufficient to markedly diminish angiogenesis. These data provide a mechanism for the reduced cancer incidence in Down’s syndrome and identify the calcineurin signalling pathway, and its regulators DSCR1 and DYSRK1A, as potential therapeutic targets in cancers arising in all individuals.

Down’s syndrome is the most common genetic cause of mental retardation in humans, occurring in 1 out of 700 live births. Epidemiological studies suggest that although individuals with Down’s syndrome have an increased risk of leukaemia, they have a considerably reduced incidence of most solid tumours1-4. In the largest study to date involving 17,800 Down’s syndrome individuals, the mortality from cancers was <10% of expected5. Such data indicate that one or more of the 231 trisomic genes on chromosome 21 is responsible for protecting these individuals against cancer. Of note, Down’s syndrome individuals also have a reduced incidence of other angiogenesis-related diseases, such as diabetic retinopathy11 and atherosclerosis12, suggesting that cancer protection in the Down’s syndrome population may be due, in part, to angiogenesis suppression. We observed considerable growth suppression of both Lewis lung and B16F10 tumour cells in Ts65Dn mice relative to littermate controls (Fig. 1b), correlating with a significant decrease in microvessel density (Fig. 1c). Endothelial cells isolated from Ts65Dn mice demonstrated upregulation of Dscrl mRNA in contrast to diploid littermates (Supplementary Fig. 1c) and were notably less responsive to VEGF-mediated proliferation in vitro (Supplementary Fig. 1d), further implicating an angiogenic defect in these mice. Thus, trisomy for orthologues of half the genes on human chromosome 21 was sufficient to slow ectopic tumour growth.

To validate that the compromised angiogenesis we observed in marine models of Down’s syndrome extended to human cells carrying trisomy 21, we compared microvessel density in teratomas derived from Down’s syndrome induced pluripotent stem (iPS) cells versus normal iPS cells from a healthy volunteer8,9. The iPS cells were differentiated into teratomas and implanted into SCID mice. As expected, microvessel density was significantly lower in teratomas derived from Down’s syndrome iPS cells than in control iPS cells (Fig. 2a), consistent with the decreased capacity to induce angiogenesis by DSCR1.
Measure in eyelid biopsies of severe ocular rosacea patients: CD31, CD39, vWF, VEGR, VEGFR1, VEGFR2

Create classification system, with face and content validity, to define mild, moderate, and severe ocular rosacea.

Measure in conjunctiva of severe ocular rosacea patients: CD31, CD39, vWF, VEGR, VEGFR1, VEGFR2

Create database of all rosacea and ocular rosacea patients.

Measure in plasma of severe ocular rosacea patients: Endostatin, Thrombospondin, [MMP-9, VEGF-A, CRP] Circulating Endothelial Cells, Circulating Progenitor Cells

Coordination with dermatology, oncology, epidemiology and biostatistics collaborators to follow patients through time.

Complete database of Down syndrome patients to evaluate prevalence of rosacea and ocular rosacea.

Report incidence of cancer in cases and controls; control for confounders.

Photographic documentation of effect of doxycycline cream on eyelid margin angiogenesis

Evaluate incidence of other diseases dependent on angiogenesis: wet ARMD, proliferative diabetic retinopathy, etc to see if severe OR pts have an increased risk.

Show pathologically the central role of angiogenesis in rosacea and ocular rosacea.

Evaluate if severe ocular rosacea patients are at increased risk of angiogenesis and have an increased incidence of cancer.

PHASE I

PHASE II
SEVERITY CRITERIA OF OCULAR ROSacea (SCOR): A Practical Method to Evaluate the Severity of Rosacea

Jae Yong Kim, MD, PhD,1,2 Ednan Ahmed, MD,1 Neetu Brar, MD,1 Andrea Lora, MD,3 Sandra Lora Cremers, MD, FACS.1

1 Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA
2 Department of Ophthalmology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea. 3 Bascom Palmer Eye Institute, University of Miami, School of Medicine, Miami, FL

Material has been previously presented at the American Academy of Ophthalmology Annual Meeting, November, 2006.

None of the authors have any financial interest in any products or materials in this study.

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Corresponding Author:
Sandra Lora Cremers, MD, FACS
Harvard Medical School, The Massachusetts Eye and Ear Infirmary
243 Charles Street, Boston, MA 02114
# SEVERITY CRITERIA OF OCULAR ROSACEA (SCOR):

**Dear Patient:** Please CHECK-off boxes in the top portion of the sheet (Questions 1-14) according to question: "How often do you have these symptoms based on % of time?"

<table>
<thead>
<tr>
<th>Patient Reported Symptoms &amp; Signs: Patient or MD can complete this section.</th>
<th>Absent= 0 0% of wk Never</th>
<th>Mild= 1 Rarely</th>
<th>Moderate= 2 50% of week Sometimes</th>
<th>Severe= 3 Often</th>
<th>Very Severe= 4 100% of week All the Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Itchy eyes</td>
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<td>2. Dryness of eyes</td>
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<td>3. Tearing/Discharge</td>
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<td>4. Foreign Body Sensation</td>
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<td>5. Burning/stinging of eyes</td>
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<td>6. Light sensitivity/photophobia</td>
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<td>7. Swelling</td>
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<td>8. Crusting of eyelids</td>
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<td>9. History or current chalazion/stye</td>
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<tr>
<td>10. Loss of lashes</td>
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<td>11. Eye pain</td>
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<td>12. Blurred vision</td>
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<tr>
<td>13. Redness of eyes/eyelid</td>
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<tr>
<td>14. Facial/nose/cheek redness</td>
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</tbody>
</table>

**Ocular Signs: Eye MD to fill in.** Absent= 0 Mild= 1 Moderate= 2 Severe= 3 Very Severe= 4

(Recurrent=4 points)
Results: Patient 3, CD 31+
Results: Patient 1, CD31+
Results: Patient 1, VEGF+
Doxycycline Magical Properties:

1. Anti-Angiogenic at low doses
2. Anti-bacterial at higher doses
Doxycycline's Effect on Ocular Angiogenesis: an In Vivo Analysis

Constance A. Cox,1A Juan Amalar,1A Rita Salloum,1B Liliana Guedez,1B Ted W. Reid,2 Cindy Jaworski,1A Moly John-Anrakalayil,1B Ken A. Freedman,1B Mercedes M. Campos,1A Alfredo Martinez,1B S. Patricia Becerra,1A and Deborah A. Carper1A

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Abstract

Purpose

To determine the in vivo effect of doxycycline (doxy) on choroidal angiogenesis and pterygium growth by using a choroidal neovascular murine model (CNV), a directed in vivo angiogenesis assay (DIVAA) and a pterygium murine model.

Design

Experimental Study

Participants

3 murine models were investigated with 4 mice minimum per group and 22 maximum per group.

Methods

Mice received water with or without doxycycline (Leiter’s Pharmacy, San Jose, CA). For the CNV, the neovascular lesion volume was determined in choroid-retinal pigment epithelial (RPE) flat mounts using confocal microscopy seven days after laser induction. For DIVAA, silicone capsules containing 10,000 human pterygium epithelial cells were implanted in the flanks of mice subcutaneously. After eleven days neovascularization (NV) was quantified using spectrofluorimetry after murine tail-vein injection of fluorescein isothiocyanate (FITC)-labeled dextran. A pterygium epithelial cell model was developed by injecting 10,000 human pterygium epithelial cells in the nasal subconjunctival space in athymic nude mice. Doxy was started on day six at 50 mg/kg/day; corneal lesions that resulted from the injections were compared at days six and fifteen.

Main outcome measures

Student’s t-test was used to evaluate the data for the CNV and DIVAA models and histologic preparations were used to evaluate pterygia lesions.

Results

There was significantly less NV and lesion volume with doxy taken in drinking water versus plain water. With doxy treatment, the laser-induced CNV showed a maximal 66% decrease in choroidal blood vessel volume (p≤0.008) and the DIVAA showed a 30% reduction of blood vessel growth and migration (p<0.004). Histologic preparations demonstrated that pterygium cell lesions regressed when mice were administered doxy for 9 days.

Conclusions

Doxycycline significantly inhibited angiogenesis in three murine models. The most dramatic effect was found in the choroidal neovascularization model followed by the pterygium epithelial cell DIVAA model. The anterior segment pterygium model also showed regression histologically. This suggests that doxycycline may be successful as an adjunctive treatment for choroidal neovascularization and pterygia in humans; clinical trials would be necessary to determine if there is a benefit.
Central Theory of Rosacea by Sandra Lora Cremers, MD, FACS

NGF

Neuronal-Driven Angiogenesis

+Photo/Sun/UV damage
+Genetics
+Infection
+Smoking

Demodex
H. pylori
Fungus
HTLV-I
Herpes Zoster
+Excess Cathelicidin

+VGEF
PDGF

MMP-9

ANGIOGENESIS due to the stimulation of the MAPK and PI3K pathways when VEGF links the TK receptor located in the endothelial cell surface

Inflammation
- Rhinophyma
- Scar tissue
- Corneal ulcers

Tumor Growth
- Cancer and Metastasis

Apoptosis of endothelial cells

(-)

ENDOSTATIN

Grants: Harvard's 50th Anniversary Scholars Grant; National Rosacea Society; Lion's Eye
Central Theory of Rosacea by Sandra Lora Cremers, MD, FACS

Low Oxygen state

Neuronal-Driven Angiogenesis

NGF

+VGF

PDGF

low dose 0.5 mg/kg/d significantly reduces BV growth & migration

Doxy

- +Genetics
- +Photo/Sun/UV damage
- +Smoking
- Infection
- Demodex
- H. pylori
- Fungus
- HTLV-I
- Herpes Zoster
- +Excess Cathelicidin
- +Follicular based immune response

mitochondrial genes, ER stress cascade, growth factors, interleukins, cell cycle regulators, integrins, and components of the extracellular matrix; TNF-alpha, IL-10 and IFNgamma

Grant provided by National Rosacea Society
Rosacea is a multifactorial, hyper-reactivity, vascular and neural based disease with a broad range of facial and ocular manifestations where normal vasodilation is greater and more persistent and involves an autoimmune component where microscopic amounts of extravasated plasma induce localized dermal and meibomian gland inflammation and where repeated external triggers lead to angiogenesis (the recruitment of new blood vessels), vasodilation, teleangiectasias, redness with eventual fibrosis and hypertrophic scarring of the dermis and meibomian glands.

Likely a central underlying factor in all subtypes of rosacea, particularly ocular rosacea, involves VEGF and similar angiogenic factors.
Future Research For Ocular Rosacea

1. Is Severe Ocular Rosacea due to increased angiogenesis activity at the lid margin?

2. Would they benefit from topical anti-angiogenic medications?
1. Do severe ocular rosacea patients have an increased risk of systemic angiogenesis?

2. Do these patients need to be evaluated for an increased risk of internal tumors or metastasis if primary tumors present?
Recommendations for Ocular Rosacea Patients:

1. Avoid inflammatory factors (triggers, sun, smoke)

2. Eat antioxidants, Omega 3s,

2. If must treat with doxycycline, use lowest dose

Start with 20mg q day; 40-mg, controlled release formulation of doxycycline monohydrate is an anti-inflammatory drug

3. General medical check ups
Thank you for your attention.

REMEMBER THE TWENTY EXTRA YEARS YOU ADDED TO YOUR LIFE THROUGH CLEAN, HEALTHY LIVING? - WELL, THESE ARE THEM.
References:


3.


http://www.rosacea-treatment.org/


9. Del Rosso JQ, Bikowski JB. Multicenter, doubleblind, randomized, placebo-
