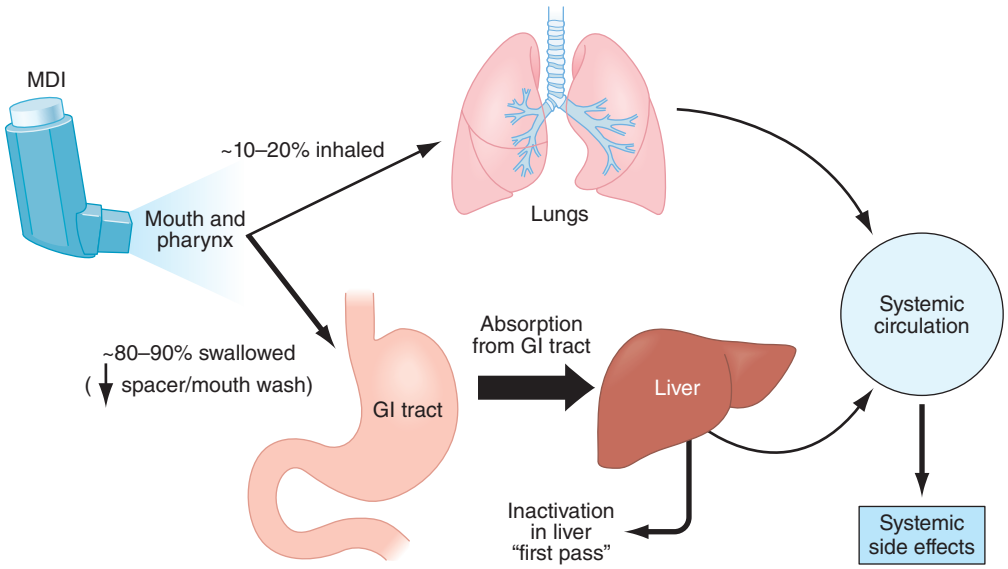

FIGURE 309-7 Pharmacokinetics of inhaled corticosteroids. GI, gastrointestinal; MDI, metered-dose inhaler.

Intramuscular triamcinolone acetonide is a depot preparation that is occasionally used in noncompliant patients, but proximal myopathy is a major problem with this therapy.

Antileukotrienes Cysteinyl-leukotrienes are potent bronchoconstrictors, cause microvascular leakage, and increase eosinophilic inflammation through the activation of cys-LT_1-receptors. These inflammatory mediators are produced predominantly by mast cells and, to a lesser extent, eosinophils in asthma. Antileukotrienes, such as montelukast, block cys-LT_1-receptors and provide modest clinical benefit in asthma. They are less effective than ICS in controlling asthma and have less effect on airway inflammation, but are useful as an add-on therapy in some patients not controlled with low doses of ICS, although less effective than LABA. They are given orally once or twice daily and are well tolerated. Some patients show a better response than others to antileukotrienes, but this has not been convincingly linked to any genomic differences in the leukotriene pathway.

Cromones Cromolyn sodium and nedocromil sodium are asthma controller drugs that appear to inhibit mast cell and sensory nerve activation and are, therefore, effective in blocking trigger-induced asthma such as EIA and allergen- and sulfur dioxide–induced symptoms. Cromones have relatively little benefit in the long-term control of asthma due to their short duration of action (at least four times daily by inhalation). They are very safe and were popular in the treatment of childhood asthma, although now low doses of ICS are preferred because they are more effective and have a proven safety profile.

Steroid-Sparing Therapies Various immunomodulatory treatments have been used to reduce the requirement for OCS in patients with severe asthma who have serious side effects with this therapy. Methotrexate, cyclosporin A, azathioprine, gold, and IV gamma globulin have all been used as steroid-sparing therapies, but none of these treatments has any long-term benefit, and each is associated with a relatively high risk of side effects.

Anti-IgE Omalizumab is a blocking antibody that neutralizes circulating IgE without binding to cell-bound IgE and, thus, inhibits IgE-mediated reactions. This treatment has been shown to reduce the number of exacerbations in patients with severe asthma and may improve asthma control. However, the treatment is very expensive and is only suitable for highly selected patients who are not controlled on maximal doses of inhaler therapy and have a circulating IgE within a specified range. Patients should be given a 3- to 4-month trial of therapy to show objective benefit. Omalizumab is usually given as a subcutaneous injection every 2–4 weeks and appears not to have significant side effects, although anaphylaxis is very occasionally seen.

Immunotherapy Specific immunotherapy using injected extracts of pollens or house dust mites has not been very effective in controlling asthma and may cause anaphylaxis. Side effects may be reduced by sublingual dosing. It is not recommended in most asthma treatment guidelines because of lack of evidence of clinical efficacy.

Alternative Therapies Nonpharmacologic treatments, including hypnosis, acupuncture, chiropraxis, breathing control, yoga, and speleotherapy, may be popular with some patients. However, placebo-controlled studies have shown that each of these treatments lacks efficacy and cannot be recommended. However, they are not detrimental and may be used as long as conventional pharmacologic therapy is continued.

Future Therapies It has proved very difficult to discover novel pharmaceutical therapies, particularly because current therapy with corticosteroids and β_2-agonists is so effective in the majority of patients. There is, however, a need for the development of new therapies for patients with refractory asthma who have side effects with systemic corticosteroids. Antagonists of specific mediators have little or no benefit in asthma, apart from antileukotrienes, which have rather weak effects, presumably reflecting the fact that multiple mediators are involved. Blocking antibodies against IL-5 may reduce exacerbations in highly selected patients who have sputum eosinophils despite high doses of corticosteroids, whereas anti-TNF-α antibodies are not effective in severe asthma. Novel anti-inflammatory treatments that are in clinical development include inhibitors of phosphodiesterase-4, NF-κB, and p38 MAP kinase. However, these drugs, which act on signal transduction pathways common to many cells, are likely to have troublesome side effects, necessitating their delivery by inhalation. Safer and more effective immunotherapy using T cell peptide fragments of allergens or DNA vaccination is also being investigated. Bacterial products, such as CpG oligonucleotides that stimulate T_H1 immunity or regulatory T cells, are also currently under evaluation.

MANAGEMENT OF CHRONIC ASTHMA

There are several aims of chronic therapy in asthma (Table 309-2). It is important to establish the diagnosis objectively using spirometry or PEF measurements at home. Triggers that worsen asthma control, such as allergens or occupational agents, should be avoided, whereas triggers, such as exercise and fog, which result in transient symptoms, provide an indication that more controller therapy is needed. It is important to assess asthma control, determined by