Turkish Congress 2013
Uveitis Course

Viral Retinitis

Carlos Pavesio MD FRCOphth
Moofields Eye Hospital
Viral Agents associated with Retinitis

- Varicella Zoster Virus (VZV)
- Herpes Simplex Virus 1 and 2 (HSV)
- Cytomegalovirus (CMV)
- Epstein-Barr Virus (EBV)
- HHV-6,7
## Acute Retinal Necrosis

### Table 1  American Uveitis Society diagnostic criteria (1994)

- One or more foci of retinal necrosis in peripheral retina (± macula) with circumferential spread
- Evidence of occlusive vasculopathy
- Inflammatory reaction in vitreous and anterior chamber
- Not dependent on extent of retinal necrosis, gender, race, age, immune status
most frequently caused by

- **VZV** and **HSV**
  - VZV 2x more common than HSV
  - reports exist implicating EBV and CMV

**Incidence**

- 3 – 4 / million per year (Sims 2009, Melbourne, Australia)
- 1 case per 1.6 to 2.0 million population / year (Muthiah 2007, BOSU, UK)

Clinical Findings: Symptoms

- rapidly reducing vision (85%),
- photophobia (55%),
- ocular pain (26%),
- flu like symptoms (16%)
- NB: Red eye in only 16%
Clinical Findings: Signs

- Anterior uveitis with fine or granulomatous KPs
- Vitritis - may be severe
- Occlusive retinal vasculitis - arteritis with haemorrhages
- One or more focus of retinitis located in the retinal periphery with circumferential spread that extend towards the posterior pole
- Optic disc swelling
- Episcleritis or scleritis
Because dilated fundus examination is not performed / inadequately assesses the periphery

‘Just Acute Anterior Uveitis’

Don’t forget to always examine both eyes
ARN is a clinical diagnosis

- So lab tests are not necessary to make the diagnosis
- Confirmation by PCR
  - vitreous early on: precise identification of virus
  - aqueous is positive in 80% of the cases (Tran THC Br J Ophthalmol 2003)
- Also diagnostic vitrectomy may be needed in atypical presentations (usually associated with immunodeficiency) to exclude other agents such as *T. gondii* / bacteria / masquerade etc (cytology, PCR)
Fluorescein Angiography

- Occlusive arteritis and retinal ischaemia
- Periphlebitis and venous thrombosis
- Leakage from retinal venules, arterioles, capillaries.
- Optic disc swelling
- Areas of non-perfusion
- Serous retinal detachment (uncommon)
Bilateral ARN

- 24 to 80% (when no Rx)
- Mostly within 3 months/1 year, but much longer intervals reported
- As compared to no treatment, treatment with systemic acyclovir decreases the risk of fellow eye involvement from 70% to 13%.

Second eye once treatment started
Lau et al. 22 patients
5/22 (22.7%) had BARN
  2/22 presented with BARN
  3/22 developed ARN in the fellow eye on day 14 (day 9 on acyclovir treatment), day 53 (day 53 on acyclovir treatment), and day 166 (day 110 after 56 days on acyclovir treatment), after first-eye presentation.

ARN in AIDS

- AIDS patients with only mild immune dysfunction and elevated CD4 counts
- ARN is more extensive,
  - bilateral 90%,
  - less responsive to antiviral agents,
  - tendency for recurrence same eye,
  - retinal detachment 80%,
  - poor visual acuity, dismal prognosis

HSV 1 and HSV 2

- Younger individuals
- Exudative retinal detachment
- Association with HSV encephalitis or meningitis
Herpetic Encephalitis as a Risk Factor

- Brain-to-eye transmission of the herpesvirus
- The overall interval between the encephalitis and ARN was 20.6 months average (range 14 days to 5 years).
Immunocompetent 50 year old lady
Vitreous CMV PCR positive (negative for HSV/VZV)
Initially treated with acyclovir, progressed → intravitreal foscarinet then Intravitreal and iv gancyclovir and oral pred
2 months later RD→ phaco-vity-oil
VA 6/36 → 6/12 at 12 months

Fig. 1 Right eye fundus showing necrotizing retinitis lesions (arrow marks) in the periphery
Peripheral 360° necrosis and severe panuveitis
Complications

- Retinal detachment in 75%
- Ischemic neuropathy, optic atrophy
- Arterial occlusions
- Macular damage
- Cataract
- Glaucoma
- Phthysis bulbi
All current treatment options for ARN are based on anecdotal evidence.

- Antiviral agents
- Corticosteroids
- Management and prevention of RD
Antiviral Therapy

- Immediate start
- **Intravitreal antiviral**
- **Systemic therapy – acute phase (10-14 days)**
  - Intravenous acyclovir: 10mg/kg tds
  - Oral valacyclovir: 2gr tds
- **Systemic therapy following acute phase**
  - Oral acyclovir: 800mg, 5x for 12 weeks
  - Oral valacyclovir: 1gr, 3x for 12 weeks
The vitreous concentrations achieved in non-inflamed eyes are within the reported inhibitory ranges for most strains of HSV (1 and 2) and VZV.

If oral Rx: Use 1-2g tds-valacyclovir

Rapid good absorption

Always watch out for non response
  - Consider increasing dose and adding intravitreal Foscarnet (2.4mg)
Antiviral Therapy

- Indefinite therapy:
  - Immunocompromised (depending on reason)
  - Previous history of Herpetic encephalitis?
Famciclovir (500 mg tds)

Oral administration of famciclovir (Famvir, Novartis Pharmaceuticals) → vitreous concentrations of penciclovir (Denavir; GlaxoSmithKline) within the inhibitory ranges for HSV-1, HSV-2 and VZV

What is the advantage?

- famciclovir has a better oral bioavailability and pharmackinetic profile then acyclovir.
- Less toxicity at high dose of valacyclovir and valganciclovir
- May be useful in acyclovir-resistant VZV-ARN
  - but penciclovir has a similar dependence on thymidine kinase for activation

Vitreous Penetration of Orally Administered Famciclovir

DEBORAH Y. CHONG, MARK W. JOHNSON, TONY H. HUYNH, EDWARD F. HALL, GRANT M. COMER, AND DOUGLAS N. FISH

AJO 2009;148:38-42
Any role?
- Optic disc involvement: pale swelling
- Intense inflammation?

When to start
- Delay 24-48 hours
result of combination of retinal necrosis and vitreoretinal traction,
breaks can occur posteriorly as well as at the vitreous base....usually at junction of diseased and healthy retina
Presentation: 0 days - 4 years following diagnosis of ARN (median 4-5 weeks).
**RD treatment**: vity / silicone oil
- Optic nerve or Photoreceptor damage limits final visual results despite anatomical success
Any role for laser prophylaxis?

- Unclear
- because the conclusions are based on
  - small case series of 5 to 13 eyes
  - weak level of evidence
  - active retinitis will progress through laser scars
  - worse disease → greater vitritis → lose the view → can’t laser
  - ? Laser group has milder ARN

ARN studies compared laser treatment against no laser treatment in two heterogenic study populations.

Milder cases of ARN with limited vitreous opacification and/or retinitis did better after laser treatment compared with more severe cases of retinitis, which did worse without laser, resulting in higher rates of retinal detachment.

Role of pre-existing posterior vitreous separation unknown

May do some harm? hole formation and, possibly, promote RD
81 eyes, 74 patients

Visual outcome in HSV-ARN (33 eyes) better than in VZV-ARN (48 eyes).

2.5-fold greater chance of RRD in VZV-ARN > HSV-ARN

Intravitreal foscarnet useful adjunctive treatment → reduced rate of RRD

- The results for VZV-ARN showed a 40% reduction in RRD frequency between the foscarnet group and the standard treatment group (54% vs 75%; P 0.23)
Milder disease at initiation of therapy
- in 77% of the eyes, less than 25% of retina involved

Final VA was 20/40 or better in 6 eyes (46%), and 20/400 or better in 12 eyes (92%).

Better initial VA = Better final VA

N= 13 eyes, Follow-up period = 3 to 21 months

Progressive Outer Retinal Necrosis
VZV retinitis
PORN: a disease of severely immunocompromised patients

- Defined in AIDS patients
- **Minimal** inflammation
- Multifocal retinitis, grey-white opacified lesions in the outer retina that rapidly progress and involve the periphery
- Rapid progression to involve second eye
- → Bilateral in 70%
Treatment is with multiple agents

- **1st line**
  - iv Ganciclovir & Foscarnet
    - Plus intravitreal ganciclovir +/- foscarnet
- **2nd line**
  - iv Cidofovir
  - Plus intravitreal ganciclovir +/- foscarnet

- Some eyes may not respond to multi drug therapy even if patient responds to HAART
PORNT: poor prognosis

- Visual loss due to:
  - early macular involvement
  - progressive infection,
  - retinal detachment (70–85% of patients)
  - optic nerve sheath effusion,

- Blindness is bilateral in 59%.
  - Rapid: within days or weeks
  - 2/3 patients → NPL. (Engstrom et al 1994)
Long-Term Preservation of Vision in Progressive Outer Retinal Necrosis Treated with Combination Antiviral Drugs and Highly Active Antiretroviral Therapy

- **PORN (VZV-PORN)** with preservation of 20/20 vision after combination
- **Antiviral treatment**
  - ganciclovir implant
  - intravenous acyclovir (10 mg/kg tds)
  - intravitreal foscarnet (2.4 mg)
- **HAART**
- $\rightarrow$ **20/20 visual acuity at 1 year**
CMV RETINITIS

- Immunocompromised individuals
  - CD4 < 50
    - Rare above 100
- Clinical disease: reactivation of latent infection or newly acquired
- Most common ocular infection in AIDS patients
- More common in homosexual men
- Reduction of number of cases since HAART
Fig 3.—Diagram of the retina (left) and photograph of the posterior pole (right) of a right eye, illustrating zones used to identify the location of retinal lesions in baseline ophthalmic examinations.
CMV retinitis: inactive scar
CMV is a slowly progressive infection, moving an average 250-350 μm/week. Response to treatment is indicated by transition from white active retinitis to inactive disease. There may be persistent whitening within the border that does not represent active disease. Presence of retinal oedema and small satellite lesions are best for differentiating white scar from reactivation.
CMV – importance of photographs

Movement of disease can occur with minimal retinal whitening - importance of photographs.
GANCICLOVIR

- Nucleoside analog
- Depends on *phosphorylation by viral kinase*
- Virustatic
- Effect is reversible
- Poor oral absorption
- Complications: neutropenia, thrombocytopenia, central line infection
Dose:

- **Induction:** 5mg/kg BD for 2-3 weeks
- **Maintenance:** 5mg/kg OD, 7 days/week
  6mg/kg OD, 5/7 days/week
A pyrophosphate analog
Inhibits DNA polymerase & reverse transcriptase
Does not require phosphorilation
Effect also virustatic and reversible
Intrinsic activity against HIV
Complications: nephrotoxicity, electrolyte shifts, anaemia and central line infection.
Dose:

- **Induction:** 90mg/kg BD for 2-3 weeks
- **Maintenance:** 120 mg/kg OD, 7 days/week

Infusion must be slow. Hydration with 1 L saline.
CIDOFOVIR

- Nucleotide analog
- Dose: Induction - 5mg/kg/week for 2 weeks
  Maintenance - 5mg/kg every 2 weeks
- Toxicity is primarily renal
- Probenecid
- No effect on viremia
Pro-drug of ganciclovir
- 900 mg PO bd induction, od maintenance
- Intraocular- levels as good IV Ganciclovir
- CMV control as good as intravenous ganciclovir
What if CMV progresses despite oral VGV?

- Ensure correct diagnosis!
- Ensure patient compliance
  - Consider admission for intravenous ganciclovir
- Exclude bioavailability problem
  - Malabsorption / GI causes
  - Try Oral VGV + intravitreal ganciclovir (2mg in 0.1)
    - Induction: 2 per 1st week, then weekly for 3 weeks.
    - Maintenance: every 2-3 weeks
The only definitive treatment for CMV is immune restoration

- **Individualize**
  - Cease VGV once CD4 > 100 for at least 3 months (some say > 200)
  - CMV reactivation reported with CD4 > 100
    - 6% per year CD4 100 to 200 (Jabs et al, Ophthalmology 2000)

- **Lifelong vigilance**
  - CMV likely to reactivate if CD4 drops below 100
LOCAL THERAPY

Rationale

- Site of clinical CMV disease is primarily the eye
- Systemic drug penetration into the eye is poor
LOCAL THERAPY

- Ganciclovir: 2mg in 0.05-0.1ml
- Foscarnet: 2.4mg in 0.1ml
- Cidofovir: 20μg in 0.1ml + probenecid
- Fomivirsen (ISIS-2922)
Ganciclovir implant (Vitrasert):

- 4.5mg of the drug
- releases drug at 1μg/hour
- lasts for 6-8 months
- when to replace
- technique
Immune recovery Uveitis

• More common in HAART era
• CD4 >50, usually in 100’s
• Signs:
  – A.C. activity,
  – Vitritis
  – Cystoid macular oedema
  – Epiretinal membrane
  – Optic disc neovascularisation
• Spectrum: mild to severe

Immune Recovery Uveitis
- Early recognition
- Appropriate and aggressive therapy
- Watch out for complications