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Interferon alpha-2b in the Treatment of Refractory Uveitic Cystoid Macular Edema
Introduction

- Burden of uveitic CME
  - >30%
  - Leading cause of LOV and legal blindness
  - Potentially irreversible LOV

Interferon alpha-2b

- IFN alphas
  - Species-specific cytokines
  - WBC produced
  - Antiviral, antiproliferative, immunomodulatory
  - Chronic hepatitis, leukemias/lymphomas, solid tumors
Ocular use of IFN α

- 50 patients
- 92% response rate to IFN alfa s.c.
- Mean VA improved by wk 24
  - 0.56 to 0.84 (decimal); p < 0.001
- 58 eyes with CME → 100% resolution

37 with refractory Behçet’s PU
95% response rate

12 patients, sight-threatening, refractory uveitis
9 idio, 1 sympathetic, 2 Behçet’s
83% response rate
14 eyes with CME → 100% resolution
SEs common

INTERFERON ALFA-2A: A NEW TREATMENT OPTION FOR LONG LASTING REFRACTORY CYSTOID MACULAR EDEMA IN UVEITIS?

A Pilot Study

CHRISTOPH M. E. DEUTER, MD,∗ INA KOETTER, MD,† ILHAN GUENAYDIN, MD,‡ NICOLE STUEBIGER, MD,∗ MANFRED ZIERHUT, MD∗

RETINA 26:786–791, 2006

15 eyes of 8 patients
Mean duration: 52 mos.
13/15 eyes → 100% resolution (2-4 wks)
1/8 (2 eyes) no response*; 1/7 lost response**
Of 11 eyes treated over 6 mos.
  ▪ mean CMT: 551 to 143 µm
  ▪ mean BCVA (logMAR): +0.80 to +0.42

Interventional case series
24 consecutive pts (40 eyes)
Mean duration: 36 mos.
“Effective”
- 25 eyes of 15 pts (62.5%)

“Partly effective”
- 10 eyes of 6 pts (25%)

“Not effective”
- 5 eyes of 3 pts (12.5%)
Collaborators:
- James Rosenbaum, MD and Eric Suhler, MD, MPH

Purpose:
- Interferon alpha-2b (not -2a) available in U.S.
- Is this also effective?
Methods

- Consecutive, interventional case series

- Retrospective

- Nov. 2009 thru Jan. 2011
  - IFN alpha-2b 6 million units s.c. daily
  - All patients treated included in analysis

- Stats: paired, one-tailed Student’s t-test
Table 1. Baseline Characteristics, Prior Treatments, and Longitudinal Response to Interferon Alpha 2b.

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age (start of IFN)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Treatment Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>F</td>
<td>AU and IU; ? Sarcoid; idiopathic</td>
<td>pred, MTX, IVTA</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>F</td>
<td>PU; idiopathic</td>
<td>pred, FA-imp, Dex-imp, PPV, IVTA, IVMTX, IVB, MMF, FK-506, CSA, AZA</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>sclerouveitis; systemic vasculitis; idiopathic</td>
<td>CPP, m-pred, pred, IFXB, AZA, MMF, RTX</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>PU; ? Sarcoid; idiopathic</td>
<td>POK, pred, MTX, MMF, IVTA</td>
</tr>
</tbody>
</table>
Results (baseline characteristics)

- 4 patients; 8 eyes
- Mean duration of CME = 31 mos

Table 1. (cont.) Longitudinal Response to Interferon Alpha 2b.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2-3 wks f/u</th>
<th>2 mos f/u</th>
<th>Last f/u*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMT (μm)</td>
<td>logMAR</td>
<td>CMT (μm)</td>
<td>logMAR</td>
</tr>
<tr>
<td>Mean</td>
<td>563</td>
<td>0.81 (20/129)</td>
<td>299</td>
<td>0.70 (20/100)</td>
</tr>
<tr>
<td>SD</td>
<td>206</td>
<td>0.46</td>
<td>53</td>
<td>0.47</td>
</tr>
<tr>
<td>P-value</td>
<td>0.003</td>
<td>0.02</td>
<td>0.003</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Last followup in months: 17, 7, 5.5, 5 for patients 1-4 respectively.
Patient 1

- Baseline
- 3 wk f/u
Patient 2

- Baseline

- 2 wk f/u
Patient 3

- Baseline

- 2 wk f/u
Patient 4

- Baseline
- 3 wk f/u
LogMAR VA with time (8 eyes)
- Gen: fatigue, influenza-like symptoms
- Cardio: hypotension, arrhythmias, tachycardia, cardiomyopathy, and myocardial infarction
- Skin: alopecia, erythema multiforme, injection site necrosis, psoriasis, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Endo: diabetes mellitus, disorder of thyroid gland, gynecomastia, hyperglycemia, hyperkalemia, hypertriglyceridemia, hypocalcemia, hypopituitarism, lipids abnormal, SIADH, virilization, weight loss
- GI: diarrhea, disorder of taste, loss of appetite, nausea and vomiting, pancreatitis
- Heine: anemia, neutropenia, and thrombocytopenia
- Liver: AST/SGOT level raised, biliary cirrhosis, hepatic encephalopathy, hepatotoxicity, increased liver enzymes, jaundice, liver failure
- Immune: antibody development, autoimmune disease, immune hypersensitivity reaction, lupus erythematosus, rhabdomyolysis, viral disease
- MSK: musculoskeletal pain, myasthenia gravis, myositis, rhabdomyolysis, rheumatoid arthritis
- Neuro: asthenia, cerebrovascular accident, confusion, headache, somnolence
- Psych: aggressive behavior, depression, suicidal
- Renal: nephrotic syndrome, polyuria, proteinuria, renal failure, renal impairment
- Repro: abnormal spermatogenesis, fertility problem
- Pulm: bronchitis, epistaxis, pneumonia, pneumonitis, pulmonary hypertension, pulmonary infiltrate, dyspnea, cough, pharyngitis, sinusitis, and nasal congestion, sarcoidosis
Ocular Effects?

- Case Reports abound
- Cotton wool spots, functional visual loss, optic disc edema, optic neuritis, retinal hemorrhage, **macular edema**, retinopathy, CRAO, CRVO, AION
- No ocular side effects in uveitis literature
Our Patients

- Flu-like illness, na/vo (4)
- Joint and muscle aches (4)
- LFT elevation (2)
- Hair loss (2)
- Hives (2)
- WBC suppression (1)
- Weight loss, anorexia (1)

* None were treatment limiting.
30 year-old AAM with intermediate uveitis and retinal vasculitis (non pars planitis)
  - Workup non-contributory

Prior to referral
  - 15 month h/o chronic uveitis with CME OU and optic nerve swelling

CME refractory to high dose prednisone and local steroid injections (*and* Avastin)
On presentation...

- **VA**
  - 20/80-2 (OD)
  - 20/50 (OS)

- **CFT**
  - 634 μm (OD)
  - 560 μm (OS)
After one month of IFN 6mu s.c. daily...

- **VA**
  - 20/80 (OD)
  - 20/32 (OS)

- **CFT**
  - 171 μm (OD)
  - 211 μm (OS)
But, hospitalized 3 days prior...

- Neutropenia (ANC 900 and WBC ~2000), hypokalemia, platelets 70K
- 15 lb. weight loss
- Hematemesis
- IFN stopped abruptly
Three months later with spotty therapy (Durezol, retriial of IFN, one month of CellCept)…

- **VA**
  - 20/260 (OD)
  - 20/80 (OS)

- **CFT**
  - 566 μm (OD)
  - 187 μm (OS)
After 6 weeks of IFN 3μg s.c. every other day plus Neupogen...

- **VA**
  - 20/130+ (OD)
  - 20/40 (OS)

- **CFT**
  - 167 μm (OD)
  - 172 μm (OS)

- 2 months later
  - 20/63 (OD)
  - 20/50 (OS) and
  - No CME OU on IFN 3μg s.c. q 3 days
Last f/u: ~1 year of therapy; down to IFN 3m units q7 days*

- **VA**
  - 20/40-2 (OD); PCIOL
  - 20/50-2 (OS); 1+ PSC

- **CMT (μm)**
  - 205 (OD)
  - 214 (OS)
Patient JM: case 2

- RFC: ?? Steroid sparing therapy for retinal vasculitis with CME OU (1/2013)

- HPI:
  - 70 WF s/p CEIOL OU (11-12/2011)
  - Floaters and LOV OU within weeks (no associated symptoms)
  - Dx’d: retinal vasculitis with CME
  - Workup: undifferentiated
Patient JM: case 2

- Tx failures/AEs:
  - Prior to referral
    - IVTA- resolved CME but IOP in 40s
    - Avastin- no benefit
    - Diamox- fatigue, no clear benefit
    - Prednisone- CME recurred at 20mg
  - After referral
    - Methotrexate 20mg sc weekly- incomplete effect
    - Durezol- IOP issues
Patient JM: case 2
6/2013

- Worsening vision OU
  - 20/65 OD
  - 20/50 OS

- Tx unchanged

- ???
3 weeks post IFN 3m units sc daily 8/2013

- **Improving** vision OU
  - 20/65 $\rightarrow$ 20/40 OD
  - 20/50 $\rightarrow$ 20/35 OS

- CMT ($\mu$m)
  - 647 $\rightarrow$ 228 (OD)
  - 570 $\rightarrow$ 252 (OS)
Hospitalized for pulmonary embolism

Rare association

Hematologist opinion
  ▪ “other systemic RFs”
  ▪ “cannot prove causality”
  ▪ continue if R/B/A analysis in favor

Last f/u (5/2014): down to IFN 3m sc q4 days
  ▪ 20/40+2 OD and 20/25+ OS
  ▪ OCT stable/no fluid
Patient AS: case 3

- 51 AAM w/ “possible” sarcoidosis
- Pars planitis and chronic CME
  - 8 steroid injections annually per eye
2 weeks post IFN alpha-2b 3m units sc daily

- CMT (μm)
  - 451 → 275 (OD)
  - 391 → 290 (OS)

- SEs??
  - Significant neutropenia
Mechanism

- Unknown
- Chronic CME; inflammation “burnt out”

Interferon-α 2b Enhances Barrier Function of Bovine Retinal Microvascular Endothelium in Vitro

Mark C. Gillies and Tao Su

Department of Ophthalmology, Prince of Wales Hospital and Pediatric Research Laboratories, Prince of Wales Children’s Hospital, Randwick, NSW 2031, Australia

“We conclude that interferon-α 2b can enhance the barrier function of retinal microvascular endothelium in vitro. This is consistent with the hypothesis that interferon-α is an effector of a mechanism which actively promotes tissue homeostasis and suggests that it might have therapeutic potential in diseases characterized by leakage of the vascular endothelium.”
Conclusions

- Interferon alpha-2b appears effective
- Side effects considerable
  - Careful risk:benefit analysis
  - Rarely treatment limiting
- Select patients with limited options
- Refractory to intravitreal steroid (or contraindicated)
- Refer for tx as indicated
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