New drugs in asthma

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Concepts of how asthma should be managed have changed over recent years, with greater emphasis on patients managing their own asthma according to personalised guidelines and increased involvement of specialist respiratory nurses. Primary or secondary prevention may be possible in the future, but present management focuses on avoidance of precipitants and pharmacological control of the underlying disease process. As a practical aid to improve management, the drugs in current use are ranked in the British Asthma Guidelines, ranging from step 1 (β-agonists only, as required) to step 5 (includes the need for oral steroids) (SCG = sodium cromoglicate).

Fig 1. The stepwise approach to asthma treatment according to the British Asthma Guidelines, ranging from step 1 (β-agonists only, as required) to step 5 (includes the need for oral steroids) (SCG = sodium cromoglicate).

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bations\(^6\) and may reduce asthma mortality\(^7\).

Although inhaled corticosteroids have been available for nearly 30 years, some important questions remain unanswered. Two relatively small studies suggested that the earlier an inhaled steroid is introduced the better the response\(^8,9\), but it is uncertain whether they change the natural history of asthma. In most patients, lung function rapidly declines to pretreatment levels once treatment stops\(^10,11\), suggesting that corticosteroids suppress asthma rather than bring about a true remission. However, in children, it is certainly possible that suppression of inflammation could allow the lung to develop more fully.

When an inhaled corticosteroid is first introduced, there is usually clear benefit\(^3,4,12\). Higher doses appear to help some patients who remain inadequately controlled on small doses, though the increased effect is relatively small\(^12\) and large studies have been required to show a clear dose-related effect\(^6,13\).

**Safety**

Inhaled corticosteroids have an excellent safety record, but they are absorbed from the lung and systemic activity can be demonstrated, particularly at doses above 800 mg beclomethasone dipropionate or equivalent per day by metered dose inhaler (MDI)\(^2,14\) (see Table 1 for equivalent doses). Inhaled corticosteroids have been associated with an increased incidence of glaucoma\(^15\), cataracts\(^16\) and bruising\(^17\), and a reduction in bone mineral density\(^18\), all of which may be important with long-term use. There is little information about the relative risk of these adverse effects from the different inhaled corticosteroids available.

**Efficacy**

Overall, there is probably little to choose in terms of efficacy between beclomethasone dipropionate, fluticasone propionate and budesonide, but the greater hepatic clearance of the latter two\(^18\) probably gives them a superior therapeutic ratio. The therapeutic ratio for all inhaled corticosteroids is much better than that for oral corticosteroids, so inhaled corticosteroids should be used at the lowest dose that provides adequate asthma control and thus prevents the need for courses of oral corticosteroids. Current management plans recognise the need to adjust the inhaled steroid dose as asthma fluctuates, and dose reduction should be attempted after a period of good asthma control.

**Future developments**

The ideal inhaled steroid is active in the lung but has no systemic activity. Current research goals are to develop either a corticosteroid that is metabolised in the lung or a dissociate corticosteroid with anti-inflammatory but no systemic activity.

**Long-acting \(\beta\)-agonists**

Two long-acting inhaled \(\beta\)-agonists, salmeterol and formoterol, are currently available. Formoterol is a full agonist with a fast onset of action similar to that of salbutamol, whereas salmeterol is a partial agonist with a slower onset of action\(^19\). Both provide sustained bronchodilatation for at least 12 hours\(^20\).

| Drug             | Device       | Dose equivalence (\(\mu g\)) |
|------------------|--------------|-----------------------------|
| Beclomethasone   | CFC MDI      | 100                         |
|                  | CFC-free MDI (3M) | 50                       |
|                  | DPI          | 100                         |
| Budesonide       | CFC MDI      | 100                         |
|                  | Turbuhaler (DPI) | 50                     |
| Fluticasone      | CFC MDI      | 50                          |
|                  | planned CFC-free MDI | 50            |
|                  | Accuhaler/Dishhaler (DPI) | 50       |

CFC = propellant contains chlorofluorohydrocarbons; DPI = dry powder inhaler; MDI = metered dose inhaler.

**Safety**

Short-acting \(\beta\)-agonists are not recommended for regular use since high-dose preparations of non-selective (or less \(\beta_2\)-selective) short-acting \(\beta\)-agonists were associated with epidemics of asthma deaths\(^21\). Several subsequent studies showed little or no benefit – or even deterioration – when short-acting \(\beta\)-agonists were used regularly rather than as required\(^19,22\). There were, therefore, some concerns about the safety of long-acting \(\beta\)-agonists when they were first introduced, but several large, well conducted studies have shown that in adults these drugs provide better symptom control and lung function and less nocturnal wakening than both regular short-acting \(\beta\)-agonists and placebo\(^23\). The reason for the difference between regular short-acting and long-acting \(\beta\)-agonists is uncertain, but may relate to the on-off effect seen even when short-acting \(\beta\)-agonists are taken every six hours\(^24\) (Fig 2).

**Efficacy**

Several studies in adults have shown that introducing a long-acting \(\beta\)-agonist causes a greater improvement in lung function and symptoms and rescue \(\beta\)-agonist use than doubling\(^24,25\) or even quadrupling\(^6\) the dose of inhaled steroid. In one of the studies\(^6\), though,
the higher dose of inhaled corticosteroid caused a greater reduction in exacerbations than formoterol. This suggests that, for adults taking a low dose of inhaled corticosteroids, adding a long-acting β-agonist is more likely to be beneficial for symptom control, whereas a higher dose of inhaled steroid may be more helpful if exacerbations are the main problem. Monotherapy with long-acting β-agonists is not recommended: there are few data in adults, and salmeterol was ineffective in two studies in steroid-naïve children.\(^{26,27}\)

**Adverse effects**

Most adverse effects of long-acting β-agonists such as tremor and tachycardia are predictable and dose-related. Inhalation of salmeterol from an MDI occasionally causes paradoxical bronchoconstriction\(^{28,29}\). Some tolerance to the effects of long-acting β-agonists has been seen including a small initial loss of bronchodilator response to formoterol in one study\(^{6}\), although the bronchodilator effect was subsequently maintained over a year. The bronchoprotective effect of long-acting β-agonists against provocative stimuli such as exercise shows more tolerance with regular use\(^{10}\), though this does not appear to be a major clinical problem.

**Leukotriene modifiers**

Arachidonic acid is metabolised to LTA\(_4\), an unstable compound which may be metabolised to LTB\(_4\) or to the cysteiny1 LTs (C\(_4\), D\(_4\), and E\(_4\)). Inhalation of the cysteiny1 LTs produces a small initial loss of the features of asthma, and their production is increased during asthma exacerbations\(^{31}\). Drugs have therefore been developed to reduce the production or antagonise the actions of the LTs\(^{32}\) (Fig 3).

The cysteiny1 LT antagonists montelukast and zafirlukast are now available as oral preparations in the UK, and the 5-lipoxygenase inhibitor zileuton is available in some countries. Montelukast and zafirlukast inhibit the bronchoconstrictor response to various challenges including allergen, exercise and cold air without the development of tolerance\(^{33}\), and are particularly effective against aspirin challenge in aspirin-sensitive patients.

Both currently available LT antagonists are licensed for use in patients not controlled on an inhaled corticosteroid, but their place in the stepped management guidelines has yet to be determined. More head-to-head comparisons with the long acting β\(_2\)-agonists and inhaled corticosteroids are needed. Possible advantages of the LT antagonists may include improved compliance and their ability to treat nasal and respiratory symptoms with one tablet.

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**Key Points**

- Inhaled corticosteroids remain the cornerstone of treatment for most patients with asthma
- Long-acting β-agonists provide better asthma control than regular short-acting β-agonists
- In adults, the addition of a long-acting β-agonist to low-dose inhaled corticosteroids may provide better symptom control than increasing the inhaled corticosteroid dose
- Leukotriene modifiers represent a new class of orally administered drugs which can treat both nasal and respiratory symptoms. Further comparisons with other drugs are needed to determine their role in asthma management
- New approaches are needed for the small proportion of patients who have severe asthma despite current treatment: monoclonal antibodies are perhaps the most promising
Efficacy

Regular treatment with montelukast or zafirlukast leads to an improvement in lung function within hours of the first dose. This improvement has been maintained over several weeks with no evidence of tolerance, but also with little evidence of further improvement over time. There is less bronchodilation than with a β-agonist, but the effects are additive if both drugs are given. Used alone, the effects of the current LT antagonists appear to be less than those of 400 µg/day of beclomethasone dipropionate, but again their effects are probably additive to those of an inhaled steroid.

Adverse effects

Montelukast and zafirlukast are generally well tolerated, the main adverse effects being gastrointestinal and headache. Some patients have developed a Churg-Strauss-like syndrome, usually following reduction or cessation of oral corticosteroids, so it may be due to the unmasking of an underlying condition rather than a direct drug effect.

New therapeutics

Current treatment aims to prevent the final effects of a complicated immunological cascade. When used appropri-
ately, it is extremely effective for patients with mild or moderate asthma. A smaller, but important, number of patients continue to have severe asthma despite current treatment and, for them, there is an urgent need for more effective treatment. It seems unlikely that more selective anti-
muscarinic drugs or phosphodiesterase inhibitors will have a major impact on this group of patients. Methotrexate, cyclosporin and gold have some corticosteroid-sparing effect equivalent, on average, to a reduction of about 5 mg prednisolone, but they also have important adverse effects (Table 2).

New approaches such as the use of monoclonal antibodies to modify the inflammatory process at an earlier point in the cascade look more promising. Monoclonal antibodies currently being investigated include antibodies to immunoglobulin E (eg RhuMAB E25) and interleukin (IL)-5 (eg SB240563/006). Other possible targets include IL-4, IL-13 and endothelin. Nebulised liginocaine may have a role in severe oral steroid-dependent patients, and is currently being studied.

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34 Reiss TF, Sorkness CA, Stricker W, Botto
Respiratory infections in patients with HIV

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"The lung is an important site of infection in HIV-infected individuals. Bacterial and opportunistic pathogens are commonly implicated and, despite the introduction of effective prophylaxis and the use of highly active antiretroviral therapy (HAART), these infections remain significant causes of morbidity and mortality."

Common bacterial infections

Upper respiratory tract infections are seen frequently, and present acutely as in non-HIV infected people. One study reported an incidence of 33% of such infections after 18 months of follow-up, with *Streptococcus pneumoniae, Haemophilus influenzae* and *Pseudomonas aeruginosa* commonly isolated. Sinusitis is common and may be a more chronic problem, often presenting with headache and requiring the exclusion of more sinister pathology.

HIV predisposes patients to bacterial chest infections even at relatively high CD4 counts, although the incidence increases with more advanced immunosuppression. Organisms isolated are the same as in a non-HIV setting. Intravenous (IV) drug use is a strong risk factor. Primary prophylaxis against *Pneumocystis carinii* pneumonia (PCP) with co-trimoxazole appears to provide some protection in those with more advanced disease. Radiological findings may be atypical in almost half the cases and possibly difficult to distinguish from PCP (Fig 1). *P. aeruginosa* is a cause of nosocomial and community-acquired pneumonia, both of which are associated with advanced HIV, poor response to treatment and high rates of relapse. A recent report has suggested that persistent colonisation may clear with the use of HAART.

**Pneumocystis carinii**

PCP has been the most frequent AIDS-defining illness for many years, even after the introduction of effective prophylaxis. It occurs predominantly in patients with an absolute CD4 count below 200 cells/mm³, and is thought to occur by airborne reinfection. Presentation is with symptoms of dry cough, progressive breathlessness, fever and malaise. Clinical signs in the chest are usually notable by their paucity. Arterial desaturation on exercise testing is characteristic. Although chest radiographs may be normal early in the infection, they are abnormal at presentation in over 90% of patients. The most common appearance is bilateral, peripheral air space shadowing which may become more confluent as the infection progresses (Fig 2). In a minority of cases the appearances are atypical, with unilateral consolidation, nodules and lymphadenopathy all described.

There is debate about the need to confirm the diagnosis by bronchoscopy in patients presenting with typical clinical and radiological findings, and many centres treat PCP empirically. However, bronchoscopy need not be performed before starting treatment, but can be left for up to five days if the patient is too unwell at presentation to tolerate the procedure.

**Treatment**

All patients presenting with features suggestive of PCP should begin treatment immediately. First-line therapy is high-dose co-trimoxazole (120 mg/kg) in divided doses, given either IV or