Centre for Eye Research Australia

Retina Australia 2011 Project Grant Report

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Title: Does the level of systemic inflammation influence the outcome of treatment in neovascular Age-Related Macular Degeneration?

Background:

Age related macular degeneration (AMD) is a major cause of blindness in Australia. New "anti-VEGF" (Vascular Endothelial Growth Factor) medications, which are injected directly into the eye, have revolutionised the treatment of "wet" AMD, however, 10-15% don't respond and continue to go blind.

The injections of these anti-VEGF drugs also have inherent ocular and systemic risks, so limiting their number would be desirable if the same visual result could be achieved. If we knew of a way to predict treatment outcome, then decision making could occur on an individual basis, taking into account all potential risks and benefits as they relate to the individual. We are currently not in the position to offer this personalized approach.

It is now known that inflammation plays a key role in AMD development. Several studies, including our own, have shown that markers of inflammation that are found in the blood are higher in people with AMD. As these markers may identify those with more aggressive disease that does not respond to monthly dosing with ranibizumab, we plan to investigate whether inflammatory markers in the blood can predict the response a patient with wet AMD will have to anti-VEGF treatment.

What we did:

This project was composed of two parts. The first part consisted of a large case-control study of AMD patients, consisting of early AMD, geographic atrophy (GA), choroidal neovascularisation (CNV) and controls who attended the Royal Victorian Eye and Ear Hospital and a private clinic in Victoria, Australia. AMD status was determined from clinical examination and bilateral digital fundal photographs, with angiography and optical coherence tomography to confirm CNV. Serum biomarker levels were determined via immunoassay. Cytokine levels were further analyzed according to the allelic status of the Complement Factor H (CFH) gene.

Univariate analysis demonstrated an association between:

- CC chemokine ligand-2/monocyte chemotactic protein-1 (CCL2-MCP-1) levels and CNV.
- Three CFH gene SNPs and all AMD.

Genotype-biomarker interaction revealed a significant interaction between CCL2-MCP-1 levels and one CFH gene SNP in the GA and CNV subgroups.

Therefore, from this case-control study, we found that CCL2-MCP-1 levels were associated with an increased risk of GA and CNV, particularly in those carrying certain CFH genotypes.

The second aspect of the study was a pilot, prospective, cohort study of 69 participants with newly diagnosed neovascular AMD who were recruited from the Royal Victorian Eye and Ear Hospital for the analysis of inflammatory biomarkers. Blood samples were collected at baseline and 3 months after commencing ranibizumab treatment (i.e. just prior to the 4th injection). For this pilot study, only the baseline samples were analysed with a multiplex cytokine microarray.

Participants were categorised as "responders" (stable or improved vision) or "non-responders" (any loss of vision) after 3 x monthly injections of ranibizumab treatment. Using this definition, 11 subjects (15.9%) were found to be non-responders. Using a logistic regression analysis taking into account age, gender and smoking status, possible differences in baseline inflammatory biomarker levels were determined between responders and non-responders.

In this small pilot study, we obtained data on 16 inflammatory biomarkers at baseline: c Reactive Protein (CRP), Interleukin(IL)-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-12(p70), Eotaxin, Interferon-inducible protein-10 (IP-10), MCP-1, Macrophage Inflammatory Protein(MIP)-1α, MIP-1β, Chemokine ligand 5 (CCL5), and Tumour necrosis Factor (TNF)-α. The effect of the level of a particular cytokine on the probability of a subject being a non-responder ranged from a slight increase (0.3%) to a very large decrease (-300%).

We are now in the process of analysing inflammatory biomarker levels in a larger group at baseline, in addition to the 3 month time point, in order to commence a longitudinal analysis of this cohort of patients.

Conclusions:

These results introduce the concept of "tailored medicine" where combined genetic testing and inflammatory biomarker levels may be used to predict the risk of developing AMD.

In addition, although our results with regards to biomarkers predicting treatment response are very preliminary, with only a limited sample, they do highlight our ability to detect these cytokines in our patient's serum, and show a trend that we are likely to detect a significant difference between the two treatment response groups with a larger study sample.

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Project Income Statement

51805 Retina Australia - Fighting Blindness

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	YTD Actual $
Revenue	
Research Foundations	30,000.00
Total Revenue	**30,000.00**
Expenditure	
Laboratory & Medical Supplies	30,000.00
Total Expenditure	**30,000.00**
NET SURPLUS/(DEFICIT)	**0.00**