NON TRADITIONAL MANAGEMENT OF FUNGAL KERATITIS

MOHAMED SAAD, MD
PROF. OF OPHTHALMOLOGY
ASSIUT UNIVERSITY HOSPITAL

FINANCIAL DISCLOSURE:

• No financial interest.
Fungal keratitis is a sight-threatening condition that requires immediate laboratory diagnosis and prompt therapeutic intervention to prevent loss of the eye. (Klotz, S.A., 2000 & Elgazayerly, 1997)

What are the problems of fungal keratitis?

Resistance.

Lytic activity by;
   - Microbial endotoxins.
   - PNL enzymes

Penetration.

Perforation. (Seal and Kirkness, 1995)
**CASES OF FUNGAL KERATITIS**

- Feathery margins
- Fungal plaque & hypopyon
- Infiltrates with pigmentation
- Corneal abscess

**MODALITIES**

- New long acting antifungal formula.
- Intrastromal injection of antifungal.
- Therapeutic PPK
LIPOSOMES LOADED WITH ANTI FUNGAL DROPS:  
(A NEW LONG ACTING ANTIFUNGAL FORMULA)

- Liposomes are artificial vesicles composed of concentric lipid bilayers which are separated by water compartments. (Fre´zard, F. 1999).

- Vesicular drug delivery systems:
  - Prolonged and controlled action at the corneal surface
  - Preventing the metabolism of the drug by enzymes present at the tear/corneal surface.
  - Increasing the probability of ocular drug absorption.
ANIMAL TRIAL

• 40 rabbits
• Induced bil. Candida keratitis.
• 22 ulcers treated with fluconazole loaded liposomes…cure 86%
• 18 ulcers treated with fluconazole sol……cure 50%
HUMAN STUDY

- 11 eyes with candida keratitis were treated with fluconazole loaded liposomes.
- 8 patients had complete cure.
- 1 patient got partial improvement.
- 2 patients did not improve.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration of ulcer at presentation (days)</th>
<th>Response to treatment</th>
<th>Diameter of ulcer at presentation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>65</td>
<td>5</td>
<td>improved</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>47</td>
<td>7</td>
<td>improved</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>44</td>
<td>14</td>
<td>partial improvement</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>56</td>
<td>9</td>
<td>improved</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>34</td>
<td>1</td>
<td>improved</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>54</td>
<td>3</td>
<td>no improvement</td>
<td>5.5</td>
</tr>
<tr>
<td>7</td>
<td>m</td>
<td>60</td>
<td>11</td>
<td>no improvement</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>67</td>
<td>8</td>
<td>improved</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>39</td>
<td>7</td>
<td>improved</td>
<td>6.5</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>50</td>
<td>9</td>
<td>improved</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>61</td>
<td>4</td>
<td>improved</td>
<td>6</td>
</tr>
</tbody>
</table>
Before Treatment                               One Month After Treatment
Before Treatment  
One Month After Treatment
CONCLUSION

Therapy with topical liposomal fluconazole (2 mg/ml) in treating patients with candida keratitis, carries high success rate, prolonged duration of action, higher corneal penetration, better eye tolerability and free of side effects.

A New Long-acting Liposomal Topical Antifungal Formula: Human Clinical Study
Mohamed S. Abdel-Rhaman, MD,* Wael Soliman, MD, PhD,* Fawzia Habib, PhD,† and Dina Fathalla, PhD†
Cornea ..Volume 31, Number 2, February 2012
INTRASTROMAL INJECTION OF ANTIFUNGAL DRUGS

THE ANTIFUNGAL AGENTS:

- **Polyenes** (eg, natamycin, amphotericin B).
- **Azoles** (eg, ketoconazole, miconazole, fluconazole, itraconazole).
- Fluorinated **pyrimidines** (eg, flucytosine).
• Amphotericin B .... yeasts.
• Natamycin .... filamentous organisms.
• Oral fluconazole and ketoconazole .... deep fungal keratitis.
• Ketoconazole .... Fusarium, Aspergillus, Curvularia, and Candida species.
• Fluconazole....deep fungal keratitis.
• Voriconazole....Aspergillus,Fusarium.

MOST COMMON ANTIFUNGAL DRUGS IN OPHTHALMIC USE : DOSES

<table>
<thead>
<tr>
<th>Route</th>
<th>Amphotericin B</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical</strong></td>
<td>0.15%</td>
<td>0.2%</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Subconjunctival</strong></td>
<td>Not prepared due to its high toxicity</td>
<td>2 mg/ml</td>
<td>1%</td>
</tr>
<tr>
<td><strong>Intrastromal (intracorneal)</strong></td>
<td>5 to 10 µg</td>
<td>2 mg/ml</td>
<td>50 µg/0.1 ml</td>
</tr>
<tr>
<td><strong>Intracameral</strong></td>
<td>5 to 10 µg/0.1 ml</td>
<td>Not available in literature</td>
<td>50 µg/0.1 ml</td>
</tr>
<tr>
<td><strong>Intravitreal</strong></td>
<td>1 to 10 µg/0.1 ml</td>
<td>25 µg/0.1 ml</td>
<td>50 µg/0.1 ml</td>
</tr>
</tbody>
</table>
PREPARATION OF ANTIFUNGAL:

- **Topical Amphotericin B 0.15%**:
  - **Method**: Add 10 ml distilled water to parenteral 50mg of Amphotericin B powder for injection (5 mg/ml). Draw 3 ml of this and add to 7 ml of artificial tears eye drops.
  - **Storage**: Refrigerate in 4°C
  - **Shelf life**: 7 days in refrigerator at 4°C and 4 days in room temperature
  - **Amphotericin B 5 to 10 µg/0.1ml for intracameral, intrastromal and intravitreal injection**:
    - **Method**: Prepare 5 mg/ml (as mentioned above) – take 0.2 ml solution and add to 0.8 ml BSS. Now take 0.1 ml of this solution and add 0.9 ml BSS to create 0.1 mg/ml equivalent to 10 µg/0.1ml.
    - **Use Immediately**

- **Fluconazole 0.2% (2mg/ml) for topical, subconjunctival and intrastromal routes**:
  - This concentration is available without the need for preparation. (each 1ml contains 2mg)
  - **Fluconazole 25 µg/0.1ml for intravitreal injection**:
    - **Method**: Draw 1.25 ml of 0.2% Fluconazole and add to 8.75 ml BSS to make concentration of 2.5 mg/10ml equivalent to 25 µg/0.1ml.
    - **Storage**: Refrigerate in 4°C
    - **Shelf life**: 7 days in refrigerator at 4°C and 4 days in room temperature
• **Voriconazole 1% for topical and subconjunctival use:**
  
  • **Method:** Mix 20ml ringer lactate to 200 mg Voriconazole lyophilized powder.
  
  • **Shelf life and storage:** 30 days at 4°C or room temperature
  
  • **Voriconazole 50 µg/0.1 ml for intrastromal, intracameral and intravitreal injection:**
  
  • **Method:** From 1% solution Voriconazole, take 1ml, add to 19 ml ringer lactate to make 0.05mg/ml (50 µg/0.1ml).

---

**TECHNIQUE OF INTRASTROMAL INJECTION:**

• The preloaded drug should be administered under operating microscope.

1. The needle (30 gauge) is inserted obliquely from the uninvolved clear area to just reach the abscess at mid-stromal level with the bevel down.

2. The drug is injected to produce stromal hydration.

3. Five divided doses are given around the abscess to form a deposit of the drug around the circumference of the lesion.
RESULTS OF INTRASTROMAL INJECTION OF ANTIFUNGAL DRUGS

• Example of complete cure after single intrastromal injection

• Example of complete cure after second intrastromal injection
• Example of incomplete cure after second intrastromal injection.

THERAPEUTIC PPK
INDICATIONS IN MYCOTIC ULCER

- Prolonged unresponse (how long?)
- Progression (stromal ulceration, thinning; increase hypopyon, increase IOP and perforation (Jones 1990))

Advantages over medical TTT

- Eradication of infection
- Vision restoration
- Shorter hospitalization
Disadvantages

Recurrence

Graft complications are higher than visual keratoplasty e.g. rejection, failure, glaucoma, slipped stitch, endophthalmitis.

Criteria for success;

Early interference

Small sized graft (less than 7mm)

Complete inclusion of the pathology.
IMPORTANT SURGICAL NOTES

Excision of whole infected tissue + safety margin. (0.25–0.5 mm larger than the infected area of the cornea.)

Hand held trephine is superior to vacuum trephine,

Irrigation with antimicrobial. (0.2% fluconazole)

Removal of hypopyon/membranes.

Viscoelastics is a must. (Bleeding is controlled by the use of Healon and cautery of vessels).

Graft diameter (8mm)

Trephine size in perforation.

Peripheral iridectomy (Killingsworth, 1993)

• Try to keep the graft as small as possible, because it’s likely that you’ll need a secondary optical graft later, and you don’t want that area to become vascularized and not allow the secondary graft,”

• Leave the patient phakic, even if he has the beginnings of a cataract, in order to leave a barrier to further fungal penetration or endophthalmitis.

• The excised cornea is sent to lab.
POSTOPERATIVE MANAGEMENT

- Recurrent fungal infection can be particularly difficult to treat.
- Following PKP both systemic and topical antifungal agents must be used.
- Corticosteroids were not used unless significant inflammation was present (not during first 3 days).
- If by 2 weeks after PKP recurrent fungal infection was not seen systemic antifungal agents were tapered in the following 2 weeks.
- Manage intraocular pressure with medications in the postop period because fungi have been known to destroy trabecular meshwork tissue or even require a secondary glaucoma surgery postop.“
TAKE HOME MESSAGE

- Fungal keratitis is sight threatening condition.
- Decision making in proper time is essential to save infected eyes.
- Surgical intervention with special precautions may be the only choice to save these eyes.
References: