The Anti-inflammatory Effect of Macrolide Antibiotics in Chronic Rhinosinusitis

by

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ABSTRACT

Chronic rhinosinusitis is a common disorder of chronic inflammation of the upper respiratory tract. It is associated with significant symptoms and impairment of the quality of life of sufferers. Despite recent advances in the medical and surgical management of chronic rhinosinusitis, there remains a population of patients who fail to obtain relief from their symptoms.

Chronic inflammation of the mucosa of the nasal cavity and paranasal sinuses is one of the hallmarks of chronic rhinosinusitis. This inflammation is demonstrated by an increased number of chronic inflammatory cells, elevated levels of pro-inflammatory cytokines, increased expression of adhesion molecules and metaplastic changes in the epithelium. The current medical treatments for chronic sinusitis aim to reduce this inflammation and consequently improve symptoms.

In recent years, evidence has emerged that macrolide antibiotics have an anti-inflammatory effect that is separate from their anti-bacterial effect. This effect was first described in the treatment of diffuse panbronchiolitis, a disorder of chronic inflammation of the lower respiratory tract. Following the success of macrolides in treating this condition it was trialed in chronic rhinosinusitis. Several open-label trials have subsequently demonstrated a beneficial effect.

Laboratory studies have investigated the mechanism of the anti-inflammatory effect of macrolides. These have shown that macrolides effect cytokine production, inflammatory cell apoptosis, expression of adhesion molecules, neutrophil oxidative burst, bacterial virulence and mucociliary function.

In this thesis we report a series of experiments designed to further investigate the mechanism of action and clinical effect of macrolides. In vitro studies using whole sections of chronic rhinosinusitis mucosa cultured for 24 hours in macrolide, prednisolone or control showed that macrolide and prednisolone produced significant
reductions in the production of interleukin-5, interleukin-8 and granulocyte-macrophage colony stimulating factor. The same cultured specimens also showed a reduction in expression of transforming growth factor-β. No reduction was seen in the expression of the key pro-inflammatory nuclear transcription factor Nuclear factor-κB.

In our in vivo experiments, biopsies were taken from chronic rhinosinusitis patients who had received a 3-month course of macrolide. These biopsies showed a reduction in the number of neutrophils present following treatment. There was no reduction in the number of other inflammatory cells or in the expression of TGF-β and NK-κB.

We have performed the first ever double-blinded, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. Patients receiving macrolide showed significant improvements in saccharine transit time, nasal endoscopic scoring and symptom scores following a 12 week course. Patients with low levels of serum immunoglobulin E showed significantly improved outcomes compared to those with high levels. Interleukin-8 levels in nasal lavage fluid were significantly reduced in the patients with low levels of IgE following macrolide treatment. No improvements in any of the objective or subjective outcome measures were seen in the placebo-treated patients.

We have performed a series of experiments investigating the anti-inflammatory effect of macrolide antibiotics from ‘the bench to the bedside’. These experiments have provided insight into the mechanism of action of macrolides in the laboratory setting and evidence of a beneficial effect in the treatment of chronic rhinosinusitis patients.
STATEMENT OF ORIGINALITY

The work described in this thesis was carried out in the School of Biomolecular and Biomedical Science, in the Faculty of Science at Griffith University. It was performed under the supervision of Professor Alan Mackay-Sim, Professor William Coman and Associate Professor Anders Cervin. This work has not been submitted previously for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Ben Wallwork
PUBLICATIONS ARISING FROM THIS THESIS


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ABBREVIATIONS
a2-mac  α2-macroglobulin
CRS  Chronic rhinosinusitis
DPB  Diffuse panbronchiolitis
ECP  Eosinophilic cationic protein
ELISA  Enzyme-linked immunosorbent assay
EMSA  Electrophoretic mobility shift assay
FESS  Functional endoscopic sinus surgery
GM-CSF  Granulocyte-macrophage colony stimulating factor
ICAM-1  Intercellular adhesion molecule-1
IFN  Interferon
Ig  Immunoglobulin
IκB  Inhibitory protein-kappa B
IL  Interleukin
MBP  Major basic protein
mRNA  Messenger RNA
NF-κB  Nuclear factor-kappa B
PBS  Phosphate-buffered saline
PNIF  Peak nasal inspiratory flow
RCT  Randomised controlled trial
SEM  Standard error of the mean
SNOT-20  Sinonasal outcome test-20
STT  Saccharine transit time
TBS  Tris-buffered saline
TGF-β  Transforming growth factor-β
TNF-α  Tumour necrosis factor-α
VCAM-1  Vascular cell adhesion molecule-1

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