

Atrophied glomerulus

associations between haemoglobin and mortality were found in observational studies, but evidence from randomised trials that improving haemoglobin results in a reduction of deaths is missing, and in fact the opposite was demonstrated by a meta-analysis of the largest trials.¹⁴

The challenge for the future may be to make sure that we use the epoetins correctly. There are special groups (such as home-haemodialysis patients self-administering an epoetin, children, patients with stage 2–4 chronic kidney disease, transplant recipients, and peritoneal dialysis patients receiving subcutaneous injections) that might more obviously benefit from a longer dosing interval. But other outcomes are also possible in these patients, such as reduced compliance because of longer times between self-administrations.

MAXIMA certainly makes a contribution to our understanding of the complexities of managing anaemia in chronic kidney disease. But, before we can concur on a precise clinical role for this new molecule, we need to explore issues other than simply the non-inferiority with other epoetins to reach certain unvalidated surrogates. Different doses and molecular characteristics of epoetins may affect patient-level endpoints, independent of achieved haemoglobin. When these issues are examined, we might be truly confident that a newer molecule is non-inferior to existing ones.

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Th2 cytokines in the asthma late-phase response

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Global surveys of asthma rates in children show that, despite some recent reductions in developed countries with high prevalences, asthma continues to increase in many parts of the world and is a major burden on health-care systems.¹ In developed-world countries, atopic asthma is the predominant phenotype in older children and the one most likely to persist. The hallmark of atopic asthma is the chronically inflamed and remodelled air-

way mucosa with characteristic infiltrates of eosinophils and CD4+Th2 cells.² Although the dominant factor at the severe end of the asthma exacerbation spectrum is acute virus-induced airways inflammation,³ such triggers are maximally effective against a background of chronic airways inflammation, driven in particular by atopy.^{4,5}

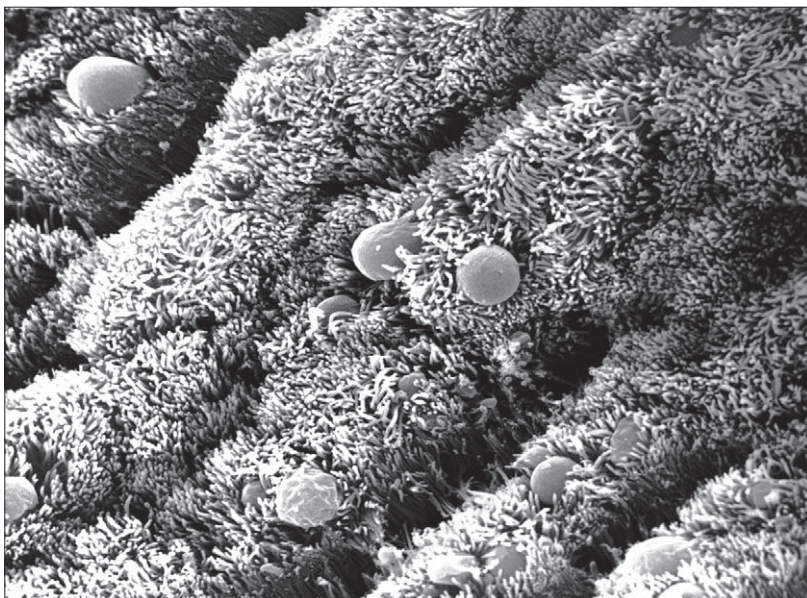
On the basis of a long history of animal studies complemented by clinical investigations in human

beings, Th2 cytokines have been ascribed prime roles as pathogenic factors in chronic atopic airways inflammation. The specific processes that drive this inflammation are the biphasic cellular immune reactions which follow inhalation of allergen. The acute-phase component of this response is initiated by cross-linking of IgE receptors on mast cells and basophils in the airway wall, which triggers the release of a burst of Th2 cytokines, including interleukins 4, 5, and 13 together with constrictor mediators, and which induce an acute fall in lung function.^{1,6} As shown by Sally Wenzel and colleagues in today's *Lancet*,⁷ this acute-phase response is short-lived and generally self-limiting, with lung function returning to normal within 30–60 min. As these researchers also show, in a subset of patients with atopic asthma these acute-phase responses are followed by a secondary fall in lung function 2–12 h after initial exposure. This secondary fall lasts longer, is potentially more severe, and is often associated with heightened bronchial responsiveness. This late-phase response is mediated by a combination of mediators from eosinophils^{1,6} and especially from CD4+Th2 cells.⁸ The late-phase response is believed to provide the principal inflammatory drive for the airways remodelling which develops as the disease progresses.^{2,9}

Support for this general model of atopic asthma pathogenesis has grown progressively since the 1980s. The perceived central role of Th2 cytokines in pathogenesis has stimulated intensive efforts by the drugs industry to develop Th2 antagonists for asthma treatment. However, trials of the first generation of these drugs in adult patients with asthma were disappointing, and led to widespread suggestions that inhalant allergy may be a consequence as opposed to a contributory cause of asthma. Counterarguments include the suggestion that Th2 mechanisms have a diminishing role in asthma pathogenesis beyond childhood as chronicity develops,¹⁰ or the fact that redundancies within the Th2 pathway necessitate targeting more than a single cytokine to accrue reductions in airways inflammation of sufficient magnitude to modify disease progression. An archetypal example may be the case of interleukin 4R α , which can bind both interleukins 4 and 13.¹¹ The implication here is that targeting either of these cytokines alone would be unlikely to efficiently attenuate Th2-dependent inflammatory processes driven through this ubiquitously expressed receptor.¹²

Wenzel and colleagues tackle this question directly, by using a recombinant human interleukin 4 variant called pitrakinra, which competitively inhibits the interleukin 4R α complex and thus interferes simultaneously with the actions of interleukins 4 and 13. The investigators present convincing evidence for reduction in the late-phase response to allergen challenge in patients with atopic asthma. Both the maximum fall in forced expiratory volume in 1 s (FEV₁) and the area under the FEV₁ time curve after challenge showed impressive reductions with active treatments after either subcutaneous or inhaled administration of pitrakinra (the two routes formed the basis of these phase 2a studies).

An additional observation, not addressed by Wenzel and colleagues, is the accelerated recovery from the initial acute fall in lung function after allergen challenge, particularly in the group treated by inhalation. This result suggests a possible role for interleukin 4R α in upregulation of the intensity or duration of the acute-phase response, which is consistent with findings that interleukin 4 interacts synergistically with stem-cell factor to promote IgE-dependent release of mediator from mast cells.⁶ An additional question relates to the duration of the effects of pitrakinra. Notably, Wenzel's studies were truncated at 10 h by administration of bronchodilator—ie, before the end of the late-phase response and return to baseline levels of lung function.



Allergens on ciliated epithelium of nose

Thus follow-up trials of longer duration are required to confirm that the effects of pitrakinra are not just restricted to alterations in the kinetics of the late-phase response. Issues concerning efficacy in patients with more severe asthma, and the potential for genuine disease modification with longer-term treatment, especially in children, also remain to be addressed.

These latest findings with pitrakinra are exciting and novel, and will breathe new life into the debate surrounding the role of the Th2 cytokine cascade in asthma pathogenesis and how best to design drugs to attenuate their effects.

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Transient ischaemic attacks: unstable, treatable, neglected

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Stroke affects 15 million people worldwide every year, and is the leading cause of acquired disability.¹ Unfortunately, despite ample evidence that thrombolytics improve outcome after an acute ischaemic stroke, very few patients receive this treatment.² In view of these dismal statistics, high priority should be accorded to stroke prevention. Results from several randomised trials have shown that the risk of ischaemic stroke in high-risk individuals can be significantly reduced by strategies such as blood-pressure lowering, statin therapy, antithrombotic drugs, and carotid endarterectomy.³ About 30–40% of patients with ischaemic stroke have had an earlier transient ischaemic attack (TIA) or minor stroke.⁴ Recent studies suggest that, after a TIA, the 90-day risk of a subsequent stroke is as high as 10.5%, and almost half these strokes could occur within the first 2 days.⁵

In today's *Lancet*, Peter Rothwell and colleagues present the results of the Early use of Existing Preventive Strategies for Stroke (EXPRESS) study.⁶ The investigators compared the usual UK practice of delayed assessment and treatment of patients with TIA or a minor stroke (phase 1) with a revised protocol of prompt assessment and introduction of therapy within 24 h of the event (phase 2). Their find-

ings show that rapid assessment and early treatment after a TIA results in a much lower 90-day risk of recurrent stroke (10.3% in phase 1 vs 2.1% in phase 2, $p=0.0001$).

There are, however, a few issues that need attention. In the referrals to the study clinic, the number of strokes after a TIA (16 in phase 1 vs one in phase 2) or after minor stroke (17 vs five) was low, and the results therefore require cautious interpretation. Furthermore, the investigators used a short course of dual antithrombotics (clopidogrel and aspirin). In the MATCH trial,⁷ long-term dual therapy in patients with ischaemic stroke and TIA did not offer any additional benefits than did clopidogrel alone, but in fact increased the risk of life-threatening haemorrhage at 18 months. However, there is preliminary evidence that dual therapy might have a better risk-benefit ratio in selected patients⁸ or if started early after a TIA.⁹ In EXPRESS, the risk of haemorrhagic complications in patients on dual therapy was low in the 30-day follow-up.⁶ Additionally there was no attempt to separate patients with high-risk TIAs (age ≥ 60 years, motor symptoms, speech impairment, presence of vascular risk factors, and symptom duration of more than 60 min) in whom the risk of subsequent stroke is especially high.⁵ Demonstration of