The yin and the yang of immunosuppression with inhaled corticosteroids

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A patient who is immunosuppressed is susceptible to mycobacterial infection: are you surprised? Before you jump to conclusions, you might wish to clarify the nature and extent of immunosuppression, and whether it is through disease, therapy, or both, reserving judgement until you know more.

Patients are often concerned about immunosuppressive effects of inhaled and oral corticosteroids. Asthmatics are used to infections putting them in hospital, and not unreasonably view with suspicion any treatment option that might make this more likely to happen. However, healthcare providers know that for asthmatics, more likely to happen. However, healthcare providers know that for asthmatics, use of ICS increases the risks of infections putting them in hospital, and their common message needs to give us pause for thought. Their complementary nature in differing populations reinforce the likely existence of mechanisms of mycobacterial control that are affected by ICS. Lee et al provide evidence that people from a population with a significant rate of TB latency show increased risk of active TB infection after treatment with steroids.10 Brascard et al show a similar risk of ICS-related TB infections, but in people less likely to have latent disease.9 Finally, Andrejak et al show a risk of ICS, particularly in the presence of structural lung disease, for non-tuberculous mycobacterial infection.8 Pneumococcal pneumonia and mycobacterial infections feature a prominent role for alveolar macrophages in pathogen killing and containment, and a requirement for T cell responses to optimise macrophage effector function. Mycobacteria reside in and replicate within macrophages, hidden from the worst the immune system can throw at them, living often in a state of relative suspended animation. Suppression of macrophage function, for example, with drugs targeting TNFα, increases risks of reactivation of TB, and protocols are in place to define risk and screening for patients starting such therapies. Interestingly, among a myriad of effects of ICS, they reduce TNFα production by macrophages,11–12 and in theory this could reduce the T cell responses required to aid macrophage control of specific pathogens.

Importantly, our genetic background heavily modifies the risks of developing the underlying lung disease, the efficacy of the epithelial barrier, and multiple aspects of the subsequent immune response to noxious stimuli and infections. Thus, whether the risks of ICS-mediated immunosuppression are actually very small in some individuals, and much greater than

MESSAGE 1: CORRECTLY USED, ICS SAVE LIVES

This is not a surprise. Guideline-based management for asthma, focussing on the use of ICS in all but the mildest disease, has been the great life-saving and symptom-modifying thrust of therapy over recent decades. The exact place of ICS and their optimal dosing remains more unclear in COPD, but TORCH clearly showed the potential for a fluticasone/salmeterol combination to reduce exacerbations. Nothing should detract from the correct therapeutic use. We have no good alternatives that can safely deliver local therapeutic manipulation of immune inflammation, and the benefits of ICS appear for now to clearly outweigh the risks of infectious complications.

MESSAGE 2: ICS USE HAS SOME HITHERTO OVERLOOKED INFECTIVE RISKS

So, do ICS actually increase the risk of some pulmonary infections? Recent studies suggest they may. TORCH linked ICS use with an increased risk of an epidemiological signature of community-acquired pneumonia,1 6 data supported by other studies.7 A series of studies, including two recent articles in Thorax, have also linked ICS usage with increased risk of tuberculous or other mycobacterial infections.8–10 While these studies are epidemiological and not mechanistic, they encompass large populations, and their common message needs to give us pause for thought. Their complementary nature in differing populations reinforce the likely existence of mechanisms of mycobacterial control that are affected by ICS. Lee et al provide evidence that people from a population with a significant rate of TB latency show increased risk of active TB infection after treatment with steroids.10 Brascard et al show a similar risk of ICS-related TB infections, but in people less likely to have latent disease.9 Finally, Andrejak et al show a risk of ICS, particularly in the presence of structural lung disease, for non-tuberculous mycobacterial infection.8 Pneumococcal pneumonia and mycobacterial infections feature a prominent role for alveolar macrophages in pathogen killing and containment, and a requirement for T cell responses to optimise macrophage effector function. Mycobacteria reside in and replicate within macrophages, hidden from the worst the immune system can throw at them, living often in a state of relative suspended animation. Suppression of macrophage function, for example, with drugs targeting TNFα, increases risks of reactivation of TB, and protocols are in place to define risk and screening for patients starting such therapies. Interestingly, among a myriad of effects of ICS, they reduce TNFα production by macrophages,11–12 and in theory this could reduce the T cell responses required to aid macrophage control of specific pathogens.

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we are aware of in others, is not yet known, but may well be the case. Furthermore, differences may exist between ICS molecules, since Andrěják et al noted greater odds of non-tuberculous mycobacterial infection in patients on fluticasone versus budesonide (BUD), and we will return to this theme below.

These new data remind us again of the necessity to use ICS at the lowest appropriate dose to maintain good control of detrimental inflammation within established guideline-based management, and to be cautious of assumptions extending their use beyond where there is a good evidence base.

**MESSAGE 3: ICS MIGHT PROTECT AGAINST SOME INFECTIONS?**

The majority of asthma exacerbations, and many of COPD, are viral in nature. Asthmatics have a pre-existing immune deficit such that their epithelial cells fail to produce some interferons in response to viral infections. Yet despite the determinedly suppressive actions of ICS on viral-induced proinflammatory cytokine production by the epithelium, in some circumstances ICS appear to be the opposite of immunosuppressive: infective exacerbations of COPD are lessened by appropriate use of ICS in the right patients, and asthmatics with sufficient ICS to control their disease experience fewer clinically significant respiratory infections.

The mechanisms underlying steroid-induced resistance to infection, or the sequelae of infection, are less clearly defined. ICS use will decrease excessive inflammatory responses to infections, limiting lung damage. Additionally, reductions in persistent inflammation may restore a more normal epithelial and airway architecture, which will enable a response to infection that is more typical of the healthy airway. In keeping with this idea, we have recently observed that ICS counteract the airway epithelial barrier dysfunction induced by a viral mimetic in vitro, which may lead to reduced accessibility of pathogens to submucosal inflammatory cells in vivo. Hinting again at potentially relevant differences between ICS molecules, BUD protects better against cigarette smoke-induced epithelial barrier dysfunction than fluticasone propionate (FP), while fluticasone furoate is more effective than FP or BUD in protecting epithelial cells from elastase-induced damage.

BUD-based regimes may also be associated with fewer pneumonia events in people with COPD than FP-based treatments.

Animal models show that viral airways infections can cause a profound persistent impairment of innate immune responses to bacteria, increasing risks of secondary bacterial infections. Furthermore, while ICS dampen production of proinflammatory cytokines, they might also stimulate an increase in the pathogen-driven expression of other epithelial-derived host defence molecules. Thus, ICS treatment may limit an excessive response to viral pathogens, and thus help reduce persistent immune tolerance in the airway, and through increases in or preserved production of antimicrobial molecules reduce the risks or severity of secondary bacterial infections.

**CONCLUSIONS**

ICS are profoundly beneficial in the right circumstances, when used in guideline-based and evidence-based strategies. It is becoming evident that people treated with ICS are at increased risk of mycobacterial and other bacterial infections, and this should be borne in mind when monitoring people on these drugs, but ICS also have protective roles, reducing risks and harm of some infections. Future genetic studies combined with epidemiological approaches may define those at greatest risk of specific infectious complications of ICS use. We also need clearer data determining if risks are particularly associated with individual ICS molecules, and if so, whether this simply results from their relative potency, perhaps modulated by genetic factors in the treated individual, or through other subtleties of their mechanisms. It is also likely that a better understanding of these risks will provide new insights into the pathogenesis of pulmonary infection. We can hope that non-ICS anti-inflammatory drugs will come forward and change the landscape of disease, but like almost all disease-modifying anti-inflammatory drugs, these will almost certainly also be associated with generic or therapy-specific infective risks, as part of the inevitable yin and yang of targeting a set of pathways designed through evolution to stop us dying from or being significantly injured by pathogens.

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