Evolving therapies for posterior uveitis

Sam Dahr, M.D.
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Midwest Ophthalmology Conference

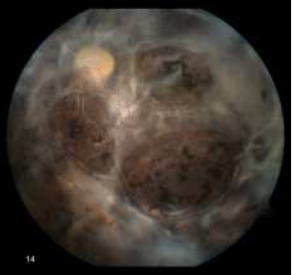
CINCINNATI EYE INSTITUTE

Infliximab (Remicade)

- FDA approved for Crohn's disease, rheumatoid arthritis, and psoriatic arthritis

Emerging therapy for posterior uveitis

- Infliximab (Remicade)
- Daclizumab (Zenapax; HAT)
- Fluocinolone implant (Retisert)



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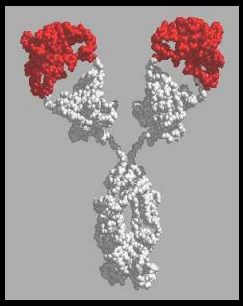
Infliximab: pharmacology

- Mouse-derived chimeric monoclonal antibody directed against TNF-α
- Binds soluble and membrane-bound TNF- α
- Affects IL-1, IL-6, leukocyte migration, neutrophil and eosinophil activity



Chimeric antibody

FDA-approved monoclonal antibody therapy

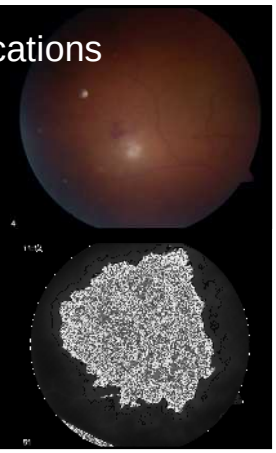
Product	Target	Indication	Approval yr	Ab type
OKT®3	CD3	Transplant rejection	1986	Mouse
ReoPro®	Platelet GP IIb/IIIa	Cardiovascular	1994	Chimeric
Zenapax®	IL-2 receptor	Transplant rejection	1997	Humanized
Remicade®	TNF	Crohn's disease, RA	1998	Chimeric
Simulect®	IL-2 receptor	Transplant rejection	1998	Chimeric
Rituxan®	CD20	Lymphoma	1997	Chimeric
Synagis®	RSV	Prevent RSV infection	1998	Humanized
Herceptin®	HER2	Breast cancer	1998	Humanized
Mylotarg®	CD33	Acute myeloid leukemia	2000	Humanized
MabCampath™	CD52	Chronic lymphocytic leukemia	2001	Humanized

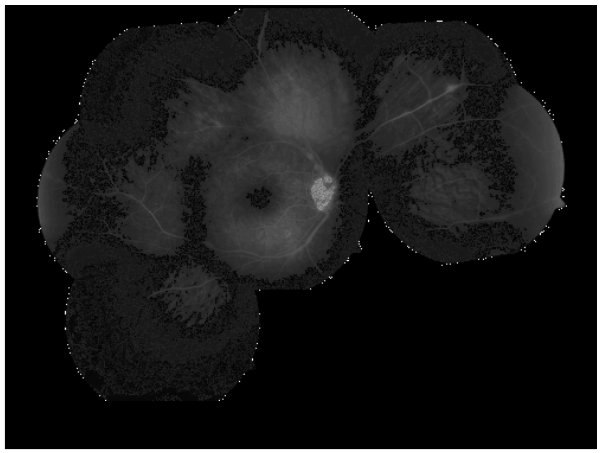
Infliximab: evidence for efficacy

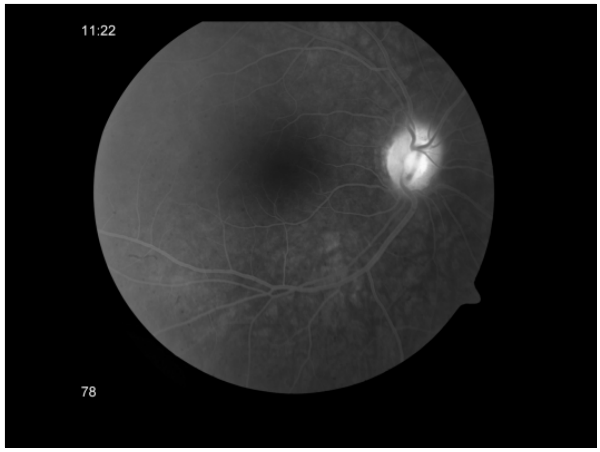
- Case series, mainly for Behcet's disease and scleritis
- No randomized controlled trials in uveitis

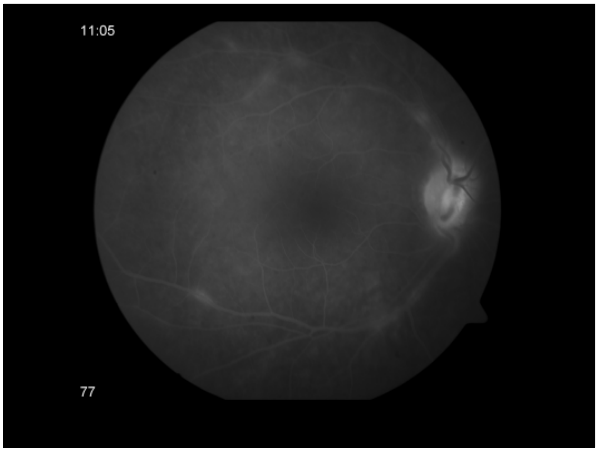
Infliximab: Indications

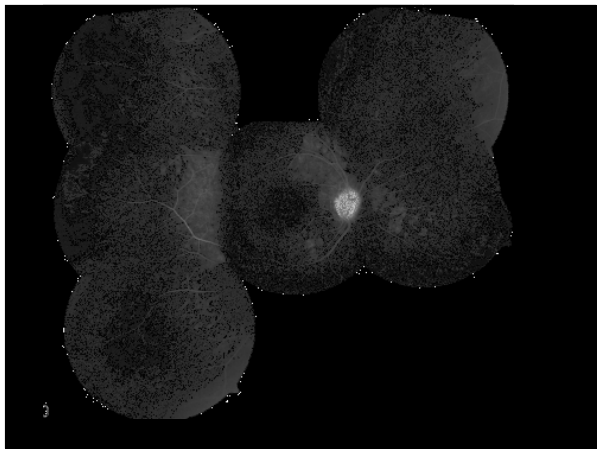
- Behcet's disease--first line?
- Idiopathic retinal vasculitis
- Scleritis

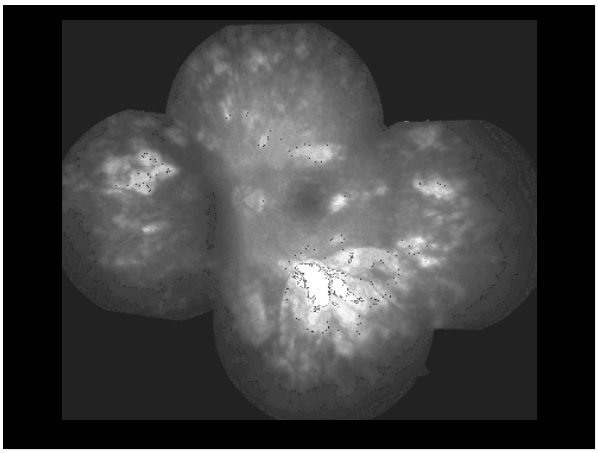








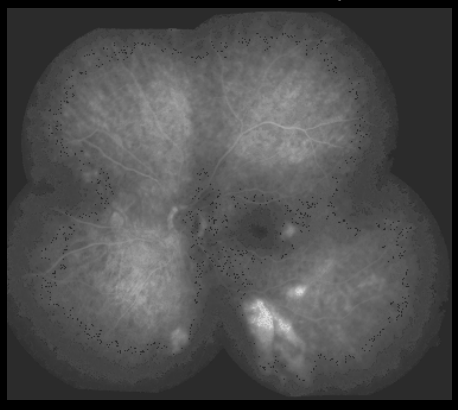




Infliximab: Contraindications

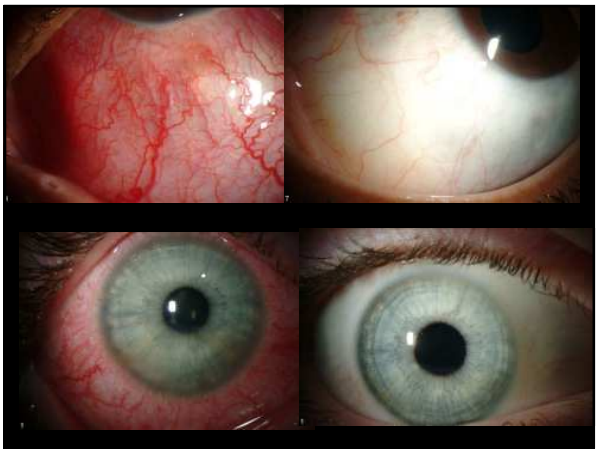
- Hepatitis B chronic carriers
- Heart failure
- History of tuberculosis

Infliximab and azathioprine



Infliximab

- No known carcinogenic or mutagenic effects in humans (mouse studies: no effect)
- No known impairment of fertility in humans (mouse studies: no effect)
- Pregnancy category B (effect on human reproduction unknown; no effect shown in animal studies)



Infliximab: dosage and administration

- 3-5 mg/kg at 0, 2, 6 weeks
- Repeat every 4-8 weeks
- Dosage as high as 10 mg/kg
- Often co-induced with MTX or MMF

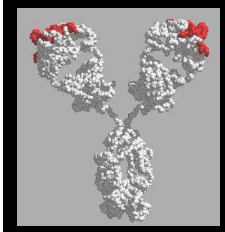
Infliximab: adverse effects and monitoring

- Reactivation of latent tuberculosis (9-41 per 100,000 patient years of infliximab treatment), histoplasmosis--often EXTRAPULMONARY
- CNS: optic neuritis, MS-like lesions, cerebral vasculitis, seizures
- Lymphoma
- Lupus-like syndrome
- Liver injury
- Cytopenias

Daclizumab: evidence for efficacy

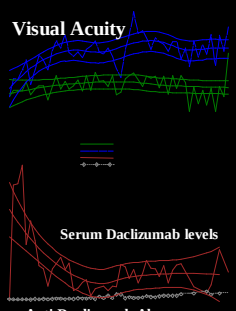
- Transplantation: phase III masked randomized trials have shown efficacy and safety
- Uveitis: phase I/II non-randomized open label study with long term followup

Daclizumab (Zenapax) (HAT)



Humanized antibody–90% human

- FDA approved for the prevention of renal allograft rejection
- Worldwide use in > 16,000 patients



Long term results in a study using daclizumab as the sole immunosuppressive agent for the treatment of uveitis: 4 year experience.

VA, serum daclizumab, and anti-daclizumab levels averaged over the 7 patients receiving drug for 4 years

Locally weighted quadratic smoothed curves (LOESS) with the corresponding 95% CIs overlaid on the point-averaged values

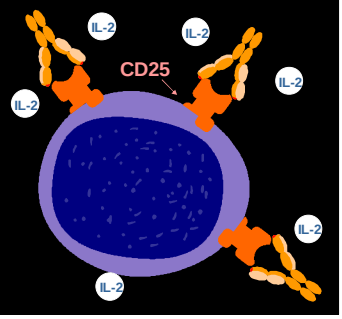
	Baseline	1 yr
Best Eye	20/32	20/32
Worst Eye	20/63	20/50

J Autoimmunity 2003 21:283-293

Slide courtesy of Dr. R. Nussenblatt

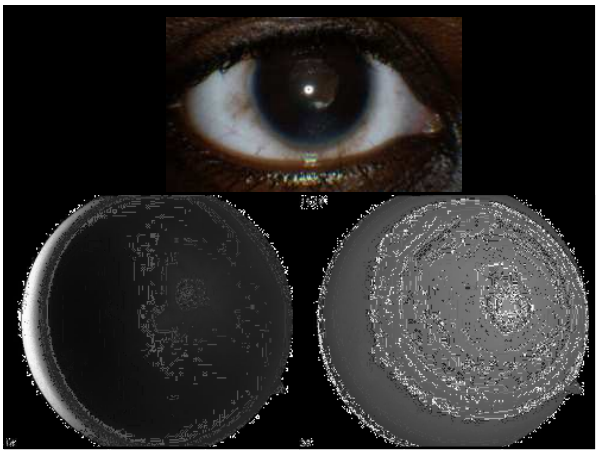
Pharmacology: Daclizumab interrupts autocrine and paracrine feedback cycle of IL-2

- Targets CD25 (α-chain of the IL-2 receptor), hence blocking IL-2 binding
  - Inhibits cell proliferation
  - Decreases additional IL-2 production



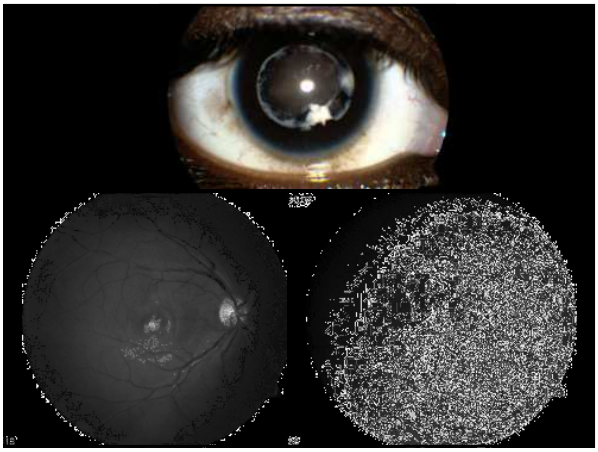
Daclizumab: indications

- Granulomatous disease--sarcoidosis, VKH
- Vasculitis/Behcet's disease--not recommended
- "Hot eye"



Daclizumab: dosage and administration

- 2 mg/kg IV at 0 and 2 weeks followed by 1 mg/kg infusions q 4 weeks
- Intravenous medication is FDA-approved and widely available.
- Subcutaneous form is investigational and is not commercially available.



Daclizumab: adverse effects and monitoring

- 629 renal allograft patients: 336 received Daclizumab and 292 received placebo
- No increase in adverse effects in Daclizumab group compared to placebo
- No increase in malignancy

Daclizumab: contraindications

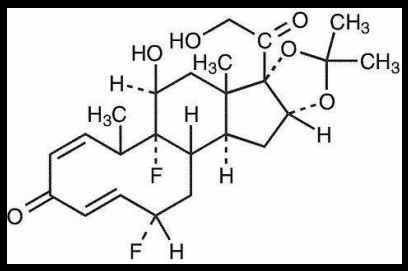
- No major contraindications
- Pregnancy category C (effect on human reproduction unknown; no animal studies performed)
- Animal studies to evaluate carcinogenesis or fertility effects have not been performed.

Daclizumab Adverse Events in Uveitis Patients: NEI 7 year experience

- Granulomatous hepatitis (1)--patient had sarcoidosis, no treatment.
- Mild elevation of alkaline phosphatase (1)--no treatment.
- Polyradiculopathy (1) involving left side of chest--spontaneous resolution.
- Renal cell carcinoma (1). Removed surgically 8/01, no further therapy. Patient has continued Daclizumab.
- Peripheral Edema (2). One with spontaneous resolution, other managed with furosemide.
- Dermatologic (3)--eczema (1), pityriasis rosea (1), cutaneous granuloma (1), mild shingles (1) treated with famciclovir.
- Culture negative oral fungal infection (1).

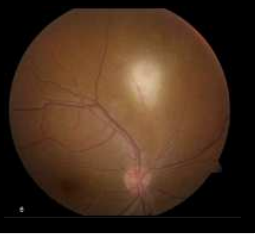
Fluocinolone implant (Retisert)

- Synthetic fluorinated corticosteroid



Fluocinolone: contraindications

- Glaucoma
- HSV/VZV/fungal keratitis
- Infectious uveitis

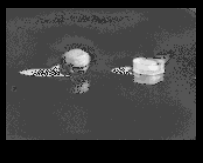


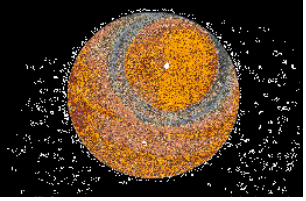
Fluocinolone: evidence for efficacy

- 2 RCTs, 227 patients total, showed decreased recurrent episodes in 34 weeks post-implantation (7%, 14%) versus pre-implantation (40%, 54%)

Fluocinolone: dosage and administration

- 0.59 mg, encased within a silicone elastomer, attached to a polyvinyl alcohol suture tab
- Delivers 0.3-0.4 ug/day for 30 months





Fluocinolone: indications

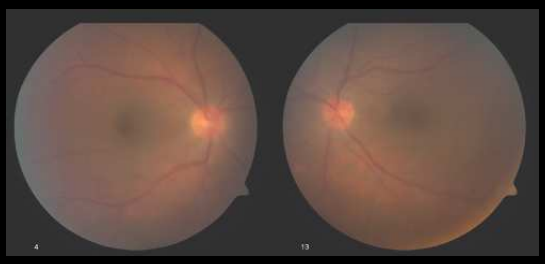
- Noninfectious intermediate and posterior uveitis
- Better for unilateral disease
- Systemic therapy contraindicated by malignancy

Fluocinolone: adverse effects and monitoring

- Surgical procedure: temporary VA decline, retinal detachment, choroidal hemorrhage, vitreous hemorrhage, endophthalmitis
- Cataract--close to 100% within 2 years
- IOP elevation--60% need drops within 34 weeks, 32% need filtering procedure within 2 years

Fluocinolone

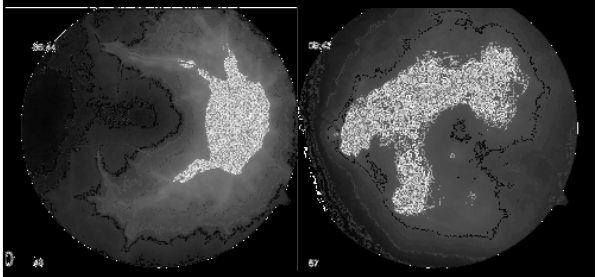
- Pregnancy category C (effect on human reproduction unknown; no animal studies performed)
- Animal studies to evaluate carcinogenesis or fertility effects have not been performed.
- Serum levels were undetectable in humans in the phase III trials



Final word on Retisert: Mainline treatment or niche therapy?

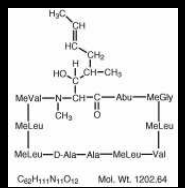
- Multicenter Uveitis Steroid Treatment (MUST) Trial Phase IV randomized trial to compare systemic therapy with corticosteroids and steroid-sparing medications to local therapy with the fluocinolone implant
- 22 centers
- 400 patients

"Nothing can be done."

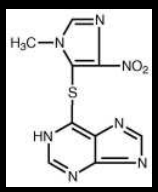


Mainline therapies

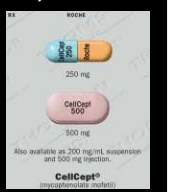
- Cyclosporine (Neoral, Gengraf)
- Azathioprine (Imuran)
- Mycophenolate (Cellcept)
- Methotrexate (Trexall, Rheumatrex)

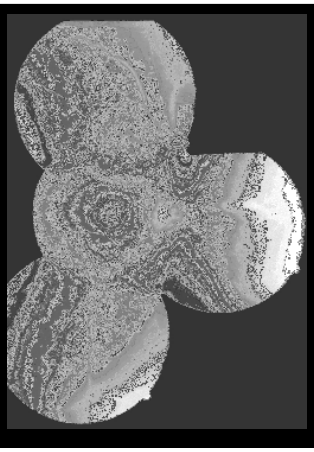


Cyclosporine

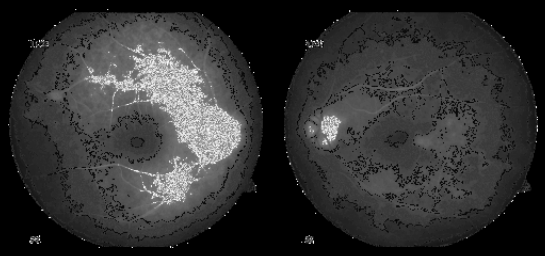


Azathioprine





Prednisone and cyclosporine



Doctor, can I get an eye transplant?

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Other established therapies

- Cyclophosphamide
- Chlorambucil

Therapy: Principles

- Define why vision is down.
- Each patient receives an individualized regimen that will evolve over time.
- Two to three months must pass to evaluate full response to a particular regimen.
- Weigh risks and side effects versus potential benefit.
- Phase in steroid sparing agents over time.
- Do not expect to eliminate systemic steroids totally.