The yin and the yang of immunosuppression with inhaled corticosteroids

Ian Sabroe,[1,2] Dirkje Postma,[3,4] Irene Heijink,[3,4,5] David H Dockrell[2,6]

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, appropriate local immunomodulation in the lung with inhaled corticosteroids (ICS) is associated with decreased exacerbations arising from viral infections, fewer symptoms, improved lung function and better outcomes. In subsets of patients with COPD, high-dose fluticasone with salmeterol reduces exacerbations and improves quality of life.[1] Thus, if the only exposure of patients to anything remotely immunosuppressive is ICS, you might conclude the extent of immunosuppression is insufficient to regard the patient as immunocompromised.

But will use of ICS increase susceptibility to some infections? The innate immune networks active in the lung, with their multifaceted humoral and cellular components, show intrinsic competence in keeping the human organism mostly free of serious pulmonary infection. At their heart lie strong surface barriers, an effective mechanism of sensing pathogens through a range of pattern recognition receptors,[2] the efficient killing of micro-organisms by resident and recruited phagocytes, and efficient resolution of inflammation.[3] Alveolar macrophages are the resident phagocytes, which along with epithelial cells and T cells coordinate an immune response that may require recruitment of other inflammatory cells such as neutrophils to clear invading pathogens. Clearance of bacteria such as pneumococci relies heavily on phagocyte competence which is optimised by T cell responses. When phagocyte capacity is stressed by intracellular pathogens, such as *Mycobacterium species*, there is a critical dependence on T cell function mediated via the IFNγ/IL-12/IL-23 axis.[4][5] Steroids, including ICS, have the potential to modify all such pathways.

Thus, we can happily trot out our favourite analogies describing the consequences of targeting the immune system ('double-edged sword' is a particularly egregious example which every immunologist is required by some unwritten code to use intermittently). For now, we will stick with 'yin and yang', because any immunosuppression will modify the risks of infections while achieving therapeutic benefit. When considering the immunosuppression of ICS, a few messages have become clearer, but some have yet to be fully explored.

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.[1] 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] Brassard *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] ICS, such as fluticasone, can deplete T cells by induction of apoptosis,[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

[1]Academic Unit of Respiratory Medicine, University of Sheffield, Sheffield, UK]; [2]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; [3]Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [4]Laboratory of Allergology & Pulmonary Diseases, GRIAC Research Institute, University Medical Center Groningen, Groningen, The Netherlands; [5]Laboratory of Allergology & Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; [6]Academic Unit of Immunology and Infectious Diseases, Department of Infection and Immunity, University of Sheffield, Sheffield, UK

Correspondence to Professor Ian Sabroe, Academic Unit of Respiratory Medicine, Medical School, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK; i.sabroe@sheffield.ac.uk

we are aware of in others, is not yet known, but may well be the case. Furthermore, differences may exist between ICS molecules, since Andréjak et al noted greater odds of non-tuberculous mycobacterial infection in patients on fluticasone versus budesonide (BUD),[8] 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.[13] Asthmatics have a pre-existing immune deficit such that their epithelial cells fail to produce some interferons in response to viral infections.[14] 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 mimic in vitro,[15] 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),[15] while fluticasone furoate is more effective than FP or BUD in protecting epithelial cells from elastase-induced damage.[16] BUD-based regimes may also be associated with fewer pneumonia events in people with COPD than FP-based treatments.[17]

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.[18] 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.[19] 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[19] 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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