Alternative drugs to anti-VEGF agents

The Anti-VEGF paradox in Treating Wet AMD

DME treatment in the real world doesn’t match randomized clinical trials

The Current State of Play

Anti-VEGFs are the mainstay of ocular chronic disease treatments

New variations / combinations and better delivery offer increased chance of success

BUT:

- >50% of patients don’t improve BCVA after anti-VEGF
- 10% don’t respond to the treatment at all
- No treatment for dry AMD / Geographic atrophy
- We’re only treating a late stage sign of disease
- Anti-VEGF cannot distinguish between bad and good blood vessels
- VEGF is just one cytokine upregulated in the vitreous of AMD/DR Patients
  (others include IL-1, IL-6, IL-8, TNF-α, and MCP) – we’re not shutting down the disease

Commercial Relationships

Speaker Disclosure: Colin Green
Founder Scientist CuDaTherapeutics (NZ) Ltd
Founder Scientist OcunNexTherapeutics, Inc. USA
Stockholder OcunNexTherapeutics, Inc. USA
Inventor on 280+ patents (31 patent families) related to the regulation of connexin channels

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APL-2 (Apellis) (Complement Factor C3) - Pegcetacoplan

Reduces GA spread - bimonthly or monthly injections
29% reduction in the growth of GA lesion area in the monthly treatment group (p=0.008)
20% reduction in the EOM treatment group (p=0.067) - compared to the pooled sham group.

Effect was more pronounced in the last six months of treatment, with observed reductions of 45% (p=0.0004) and 33% (p=0.009) for APL-2 monthly and EOM, respectively, compared to sham.

BUT -
- Benefit stops upon withdrawal of treatment
- 20.9% 'conversion' to Wet AMD (versus 1.2% in shams)

Inflammasome Pathway of the Innate Immune System

Pathogens
- Peptidoglycans
- LPS
- Danger signals
- Inflammatory cytokines (TNF, IL-1...)
- Chemokines
- Crystals (silica, urate, asbestos)
- Membrane attack complex (MAC)

ATP
Inflammasome Signal 2 Activator

IL-1β
IL-18
TNFα
IL-6
IL-8
MCP1
ICAM
VEGF

Inflazome

• Two drugs targeting same site as MCC950 currently in Phase 1 safety trials
• Somatil
• Anakinra - interleukin-1 (IL-1) receptor antagonist

Canacinumab (Novartis) – IL-1 blocker

Rare autoimmune conditions and to reduce further heart attacks or stroke

Been shown to stop progression of retinal neovascularisation, stabilise VA and mildly reduce retinal edema in PDR patients

No change in neovascularisation in diabetic retinopathy

Possible effects on diabetic macular edema

Anakinra - interleukin-1 (IL-1) receptor antagonist

OcuNexus - Xiflam

World Leader - Only Inflammasome targeting company at Phase II
Agreement with GSK for Xiflam Information Brochure, toxicity, carcinogenity, human safety data
1 year ahead of the pack
Once daily ORAL tablet

• Blocks hemichannel opening / reduces ATP release
• Once daily ORAL availability targeting ...
• Diabetic Eye Disease including DME, DR
• Dry (GA) and Wet AMD
• T_{1/2} ~ 3 hrs, terminal half life 24 – 40 hrs
• No accumulation
• Safe – Used in over 1000 patients (as treatment for migraine)

Xiflam shuts down the inflammasome pathway in the human retina

( Diabetic Retinopathy - Human Cadaver Retinas)

NLRP3
IL-1β
IL-18
VEGF

Tissues analysed using quantitative immunohistochemistry
Medium (cytokine secretion) analysed using Luminex cytokine bead array

Basal
Glucose + Cytokines
Glucose + Cytokines + Xiflam

+ proven efficacious in animal models of GA and DR

For Anti-VEGF alternatives watch especially:
• Apellis (Complement Factor C3 inhibitor)
• Inflazome (Inzomelid)
• OcuNexus (Xiflam)