Journal club

Mechanisms underlying the increase in mycobacterial infections in cystic fibrosis patients on azithromycin

This study investigated the increased incidence of non-tuberculous mycobacterium (NTM) infections in cystic fibrosis (CF) patients on azithromycin. The authors were particularly interested in autophagia, a process whereby intracellular material is isolated into phagosomes and then destroyed by being fused with acid-rich lysosomes. It is disrupted by other macrolides and is crucial for the clearance of intracellular pathogens.

In vitro macrophages showed decreased degradation of phagosomes when exposed to azithromycin in both healthy controls and CF patients. This was demonstrated to be mainly due to lysosomal pH being raised to levels that inhibited destructive enzymes and also due to impaired phagosome–lysosome fusion. Further disruption to immune function was caused by inhibition of cytokine release, as evidenced by decreased levels of interferon γ (IFNγ). In vivo effects were verified by infecting mice with resistant strains of *Mycobacterium abscessus*. Control groups normally cleared the pathogen within 1 month whereas mice treated with azithromycin were much more likely to develop persistent disease and show consistently altered levels of pulmonary cytokines. The authors speculated that such immunomodulatory effects may explain anti-inflammatory properties associated with azithromycin, but fear they might also render concurrently administered IFNγ therapy less effective.

The findings offer a plausible explanation for the predisposition that CF patients on azithromycin have to NTM infections; however, the processes described are not specific to this group. The increasing use of prophylactic azithromycin in chronic obstructive pulmonary disease means that physicians should be vigilant for the development of NTM infections in this cohort as well.

► **Renna M,** Schaffner C, Brown K, *et al*. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. *J Clin Invest* 2011;**121**:3554–63.

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