Drug-Induced Uveitis - Agents Old and New

Emmett T. Cunningham, Jr., M.D., PhD., M.P.H
Department of Ophthalmology, California Pacific Medical Center
Department of Ophthalmology, Stanford University School of Medicine
Francis I. Proctor Foundation, UCSF School of Medicine
West Coast Retina Medical Group
The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform

Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD; Ameet Sarpatwari, JD, PhD

Figure 1. Per Capita Spending on Prescription Pharmaceuticals

Data are derived from the Organisation for Economic Cooperation and Development (OECD), reflect expenditures in 2013 (or the nearest year), and include all countries for which values were reported. Data used with permission from OECD, Health at a Glance 2015: OECD Indicators, 2015.8

$858 / Patient / Year
~ 35M Hospitalizations

~ 3.5 M (10%) Drug-Induced
All Cause Mortality – US 2015

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diseases of the Heart</td>
<td>633,842</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>595,930</td>
</tr>
<tr>
<td>Chronic Lower Respiratory Disease</td>
<td>155,041</td>
</tr>
<tr>
<td>All Unintentional Injuries</td>
<td>146,571</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>140,323</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>110,561</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>79,535</td>
</tr>
<tr>
<td>Influenza and Pneumonia</td>
<td>57,062</td>
</tr>
<tr>
<td>Total Drug-Induced</td>
<td>55,403</td>
</tr>
<tr>
<td>Prescription Drug-Induced</td>
<td>38,403</td>
</tr>
<tr>
<td>Suicide</td>
<td>44,193</td>
</tr>
<tr>
<td>Motor Vehicle Accident</td>
<td>37,757</td>
</tr>
<tr>
<td>Alcohol-Induced</td>
<td>33,171</td>
</tr>
<tr>
<td>Homocide</td>
<td>17,793</td>
</tr>
<tr>
<td>Illicit Drug-Induced</td>
<td>17,000</td>
</tr>
<tr>
<td>HIV</td>
<td>6,465</td>
</tr>
</tbody>
</table>

TOTAL = 2,712,630
~ 2% Drug-Induced

https://www.cdc.gov/nchs/data/hus/hus16.pdf#019
http://www.drugwarfacts.org/chapter/causes_of_death
Most Deadly “Drugs” – Three are Legal

Drug-Related Deaths (US – 2015)

- **Tobacco**: 437,400
- **Alcohol**: 33,171
- **Opiod Analgesics**: 17,536
- **Heroin**: 12,989
- **Cocaine**: 6,784

https://www.vox.com/2014/5/19/5727712/drug-alcohol-deaths

< 0.5%
Referral Centers*
(Many Series None)
**EDITORIAL**

Drugs, Inflammation, and the Eye

Emmett T. Cunningham, Jr, MD, PhD, MPH1,2,3,4, Nikolas J. S. London, MD5, Ramana Moorthy, MD6, Sunir J. Garg, MD7, and Manfred Zierhut, MD8

Ocular Immunology & Inflammation, 2016; 24(2): 125–127

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**REVIEW**

Drug-induced uveitis

Nikolas JS London1, Sunir J Garg2, Ramana S Moorothy3,4 and Emmett T Cunningham Jr5,6

Journal of Ophthalmic Inflammation and Infection 2013, 3:43

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**CURRENT OPINION**

Drug-induced uveitis

Ramana S. Moorothy4,5, Nikolas J.S. London6, Sunir J. Garg7, and Emmett T. Cunningham Jr8,9

Curr Opin Ophthalmol 2013, 24:589–597

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**EDITORIAL**

Drug-induced Inflammation in Patients on TNFα Inhibitors

Emmett T. Cunningham, Jr, MD, PhD, MPH1, Sirichai Pasadhika, MD2, Eric B. Suhler, MD, MPH3, and Manfred Zierhut, MD4

Ocular Immunology & Inflammation, 20(1), 2–5, 2012
Drug-Induced Uveitis

Nikolas J.S. London, MD
Sunir J. Garg, MD, FACS
Ramana S. Moorthy, MD, FACS
Emmett T. Cunningham Jr, MD, PhD, MPH
Table 1. Naranjo Scoresheet for Assessing the Association Between a Medication and an Adverse Reaction

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>YES</th>
<th>NO</th>
<th>NOT KNOWN</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL

The maximal possible score is 13. Naranjo scores of 9 or higher imply a definite association, scores of 5 to 8 a probable association, scores of 1 to 4 a possible association, and scores of 0 make an association doubtful.

Naranjo Algorithm
14 Point Scale
(0 - 13)

Definite (9 – 13)
Probable (5 – 8)
Possible (1 – 4)
Doubtful (0)

0 1 2 3 4 5 6 7 8 9 10 11 12 13
### Heaviest Weighting to:

- **Temporal Relationship**
- **Re-challenge**
- **Lack of Alternate Cause**

### Naranjo Algorithm

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Reported Previously?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 Starts after Drug?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>3 Abates after Cessation?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4 Recurs with Re-challenge?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>5 Alternate Cause?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>6 Reaction with Placebo?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>7 Drug Level Toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8 Reaction Dose-related?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9 Past History of Similar Event?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10 ADR Confirmed Objectively?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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In Clinical Practice . . .

Score Typically ~ 5 - 7 (Probable)

Recurrence with Re-challenge, but not with placebo  ➡️  Definite

<table>
<thead>
<tr>
<th>Naranjo Algorithm</th>
<th>YES</th>
<th>NO</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reported Previously?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Starts after Drug?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abates after Cessation?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Recurs with Re-challenge?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>Alternate Cause?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
</tr>
<tr>
<td>Reaction with Placebo?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug Level Toxic?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reaction Dose-related?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Past History of Similar Event?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ADR Confirmed Objectively?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 2. Quantitative Assessment of Causation of Drug-Induced Uveitis Using Naranjo Algorithm

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>DRUG</th>
<th>NARANJO CRITERION</th>
<th>TOTAL SCORE</th>
<th>LIKELIHOOD OF CAUSATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score per Criterion</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Systemic</td>
<td>Cidofovir</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Rifabutin</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sulfonamides</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>TNF-α inhibitors</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolones</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diethylcarbamazine</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Topical</td>
<td>Metipranolol</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Glucocorticosteroids</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Brimonidine</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin analogues</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Intraocular</td>
<td>Cidofovir</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Anti-VEGF agents</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone Acetonide</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Bacille Calmette-Guérin</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Influenza</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>with measles, mumps and rubella</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Varicella</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Older reports, some of which found an association with latent syphilis infection.*
Drug-Induced Uveitis

Mechanisms
- Toxicity
- Immune activation
  - Biologics
  - Immune Modulators
  - Vaccines
# Drug-Induced Uveitis

## Systemic Medications

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Weighted Naranjo Score</th>
<th>Association with Uveitis (Casual Likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cidofovir</td>
<td>11</td>
<td>Definite</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>10</td>
<td>Definite</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>10</td>
<td>Definite</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>10</td>
<td>Definite</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>6</td>
<td>Probable</td>
</tr>
<tr>
<td>TNF-α antagonists</td>
<td>7</td>
<td>Probable</td>
</tr>
<tr>
<td>Checkpoint Inhibitors</td>
<td>7</td>
<td>Probable</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Probable</td>
<td>Probable</td>
</tr>
</tbody>
</table>
Cidofovir Naranjo SCORE = 11 (Systemic and Intraocular) (Definite)
Cidofovir Naranjo SCORE = 11 (Systemic and Intraocular)

- Nucleotide analog of cytosine monophosphate with potent, broad-spectrum antiviral activity
  - IV with probenecid/hydration
  - IVT
  - Long intracellular half-life.
Cidofovir Naranjo SCORE = 11
(Systemic and Intraocular)

- **Side Effects**
  - **Irreversible nephrotoxicity**
  - **Contraindicated with pre-existing renal disease.**
  - **Avoid other nephrotoxic agents - e.g. amphotericin B, foscarnet, aminoglycosides, Ipentamide, vancomycin, tacrolimus, NSAIDS, etc.**
  - **Hypotony – 10%**
  - **Non-granulomatous anterior uveitis 17-89% (PS common)**

Anterior Uveitis and Hypotony after Intravenous Cidofovir for the Treatment of Cytomegalovirus Retinitis

Michelle E. Akler, MD,1 David W. Johnson, MD,1 William J. Burman, MD,2 Steven C. Johnson, MD3


Dose & Time Dependent

Cumulative Proportion of Patients Without Iritis

Time Since the Initiation of Treatment with Cidofovir, days

No. of Doses of Cidofovir

50%
Cidofovir – Naranjo Score = 11
(Systemic and Intraocular)

• **Side effects less with oral Probenecid**
  - Inhibits secretion from ciliary body
• **Mechanism unknown – possible toxicity**
• **Treatment**
  - Topical/periocular corticosteroids & cycloplegic/mydriatic agents
• **Discontinuation of Cidofovir may be required**
• **Hypotony can be prolonged / permanent**
Rifabutin Naranjo SCORE = 10 (Definite)
Rifabutin Naranjo SCORE = 10

- Oral spiropiperidyl-rifamycin antibiotic
  Prophylaxis/treatment of Mycobacterium avium complex (MAC)
  - HIV positive or immunocompromised
- Mycobacterium tuberculosis and non-tuberculous mycobacteria (NTM)
- Staphylococcal chronic bone infection
- Prosthetic valve endocarditis
- Pneumococcal or staphylococcal meningitis.
• **Characteristic hypopyon iritis**
  - 8 - 38% with Rifabutin 600mg/day
  - Increased risk in combination with clarithromycin, protease inhibitors or antifungal azoles (p450 enzyme inhibitors)
  - Typically 1-2 months after initiating high dose
• < 0.01% if low dose = 300mg/day
• Intermediate uveitis, panuveitis, retinal vasculitis, CME reported
Rifabutin – HIV+

Rifabutin

Courtesy of Ramana ("Bob") Moorthy, M.D.
Rifabutin ‘Granulomatous’ Anterior Uveitis

Courtesy of N. Kevin Wade, MD
Rifabutin-associated hypopyon uveitis and retinal vasculitis with a history of acute myeloid leukemia

Wendy M. Smith • Madhu G. Reddy • Kelly A. Hutcheson • Rachel J. Bishop • H. Nida Sen


Rifabutin Retinal Vasculitis
Courtesy of Dr. Nida Sen, M.D.
Rifabutin Naranjo SCORE = 10

• **Risk Factors for uveitis**
  • Dosage
  • Duration
  • Co-administration of cytochrome P450 enzyme inhibitors

• **Treatment**
  • Intensive topical therapy
    – corticosteroid & cycloplegic/mydriatic agent
  • Dose reduction to 300mg/day
  • Discontinuation of rifabutin if required
**Sulfonamides Naranjo SCORE = 10**

- Definite: (9 – 13)
- Probable: (5 – 8)
- Possible: (1 – 4)
- Doubtful: (0)
Sulfonamides Naranjo SCORE = 10

- Old and common class of antibiotics
  - UTI; Toxoplasmosis
- Newer sulfonamide derivatives - anticonvulsants, diuretics, dermatologic agents
- Mild non-granulomatous anterior uveitis; > 40% bilateral
- Shortly after initiating drug therapy
- Recurs on re-challenged with **Trimethoprim-sulfamethoxazole**
- Treatment
  - Topical corticosteroids & Cycloplegic/mydriatic agents
  - Discontinuation of medications
Bisphosphonates Naranjo SCORE = 10 (Definite)
Bisphosphonates Naranjo SCORE = 10

- Slow Bone Loss
  - Reduce Osteoclast Activity
    - Osteoporosis
    - Malignant metastatic disease to bone
    - Paget’s disease
    - Etc . . .
Bisphosphonates

Non-Nitrogenous:

Etidronate (Didronel) — 1*  
Clodronate (Bonefos, Loron) — 10  
Tiludronate (Skelid) — 10

Nitrogenous:

Pamidronate (APD, Aredia) — 100  
Neridronate (Nerixia) — 100  
Olpadronate — 500  
Alendronate (Fosamax) — 500  
Ibandronate (Boniva) — 1000  
Risedronate (Actonel) — 2000  
Zoledronate (Zometa, Aclasta) — 10000

*potency relative to that of etidronate
Bisphosphonates Naranjo SCORE = 10

- **Ocular Inflammatory disease**
  - *Class Effect*
    - *Etidronate* - Oral
    - *Residronate* - Oral - **Nitrogenous**
    - *Pamidronate* - IV (Most Common) - **Nitrogenous**
    - *Alendronate* - Oral - **Nitrogenous**
    - *Zoledronic acid* - IV - **Nitrogenous**
  - *More common with nitrogen-containing agents*
Bisphosphonates Naranjo SCORE = 10

- Uveitis – bilateral > unilateral
- Scleritis/episcleritis - unilateral
- Orbital inflammation - most recent, bilateral

<table>
<thead>
<tr>
<th>TABLE 1. Ocular Adverse Events Reported in Patients on Intravenous Pamidronate Disodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signs</td>
</tr>
<tr>
<td>Nonspecific conjunctivitis</td>
</tr>
<tr>
<td>Uveitis</td>
</tr>
<tr>
<td>Scleritis</td>
</tr>
<tr>
<td>Episcleritis</td>
</tr>
<tr>
<td>Edema—eyelids</td>
</tr>
<tr>
<td>Optic or retrobulbar neuritis</td>
</tr>
<tr>
<td>Periorbital or orbital edema</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
</tr>
<tr>
<td>Ptosis</td>
</tr>
<tr>
<td>Blepharitis</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
</tr>
<tr>
<td>Proptosis</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>Blurred vision</td>
</tr>
<tr>
<td>Ocular pain</td>
</tr>
<tr>
<td>Photophobia</td>
</tr>
<tr>
<td>Diplopia</td>
</tr>
<tr>
<td>Visual hallucinations</td>
</tr>
<tr>
<td>Yellow vision</td>
</tr>
</tbody>
</table>

Bisphosphonates and Adverse Ocular Effects

Table 1. Bisphosphonates and Adverse Ocular Effects.*

<table>
<thead>
<tr>
<th>Bisphosphonate and Adverse Effect</th>
<th>No. of Cases Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate disodium</td>
<td></td>
</tr>
<tr>
<td>Nonspecific conjunctivitis</td>
<td>72</td>
</tr>
<tr>
<td>Uveitis</td>
<td>66</td>
</tr>
<tr>
<td>Abnormal or blurred vision</td>
<td>24</td>
</tr>
<tr>
<td>Scleritis</td>
<td>19</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>16</td>
</tr>
<tr>
<td>Photophobia</td>
<td>14</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>10</td>
</tr>
<tr>
<td>Alendronate sodium</td>
<td></td>
</tr>
<tr>
<td>Abnormal or blurred vision</td>
<td>94</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>33</td>
</tr>
<tr>
<td>Nonspecific conjunctivitis</td>
<td>30</td>
</tr>
<tr>
<td>Uveitis</td>
<td>19</td>
</tr>
<tr>
<td>Scleritis</td>
<td>4†</td>
</tr>
<tr>
<td>Etidronate disodium</td>
<td></td>
</tr>
<tr>
<td>Abnormal or blurred vision</td>
<td>18</td>
</tr>
<tr>
<td>Nonspecific conjunctivitis</td>
<td>3</td>
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<tr>
<td>Risedronate sodium</td>
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<td>7</td>
</tr>
<tr>
<td>Abnormal or blurred vision</td>
<td>2</td>
</tr>
<tr>
<td>Scleritis</td>
<td>1</td>
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<tr>
<td>Sodium clodronate</td>
<td></td>
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<tr>
<td>Abnormal or blurred vision</td>
<td>5</td>
</tr>
<tr>
<td>Photophobia</td>
<td>1</td>
</tr>
</tbody>
</table>

Conjunctivitis / Episcleritis
Uveitis
Scleritis

Only Drugs Causing Scleritis

* Data are from the spontaneous reporting systems of the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Portland, Oreg.), the Food and Drug Administration (Rockville, Md.), and the World Health Organization (Uppsala, Sweden).
† Three cases were reported by Mbekeani et al.4

The Incidence of Acute Anterior Uveitis after Intravenous Zoledronate

Dipika V. Patel, PhD, MRCOphth,1 Anne Home, MBChB,2 Meaghan House, MPH,2 Ian R. Reid, FRACP,2 Charles N. J. McGhee, PhD, FRCOphth1

Table 1. Summary of Cases

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)</th>
<th>Affected Eye</th>
<th>Time from Infusion to Onset of Symptoms (days)</th>
<th>Duration of Treatment (days)</th>
<th>Total No. of Prednisolone Acetate 1% Eye Drops (Total Dose in Milligrams Assuming 50 μl/drop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68.8</td>
<td>Both</td>
<td>2</td>
<td>50</td>
<td>Right: 273 (136.5); left: 90 (45)</td>
</tr>
<tr>
<td>2</td>
<td>77.0</td>
<td>Right</td>
<td>7</td>
<td>46</td>
<td>210 (105)</td>
</tr>
<tr>
<td>3</td>
<td>68.3</td>
<td>Left</td>
<td>3</td>
<td>12</td>
<td>119 (59.5)</td>
</tr>
<tr>
<td>4</td>
<td>67.7</td>
<td>Right</td>
<td>3</td>
<td>48</td>
<td>259 (129.5)</td>
</tr>
<tr>
<td>5</td>
<td>68.9</td>
<td>Left</td>
<td>2</td>
<td>94</td>
<td>392 (196)</td>
</tr>
<tr>
<td>6</td>
<td>80.2</td>
<td>Left</td>
<td>3</td>
<td>68</td>
<td>308 (154)</td>
</tr>
<tr>
<td>7</td>
<td>66.5</td>
<td>Right</td>
<td>4</td>
<td>14</td>
<td>70 (35)</td>
</tr>
<tr>
<td>8</td>
<td>65.6</td>
<td>Left</td>
<td>1</td>
<td>26</td>
<td>165 (82.5)</td>
</tr>
</tbody>
</table>

8 / 1001 = 0.8%  
7/8 = 88% Unilateral  
Median 3 Days
Zoledronate Anterior Uveitis  

https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-5-156
Zoledronate Scleritis/Uveitis

Courtesy of Ramana ("Bob") Moorthy, M.D.
Bisphosphonates Naranjo SCORE = 10

- **Mechanism**
  - Release of inflammatory cytokines
    - Nitrogen containing bisphosphonates – most commonly (stimulate antigenic receptors)
    - 30% have infusion reactions with flu-like illness
    - Elevated C-reactive protein, interleuken-1, interleuken-6
Bisphosphonates Naranjo SCORE = 10

- Therapy
  - Typically requires discontinuation, esp scleritis
  - Switch agents - to non-nitrogen containing bisphosphonates
  - Topical corticosteroids & cycloplegic/mydriatic agent
  - Oral NSAID or corticosteroidv–scleritis/episcleritis
  - Pre-treat with corticosteroids, acetominophine, benedryl
Fluoroquinolones Naranjo SCORE = 6 (Probable)
Fluoroquinolones Naranjo SCORE = 6

- > 40 cases of “uveitis” associated with systemic fluoroquinolones since 2004,
- Oral fluoroquinolones
  - ciprofloxacin
  - ofloxacin
  - gatifloxacin
  - levofloxacin
  - norfloxacin,
  - moxifloxacin – most commonly implicated

Moxifloxacin-Associated ‘uveitis’
Courtesy of Sarkis H. Soukiasian, MD.
‘Uveitis’
• Median two weeks after dosing
• Heavy pigment, some cells
• Bilateral – pain and blurring
• Pigment on endothelium and lens capsule
• Atonic pupil with TID
• Elevated IOP in 50%

Treatment
• Discontinue Fluoroquinolone
• Topical corticosteroids

Fluoroquinolones Naranjo SCORE = 6

Moxifloxacin-Associated ‘uveitis’
Courtesy of Sarkis H. Soukiasian, MD.
Moxifloxacin-Associated ‘uveitis’
Courtesy of Ilknur Tugal-Tutkun, MD.
Fluoroquinolones Naranjo SCORE = 6

– Mechanisms
  • “Pseudo-uveitis”
  • Possible phototoxicity
  • Predisposition to autoimmune disorders (Hinkle et al.)
    – HLA-B27 and HLA-B51 haplotypes
    – 20% and 40% of tested individuals, respectively.
  • Not described with topical or intraocular fluoroquinolones.
TNF-α Antagonists Naranjo SCORE = 7 (Probable)
**TNF-α Antagonists Naranjo SCORE = 7**

- Inhibition of TNF-α, a pro-inflammatory cytokine
  - Effective for a variety of inflammatory diseases
    - Rheumatoid arthritis
    - Juvenile idiopathic arthritis
    - Crohn’s disease
    - Psoriatic arthritis
    - Ankylosing spondylitis.
    - Uveitis
    - Scleritis
    - etc
TNF-α Inhibitors

- Enbrel (etanercept)
- Remicade® (infliximab)
- Humira (adalimumab)
- Cimzia (certolizumab pegol)
- Simponi® (golimumab)
Infliximab (Remicade)  
Chimeric – 75% Human

Adalimumab (Humira)  
100% Human

Etanercept (Enbrel)  
100% Human

Monoclonal Antibody  
Monoclonal Antibody  
Receptor-Fc Fusion (TRAP)

IV q8-10 wks  
SQ q1-2wks  
SQ 2xwks
Numerous autoimmune side-effects

- Lupus-like syndrome
- Autoimmune hepatitis
- Interstitial lung disease
- Uveitis

- Variable time to presentation
- Often non-specific anterior & intermediate uveitis
- 10% or more paradoxical; i.e., not typically seen with disorder being treated
- Variable outcome
**TNF-α Antagonists Naranjo SCORE = 7**

Do Tumor Necrosis Factor Inhibitors Cause Uveitis?
A Registry-Based Study

Lyndell L. Lim,1 Frederick W. Fraunfelder,2 and James T. Rosenbaum2

ARTHritis & Rheumatism
Vol. 56, No. 10, October 2007, pp 3248–3252

Total
- 43 Etanercept
- 14 Infliximab
- 2 Adalimumab

Excluding Known Uveitis Disorders*
- 20 Etanercept
- 4 Infliximab
- 2 Adalimumab

Etanercept Most common

*Paradoxical
LETTER TO THE EDITOR

Sarcoid Intermediate Uveitis Following Etanercept Treatment: A Case Report and Review of the Literature

Alex Fonollosa¹, Joseba Artaraz¹, Iñigo Les², Agustin Martinez-Berriotxoa², Julio Perez Izquierdo³, Alberto Saiz Lopez⁴, Jesus Gardeazabal⁵, Barbara Berasategui⁶, and Nerea Martinez-Alday⁶

Ocular Immunology & Inflammation, 20(1), 44–48, 2012

Courtesy of Alex Fonollosa, MD
TNF-α Antagonists Naranjo SCORE = 7

– Mechanisms
  • Unknown
  • Possibly TNF-α-induced and interferon suppression
  • TNF-α inhibitors elevate interferon levels in some
Checkpoint Inhibitors
Naranjo SCORE = 7 (Probable)
Checkpoint Inhibition & T cell Activation

T cell
- CTLA-4
- CD28
- TCR
- PD-1

APC or Tumor Cell
- B7
- MHC
- PD-L1

Peptide
Ipilimumab (α-CTLA-4; Yervoy)
Metastatic melanoma; trials in lung, bladder, prostate, etc
**Nivolumab (α-PD-1; Opdivo)**

Metastatic melanoma; NSCLC, RCCA, etc
Pembrolizumab (α-PD-1; Keytruda)
Metastatic melanoma; NSCLC, HNSCA, cHL, etc
Checkpoint Inhibitor Genes Linked to Autoimmune Disease

Table 1

The CTLA4, PD-1 and PD-L1 genes are linked to self-tolerance and are involved in autoimmune diseases.

<table>
<thead>
<tr>
<th>Autoimmune disease</th>
<th>Polymorphism</th>
<th>Ethnic group</th>
<th>Referred studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroiditis, Graves’ disease and Hashimoto’s disease</td>
<td>CTLA-4</td>
<td>European</td>
<td>Ueda, Nature 2003 [8]</td>
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<tr>
<td>Diabetes mellitus</td>
<td>CTLA-4</td>
<td>European</td>
<td>Vaidya, Rheumatology 2002 [72]</td>
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<td></td>
<td>Asian</td>
<td>Ueda, Nature 2003 [8]</td>
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<td>Zhernakova, Hum Genet, 2005 [73]</td>
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<td></td>
<td>Zalloua PA, Hum Immunol 2004 [10]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Jin, P of Endocrinol Investig, 2014 [74]</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>CTLA-4</td>
<td>European</td>
<td>Zhernakova, Hum Genet, 2005 [73]</td>
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<td></td>
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<td>Song, Hum Immunol, 2013 [75]</td>
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<td>Systemic lupus erythematosus</td>
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<td>Hudson, Hum Genet, 2002 [77]</td>
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<td>PD-1</td>
<td>European and Mexicans</td>
<td>Prokunina, Nat Gene, 2002 [9]</td>
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<td>Rheumatoid arthritis</td>
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<td>European</td>
<td>Bertsias, Arthritis Rheum. 2009 [78]</td>
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<td>PD-1</td>
<td>European and Asian</td>
<td>Vaidya, rheumatology 2002 [72]</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>CTLA-4</td>
<td>European</td>
<td>Lee, Z. Rheumatol. 2015 [79]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Blomhoff, J Clin Endocrinol Metabol 2004 [8]</td>
</tr>
</tbody>
</table>

**Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents**

JEFFREY S. WEBER, a MICHAEL POSTOW, b, c CHRISTOPHER D. LAO, d DIRK SCHADENDORF e

a Laura and Isaac Perlmutter Cancer Center, New York University Langone Medical Center, New York, New York, USA; b Memorial Sloan Kettering Cancer Center, New York, New York, USA; c Weill Cornell Medical College, New York, New York, USA; d Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA; e University Hospital Essen, Essen, Germany

Disclosures of potential conflicts of interest may be found at the end of this article.

**irAEs Common – Especially with Ipilimumab; α-CTLA-4**

---

**Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors**

<table>
<thead>
<tr>
<th>AE</th>
<th>NIVO a, b</th>
<th>NIVO + IPI a, c</th>
<th>IPI a, d</th>
<th>Pembro e, f</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18.8</td>
<td>0</td>
<td>33.2</td>
<td>1.9</td>
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<tr>
<td>Rash</td>
<td>25.9</td>
<td>0.6</td>
<td>40.3</td>
<td>4.8</td>
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<tr>
<td>Diarrhea</td>
<td>19.2</td>
<td>2.2</td>
<td>44.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Colitis</td>
<td>1.3</td>
<td>0.6</td>
<td>11.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>3.8</td>
<td>1.3</td>
<td>17.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>3.8</td>
<td>1.0</td>
<td>15.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.6</td>
<td>0</td>
<td>15.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
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<tr>
<td>Pneumonitis</td>
<td>1.3</td>
<td>0.3</td>
<td>6.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**IPI = Ipilimumab (α-CTLA-4); NIVO = Nivolumab (α-PD-1); Pembro = Pembrolizumab (α-PD-1)**
- irAEs Common
- Grade 1 - 2 > 3 – 5
- \(\alpha\)-CTLA-4 > \(\alpha\)-PD-1/L1
- Most Common
  - Skin
  - GI
  - Pulmonary
  - Arthralgia
- Ocular Uncommon
Many, Many Immuno-Oncology Trials Ongoing and Planned
Checkpoint Inhibitors Narango SCORE = 7

- Ipilimumab Ocular irAEs
- > 20 cases
  - Orbital Inflammation
  - Uveitis (VKH-like)
  - Episcleritis, Scleritis
  - Keratitis
Ipilimumab-induced Ocular and Orbital Inflammation—A Case Series and Review of the Literature

Evangelia Papavasileiou, MD¹, Sashank Prasad, MD², Suzanne K. Freitag, MD¹, Lucia Sobrin, MD, MPH¹, and Ann-Marie Lobo, MD¹

Ocular Immunology & Inflammation, 2016; 24(2): 140–146
Bilateral neuroretinitis and anterior uveitis following ipilimumab treatment for metastatic melanoma

Laura Hahn and Kathryn L. Pepple

*Journal of Ophthalmic Inflammation and Infection* (2016) 6:14
Checkpoint Inhibitors Narango SCORE = 7

- $\alpha$-PD-1 Ocular irAEs
- Nivolumab & Pembrolizumab
- ~10 Cases Each
  - Uveitis (VKH-like)
  - Chorioretinopathy
  - Orbital Inflammation
  - Keratitis
Bilateral uveitis and macular edema induced by Nivolumab: a case report

Claire Theillac¹,²*, Morgane Straub²,³, Anne-Laure Breton¹,², Luc Thomas¹,²,⁴ and Stéphane Dalle¹,²,⁴

Panuveitis
Posterior Synechiae
Papillitis
Serous Retinal Detachment
CME
Case of acute anterior uveitis and Vogt–Koyanagi–Harada syndrome-like eruptions induced by nivolumab in a melanoma patient

Chorioretinal Lesions in a Case of Melanoma-Associated Retinopathy Treated With Pembrolizumab

Philipp Roberts, MD; Gerald A. Fishman, MD; Komal Joshi, MD; Lee M. Jampol, MD
Erlotinib Naranjo SCORE = 6 (Probable)
Erlotinib Naranjo SCORE = 6

- Oral Epidermal Growth factor Receptor (EGFR) tyrosine kinase inhibitor
- Approved for NSCLC, and advanced pancreatic cancer
- Associated with ~5 Case reports of bilateral anterior uveitis
  - Some need discontinuation
  - Topical corticosteroids/cycloplegics/mydriatics
  - Periocular corticosteroids
Bilateral acute simultaneous onset anterior uveitis presumed secondary to erlotinib: A report of two cases

Kendra A. Klein, Christopher G. Azzoli, Lana M. Rifkin

Department of Ophthalmology, New England Eye Center, Tufts Medical Center, Boston, MA, USA


- **Bilateral Anterior Uveitis**
- **Koeppe Nodule**
# Drug-Induced Uveitis

## Intraocular Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weighted Naranjo Score</th>
<th>Association with Uveitis (Causal Likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cidofovir</td>
<td>11</td>
<td>Definite</td>
</tr>
<tr>
<td>Anti-VEGF Agents</td>
<td>11</td>
<td>Definite</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>7</td>
<td>Probable</td>
</tr>
</tbody>
</table>
Anti-VEGF Agents Naranjo SCORE 11 (Definite)
**Pegaptanib**
- Binds specifically only one VEGF-A isoform

**Bevacizumab**
- Binds all VEGF-A isoforms

**Ranibizumab**
- Binds all VEGF-A isoforms with a higher affinity than bevacizumab

**Aflibercept**
- Binds VEGF-A with higher affinity than bevacizumab and ranibizumab
- Also binds VEGF-B and PI GF

**Aptamer**

**Monoclonal antibody**

**Antibody fragment**

**Fusion protein**

Timeline:
- 2004
- 2005
- 2006
- 2011
- 2013
Early anti-VEGF agent

• Pegaptanib
• Inhibits VEGFA 165 isoform
• 14% of eyes uveitis after pegaptanib vs 6% of eyes after sham injection
• Due to preparation and/or the injection?
• Follow-up study of a smaller cohort with much higher doses had no cases of anterior uveitis or ocular inflammation.
Anti-VEGF Agents Naranjo SCORE 11

- More recent anti-VEGF agents
  - Bevacizumab
  - Ranibizumab
  - Aflibercept (the newest VEGF decoy receptor)
  - Bind and inhibit the activity of all isoforms of VEGFA
- Generally uncommon <1%
- Generally mild
Triamcinolone Acetonide
Naranjo SCORE – 7
(Probable)
Triamcinolone Acetonide

Naranjo SCORE - 7

• Severe paradoxical non-infectious or sterile endophthalmitis
  – Symptoms
    • reduced vision
    • minimal pain or conjunctival injection
  – Develops within 1-7 days after injection
  – Signs
    • anterior chamber cell
    • hypopyon
    • moderate to severe vitritis
  – Incidence varies from 0.5% to 9.7% of injections
Triamcinolone Acetonide

Endophthalmitis

Pseudo – Endophthalmitis

Courtesy of Dr. Emmett T. Cunningham, Jr and Dr. Andrew A. Moshfeghi
Triamcinolone Acetonide

- Treatment with intensive topical and/or periocular
- Visual outcomes are good
  - average final acuity of 20/75.
  - Infectious endophthalmitis suspected and empirically treated if
    - Pain
    - severe vision loss
    - intense conjunctival injection
    - Severe vitritis
## Drug-Induced Uveitis

### Topical Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weighted Naranjo Score</th>
<th>Association with Uveitis (Causal Likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topical Ocular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metipranolol</td>
<td>10</td>
<td>Definite</td>
</tr>
<tr>
<td>Brimonidine</td>
<td>9</td>
<td>Definite</td>
</tr>
<tr>
<td>Prostaglandin Analogs</td>
<td>9</td>
<td>Definite</td>
</tr>
<tr>
<td><strong>Topical Cutaneous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Podophyllum</td>
<td>7</td>
<td>Probable</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>5</td>
<td>Probable</td>
</tr>
</tbody>
</table>
# Drug-Induced Uveitis Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Weighted Naranjo Score</th>
<th>Association with Uveitis (Causal Likelihood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>9</td>
<td><strong>Definite</strong> (anterior uveitis, panuveitis, chorioretinitis)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>6</td>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>Influenza</td>
<td>7</td>
<td><strong>Probable</strong>: Orbital myositis, posterior scleritis, anterior uveitis, APMPPE, panuveitis</td>
</tr>
<tr>
<td>MMR</td>
<td>7</td>
<td><strong>Probable</strong>: Anterior uveitis and panuveitis</td>
</tr>
<tr>
<td>Varicella</td>
<td>4</td>
<td><strong>Possible</strong>: Anterior uveitis, sclerokeratitis, necrotizing herpetic retinitis</td>
</tr>
<tr>
<td>HPV</td>
<td>6</td>
<td><strong>Probable</strong>: Panuveitis, SRD</td>
</tr>
</tbody>
</table>
Anti-VEGF Agents Naranjo SCORE 11

Ranibizumab

- MARINA / ANCHOR trials
  - severe inflammation with 3+ cells or greater
  - 2% of treated eyes compared to 0% of the controlled eyes
  - increased to 7.9% of treated eyes in the ANCHOR study.
  - occurred immediately following the injection and self-limited.

- FOCUS study, Ranibizumab plus PDT vs. PDT alone
  - uveitis occurring in 12.4% of eyes treated with Ranibizumab plus PDT b. 0% of patients who received PDT alone
  - Reasons:
    - Lyophilized formulation of Ranibizumab utilized.
    - PDT timing – soon after Ranibizumab injection
Anti-VEGF Agents Naranjo SCORE 11

- Bevacizumab - sparsity of randomized controlled clinical trials
  - CATT /IVAN studies – RCT
    - rate of intraocular inflammation quite low
    - both ranibizumab and bevacizumab, 0.3% and 0.5% respectively
    - managed with topical corticosteroids and improved.
  - Other non RCTs - rates of uveitis ranging from 0.5% - 6% of eyes
    - occurring a few days after injection
    - controlled with topical corticosteroids
    - Moderate to severe inflammation has also been reported
      - one to three weeks following injection
    - rechallenge data → recurrent inflammation.
Anti-VEGF Agents Naranjo SCORE 11

• **Bevacizumab** -
  
  • **Severe anterior uveitis with fibrin +/- hypopyon**
    – within 1-3 days of injection of bevacizumab
    – similar to TASS (but no corneal edema)
    – Most had not developed uveitis with previous bevacizumab.
    – due to a toxic by-product of those present on the bevacizumab formulations in that particular lot of injections.
  
  • **Sterile endophthalmitis**
    – after a mean of around three injections
    – one to three days following the injection
    – mild discomfort and decreased vision
    – anterior uveitis and significant vitritis
    – responded well to intensive topical corticosteroids
Anti-VEGF Agents Naranjo SCORE 11

- Internet-based surveys and doctor reported adverse events
  - Uveitis - 0.1% of eyes receiving bevacizumab
- Medicare database surveys
  - after 2 years of anti-VEGF therapy
  - uveitis was twice as prevalent (0.73%) as in disease matched control groups (0.37%).
Anti-VEGF Agents Naranjo SCORE 11

• Aflibercept
  – Decoy receptor fusion protein
  – Binds through the VEGF receptor
  – Uveitis incidence much less than 1% in the clinical trials

• Treatment
  – Discontinuation of agent
  – Switch to different anti-VEGF agent
  – Topical corticosteroids and cycloplegics
Metipranolol – Naranjo SCORE 10

• **First topical agent to be associated with anterior uveitis**
• **Non-selective topical beta-blocker**
  – Treat ocular hypertension and glaucoma.
• **Original report of Akingbehin and Villada**
  – 56 episodes of granulomatous anterior uveitis
  – 26 eyes of 15 patients
  – all of the cases were associated with a .6% dose (vs. 0.3% )
  – withdrawal of the .6% dose from the commercial market.
Metipranolol – Naranjo SCORE 10

• **Uveitis - Clinical Feature**
  – *Granulomatous anterior uveitis*
  – *Develops after 6 months or more of chronic use*
  – *50% of the patients who also developed ocular hypertension*
  – *Significant rechallenge data*

• **Therapy**
  – *Discontinuation of medication*
  – *topical corticosteroids*

• **Mechanism - is unknown**
Brimonidine Naranjo SCORE = 9

- **Selective alpha2-adrenergic receptor agonist**
  - treatment of primary open angle glaucoma and ocular hypertension.

- **Clinical Characteristics**
  - granulomatous anterior uveitis
  - intraocular pressure elevations
  - Taking medication for nearly a year or longer
  - Affected only the treated eye
  -Resolved with discontinuation of the medication
    - with or without the use of topical corticosteroids.
  - 4 Original patients developed recurrent inflammation
    - within three weeks of restarting brimonidine

- **Mechanism – unknown.**
Prostaglandin Analogs
Naranjo SCORE = 9

• Effective treatment of ocular hypertension and glaucoma
  – Latanoprost, travoprost and bimatoprost
  – improve uveoscleral outflow.

• Numerous side effects
  – cutaneous pigmentation in the periorbital skin
  – change in iris color
  – conjunctival hyperemia
  – growth of eyelashes
  – development of cystoid macular edema
  – anterior uveitis
  – reactivation of herpes simplex virus keratitis.
Topical Podophyllum
Naranjo SCORE = 7

- **Extract of Podophyllum peltatum (May apple)**
  - Treat cutaneous warts.

- **Single case report**
  - Unilateral – ipsilateral lateral canthal application
  - Non-granulomatous uveitis
  - Occurred within 48 hours
  - Resolved with topical corticosteroids and drug cessation
  - Recurred even with re-application of a lesser quantity of the drug
Topical Capsacin Naranjo SCORE = 5

• Chemical that gives chili peppers their “heat.”
• used as a topical analgesic.
• Single case report
  – bilateral, acute, non-granulomatous, anterior uveitis
  – 2-24 hours after application of a capsaicin patch on the patient’s neck.
  – Symptoms
    • pain, photophobia, and redness
  – Signs
    • Anterior chamber cells and flare.
  – Laboratory workup was unrevealing.
  – Resolved with drug cessation and topical corticosteroids
  – No rechallenge was performed.
BCG Vaccine

- Prophylaxis against *Mycobacterium tuberculosis* in endemic areas.
- Prevention of childhood tuberculous meningitis and miliary tuberculosis.
- Intravesically - treatment of bladder cancer.
BCG Vaccine  SCORE = 9

• Clinical Characteristics of Uveitis
  – Acute bilateral nongranulomatous or granulomatous anterior uveitis
  – Loss of iris pigmentation
  – Respond to treatment with topical corticosteroids and cycloplegics.
  – Rare cases
    • Bilateral panuveitis, chorioretinitis, vitiligo and optic neuritis have also been reported.
BCG Vaccine

• Mechanism
  – Molecular mimicry caused by the BCG exposure.
  – Amino acid sequence homology between proteins from *M. tuberculosis*, BCG, and retinal antigens.

• PPD Skin testing
  – One case of panuveitis
  – One case resembling Vogt-Koyanagi-Harada syndrome.
  – Delayed hypersensitivity reaction etiology.
Hepatitis B Vaccine – SCORE = 6

- Used for the prevention of hepatitis B infection
- Clinical Characteristics
  - acute posterior multifocal placoid pigment epitheliopathy – single case
  - anterior uveitis
    - 32 cases in national database
    - women with a mean age of 29 years
    - symptomatic anterior uveitis
    - associated with a flu-like illness
    - a few days following vaccination,
      - initial vaccination more commonly than subsequent
  - Rechallenge - demonstrated in some patients
- Mechanism –
  - immune-mediated delayed-type hypersensitivity reaction
  - immunogenicity of the vaccine carrier
Influenza Vaccine  SCORE = 7

• Several sporadic case reports
• Clinical Characteristics
  – Bilateral panuveitis
  – Recurrent panuveitis
  – Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
• Therapy
  – Anterior uveitis
    • Topical corticosteroids and cycloplegics
  – Posterior or Panuveitis
    • Systemic corticosteroids.
• Rothova and associates reported
  – Reactivation of acute retinal necrosis (ARN) following vaccination for the H1N1 strain
Mumps/Measles/Rubella (MMR) Vaccine  SCORE = 7

• Several reports of uveitis
  – sporadic, with variable severity

• Clinical Characteristics
  – Anterior Uveitis
  – Panuveitis
    • 4 and 6 weeks following MMR
    • 12 months or longer to resolve
  – Therapy - both topical and systemic corticosteroids

• Mechanism
  • antigenic mimicry
  • Vaccine Preparation
    – contamination or faulty preservation
Varicella Vaccine  SCORE = 4

• Attenuated live viral vaccination
• Clinical Characteristics – Usually 2-7 days after vaccination
  – Anterior uveitis
  – Anterior uveitis associated with a vesicular rash
  – Keratouveititis with inflammatory glaucoma and Hutchinson’s sign
  – Sclerokeratitis with anterior uveitis (herpes zoster ophthalmicus)
  – Necrotizing herpetic retinitis (ARN)
Varicella Vaccine

• Therapy
  – Standard treatment regimens
  – Topical corticosteroids and oral acyclovir
  – Two patients with ARN required more aggressive antiviral and surgical treatment

• Mechanism
  – Reactivation of varicella virus
  – Primary infection with the attenuated virus