

Investigating Vitamin D Agonists as Therapeutic Targets for Treatment of Age-Related Macular Degeneration?

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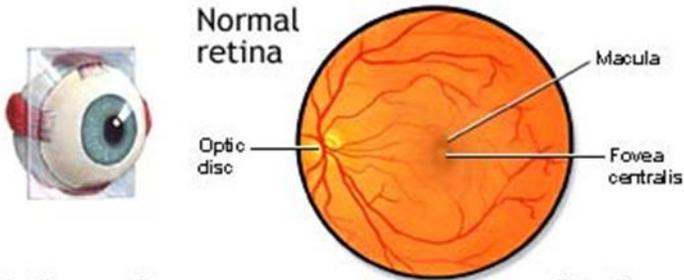


Introduction

This presentation will detail the pathology and current treatments of Age-related Macular degeneration, a common disease resulting in partial or complete blindness – the most common cause of blindness in Ireland. Furthermore it will investigate Vitamin D agonists as potential therapeutic targets in the treatment and prevention of the disease.



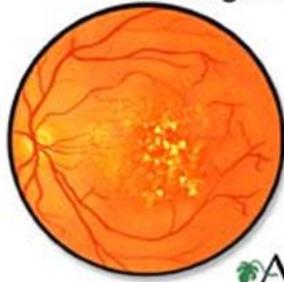
Pathology



"Wet" macular degeneration



"Dry" macular degeneration



ADAM.

What is AMD?

What are the stages of AMD?

Risk factors

How is AMD detected?

What It's Like



This is how a street scene looks with normal vision.



Example of a Macular Degeneration



Current Treatment

There is currently no cure for age related macular degeneration

Types of treatment

Wet → Dry

Wet

Dry

- Oral Supplement

- Injections
 - Ranibizumab
 - Incomplete recovery
 - Risk/distress
 - Endophthalmitis
- **Laser**
 - Permanent
 - Risk



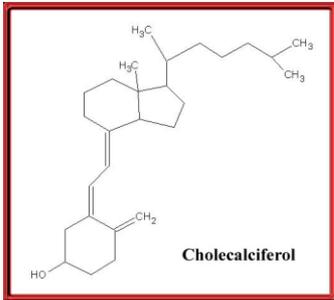
Treatment aimed at sealing leaky blood vessels.



Vitamin D signalling pathway



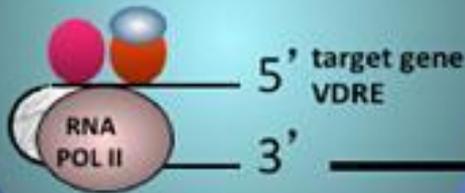
vitamin D $\xrightarrow[\text{25-hydroxylase}]{\text{liver}}$ 25D



1,25D $\xleftarrow[\text{(CYP27B1)}]{\text{1}\alpha\text{-hydroxylase}}$ 25D

1,24,25D $\xleftarrow[\text{(CYP24A1)}]{\text{24-hydroxylase}}$ 1,25D

VDR RXR



mRNA expression

Classical
calcium uptake
PTH synthesis
renal phosphate/calcium

osteoblast/osteoclast
differentiation & function

Non-Classical
Anticancer
antiproliferative
regulation of apoptosis
and angiogenesis

anti-bacterial
antigen presentation
anti-inflammatory

anti-hypertensive

RET-3D™

Soft Gelatin Capsules



The World's First
Sunshine Supplement to
Prevent Vision Loss

Vitamin D signalling pathway

→ Vitamin D : supplements or made by the skin when exposed to sunshine.

- not immediately active,
- modified in the liver and kidney to form the active metabolite Cholecalciferol.

⇒ The vitamin D receptor (VDR) is a nuclear, ligand-dependent transcription factor.

- regulates the expression of more than 900 genes

⇔ VDR dimerizes with RXR and translocates to the nucleus.

- binds to vitamin D response elements (VDRE)
- co-activators or co-repressors
- induce or repress gene transcription

→ Studies show Cholecalciferol :

- counteracts inflammation, angiogenesis, oxidative stress, and fibrosis



How does Cholecalciferol work?

Cholecalciferol

Dual action age-related macular degeneration (AMD) protection

ANTI – INFLAMMATORY ACTION

Decreases proliferation of T helper cells, T cytotoxic cells, and natural killer cells

Decreases production of pro-inflammatory agents such as IL-2, IL-6, IL-8, IL-12. Thereby reducing retinal macrophage numbers.

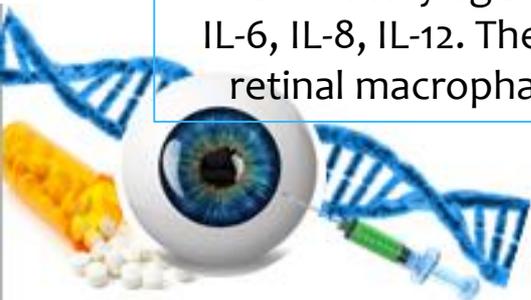
Enhances T suppressor cell activity

Antiangiogenic Action

Potent inhibitor of angiogenesis

Endothelial cell effects and reduction in amyloid beta (AB) accumulation in the retina.

Interrupts signalling pathways that are key to angiogenesis particularly in tumorigenesis.



Future Developments

Macrophages, fibroblasts & lymphocytes - ↑ Hallmarks neovascularisation

Atrophy of RPE cells and Breakdown of Bruch's membrane

Vitamin D is known to prevent T-cell proliferation, maturation and differentiation

Also prevents secretion of Th1-type molecules ; **IL-17**, IFN and IL-2 (among others)

IL17 – Cytokine family

- Produced by Th17 cells
- Pro-inflammatory
- Matrix destruction and Neovascularisation
- Harm RPE cells
- ↑ levels in AMD lesions
- VEGF-mediated angiogenesis

PROPOSAL:

- Research
- *Refine*
- **Reduce**

