Background and Aims  Viral-induced disease exacerbation is common in asthma and studies have identified that both bronchial epithelial cells and alveolar macrophages (AM) from asthmatics have a reduced interferon (IFN) response to rhinovirus infection. The mechanism behind this defect is unclear. As asthmatic peripheral blood mononuclear cells have been reported to have defective toll-like receptor (TLR) 7 function, we investigated the expression of microRNAs (miRNAs) in AM from healthy control (HC) and severe asthma (SA) volunteers with relevance to TLR7-viral interactions. MicroRNAs are non-coding RNAs that down-regulate gene expression by suppressing translation. We identified and focused on 3 miRNAs that could target TLR7. Additionally, we investigated if manipulating the expression of these miRNAs can ameliorate the defective IFN response in AM.

Methods  26 HC and 30 patients with SA (BTS Step 4/5) were recruited for bronchoscopy. AM were isolated from bronchoalveolar lavage using the adherence to plastic technique. Expression of miRNAs and TLR7 was determined by qRT-PCR and western blotting. AM were transfected with a combination of antagonists, specifically directed against the 3 miRNAs, and then treated with imiquimod (5µg/ml), a TLR7 agonist, or human rhinovirus-16 (HRV16) and IFN-β expression was determined after 24 hours using qRT-PCR and ELISA.

Results  Expression of all three miRNAs was significantly increased in SA compared to HC. TLR7 mRNA was found to be significantly reduced in AM from volunteers with SA compared to HC. Western blotting confirmed reduced expression of TLR7 protein in AM from SA compared to HC. Compared to mock transfected AM, AM transfected with the 3 antagonists showed significantly increased imiquimod-induced IFN-β mRNA and protein expression and significantly increased HRV16-induced IFN-β mRNA production.

Conclusion  TLR7 expression is significantly reduced in SA compared to HC. The differential expression of the miRNAs identified may lead to impaired viral sensing by asthmatic AM and contribute to the defective IFN response to rhinovirus. Importantly, TLR7 induced IFN-β production by human AM can be significantly augmented by inhibition of these miRNAs. The identification of these miRNAs and our ability to manipulate their expression in human AM offers the potential for future miRNA-based therapies in asthma.