

REVIEW

Alternative strategies in the treatment of bronchial asthma

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Introduction

Bronchial asthma is a common disease, of which most patients are adequately treated by standard therapy [1]. However, a small but worrying group of patients with asthma has severe, unremitting disease that cannot be controlled by conventional strategies, including cromones, theophylline, maximal bronchodilator therapy, and high doses of inhaled corticosteroids [1]. Management of patients with difficult asthma should include evaluation of medication compliance, identification of factors that precipitate exacerbations, as well as early assessment of progressive deterioration of the disease [2]. Nonetheless, these patients often require long-term systemic corticosteroid treatment resulting in unwanted and potential serious side effects, such as osteoporosis, skin thinning, diabetes, hypertension and cataract formation [3]. To avoid these effects of systemic steroid therapy, a number of immunosuppressants and other agents with putative anti-inflammatory activity have been investigated.

In the following, we will focus on proposed alternative approaches in the treatment of asthma. Strategies previously suggested in the treatment of mild as well as severe intractable asthma will be reviewed. In addition, future needs and developments will be discussed.

Nutritional factors

Dietary factors appear to be responsible, at least in part, for the increase in prevalence of asthma [4]. Nutritional modification of these factors therefore might have the potential to reduce prevalence as well as disease severity.

Sodium chloride

An epidemiological survey showed a correlation between an increase in male asthma mortality and regional sales of table salt [5]. Several controlled studies showed a small but significant improvement of asthma disease control in men (but not women), when comparing low-dose with high-dose sodium chloride intake [6–8]. Low-dose sodium chloride

intake resulted in a decrease in symptom score and rescue medication usage, and improvement in lung function and airway hyperresponsiveness. The effects are probably mediated by the sodium, not chloride, ion [8]. The mechanism of action remains to be elucidated, but might be related to an increased airway smooth muscle tone or a fall in circulatory catecholamines [9].

Selenium

Selenium is a spore element, essential for the formation of the anti-oxidative enzyme glutathione peroxidase (GSH-Px) [10,11]. It has been shown that GSH-Px activity is decreased in aspirin-sensitive asthma [12]. In addition, selenium plays a role in arachidonic acid metabolism, and influences phagocytosis and immunoglobulin synthesis [10].

Flatt and coworkers demonstrated a relation between lowered selenium intake, decreased GSH-Px activity and asthma prevalence in New Zealand [11]. Therefore, selenium depletion, and subsequent supplementation might influence asthma. Double-blind, placebo-controlled supplementation of selenium improved symptom scores slightly but significantly. It did not result, however, in improvement of lung function parameters [13]. Hence, selenium supplementation cannot be regarded as relevant therapeutic option in asthma therapy.

Fish oil

Fish oil is rich in polyunsaturated fatty acids which have been shown to interfere with arachidonic acid metabolism resulting in formation of leukotrienes and prostaglandins with reduced biological activity [14]. Furthermore, incorporation of these fatty acids in the cellular membrane attenuates neutrophilic chemotaxis and cell adhesion [14].

Indeed, epidemiological studies suggested that high dietary intake of oily fish was associated with a decreased risk for asthma [15–17]. Although the results of some pilot studies were promising [14,18,19], controlled studies could not support the hypothesis that fish oil consumption plays a role in asthma therapy [20–23].

Magnesium

An excess of magnesium blocks calcium, thereby possibly

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interacting with bronchial smooth muscle contraction. Moreover, a deficiency of magnesium might enhance the effects of calcium thereby contributing to asthma severity [24]. Magnesium levels appear to be lower in patients with asthma compared with healthy subjects [25]. This deficiency might be amplified by the use of β_2 -agonists or theophylline [25–27]. Intravenous bolus administration of magnesium (2 g magnesium sulphate) in acute severe asthma might be of benefit [28,29], however, data are conflicting [30,31]. A surplus in dietary magnesium intake in chronic asthma did not show objective improvement [32,33].

Vitamin B6

The amino acid tryptophan is the precursor of serotonin, a potent bronchoconstrictor. Serotonin might accumulate in patients with asthma due to a partial block in the tryptophan metabolism [34]. A double-blind, placebo-controlled diet with and without tryptophan restriction revealed a significant increase in peak expiratory flow (PEF) [34]. Vitamin B6 (pyridoxine) can incite tryptophan metabolism, thus lowering serotonin levels. Whereas one study demonstrated an improvement in childhood asthma by reduction of rescue medication use after a 5-month double-blind treatment with pyridoxine [35], another study with an even higher dosage of vitamin B6 (300 mg daily) failed to improve outcome variables in steroid-dependent asthma [36].

Vitamin B12

Theoretically, vitamin B12 (cyanocobalamin) might be of use in patients with asthma due to sulphite intolerance, by catalysing the extracellular oxidation of sulphite. A single-blind oral dosage of 1.5 mg cyanocobalamin attenuates metabisulphite-induced bronchoconstriction in four out of five asthmatic children with proven metabisulphite intolerance [37]. Currently, there are no other data available supporting the value of vitamin B12 in asthma therapy.

Vitamin C

Vitamin C (ascorbic acid) might influence the course of asthma in several ways: ascorbic acid accelerates histamine degradation, has a direct relaxing effect on smooth muscle cells, and influences cyclic adenosine monophosphate (cAMP) and prostaglandin metabolism. In addition, it reduces oxidative stress [38,39]. Decreased serum levels of ascorbic acid seem to be associated with an increased risk for bronchitis and wheezing [39]. Ascorbic acid dietary supplements, however, do not seem to be efficacious in the treatment of bronchial asthma [40–43]. At most, there might be a slight improvement in exercise-induced bronchoconstriction [38,44].

Conclusion

Although theoretically dietary factors might influence the natural course of asthma, nutritional intervention does not seem to be of value in the treatment of mild or severe asthma. In view of the important therapeutic implication of intravenous magnesium in the management of severe uncontrollable exacerbations, further research is warranted to evaluate efficacy.

Inhaled gasses

It is a well-known clinical observation that local anaesthetics reduce airway obstruction in severe asthma. More recently, inhalation of a mixture of helium and oxygen have been suggested to be advantageous in severe airway narrowing.

Halothane

Halothane (0.5–1%), an inhalation anaesthetic, has been described in retrospective series and case reports as last-resort treatment in patients with status asthmaticus refractory to conventional therapy [45–50]. The mechanisms by which halothane exerts its bronchodilatory action remain unclear, however, the blockage of vagal airway reflexes seems to be of relevance [45]. Haemodynamic side effects are the major drawbacks for the use of halothane. These effects include myocardial depression and ventricular dysrhythmias, that are probably potentiated by theophylline and β_2 -agonist bronchodilator therapy, and by hypoxemia [45,51]. Up to now, controlled studies evaluating the potential role for halothane in the treatment of refractory exacerbations have been lacking.

Heliox

Heliox is a blend of helium and oxygen without inherent therapeutic effects. Heliox has a gas density less than that of room air and has thereby the potency to decrease airway resistance [52,53]. Therefore, heliox might be used in patients suffering from a status asthmaticus with severe therapy-resistant bronchoconstriction. Gluck and colleagues were one of the first to report a potential beneficial effect in seven mechanical ventilated patients with respiratory failure due to status asthmaticus. Heliox resulted in a rapid reduction in airway pressure, CO₂ retention and consequently respiratory acidosis without side effects [52]. An open study by Kass and Castriotta was in line with these data [54].

Theoretically, heliox can be used in spontaneously breathing asthmatic patients to relieve dyspnea and allow time for therapeutic agents like corticosteroids to work for the resolution of airway narrowing [55]. Heliox appeared to

decrease pulsus paradoxus and increase peak flow significantly in nonintubated patients with a severe exacerbation as compared with room air [56]. Carter *et al.* confirmed a small but significant effect in favour of heliox vs room air on peak flow in a randomized, double-blind, crossover trial in 11 asthmatic children with status asthmaticus [53]. Nonetheless, they could not demonstrate an effect on dyspnea scores or other clinical parameters. So far, heliox might be of value in the intensive care unit, but should not be regarded as standard therapy in refractory bronchoconstriction.

Conclusion

Inhaled halothane as well as heliox might be of relevance in the treatment of severe intractable asthma. These strategies, however, should be restricted to a small group of patients during severe therapy-resistant exacerbations with concomitant respiratory failure.

Immunotherapy

Allergic sensitization in early childhood is the most important risk factor for developing asthma [57]. In addition, it has been suggested that sensitization and exposure to indoor allergens is associated with exacerbations [58,59]. Allergen avoidance and modification of the allergic response by therapeutic intervention could therefore be beneficial in modifying asthma severity.

Allergen hyposensitization

Allergen immunotherapy by recurrent low dose injection of allergen could reduce hyperresponsiveness to that specific allergen, possibly by T-lymphocyte modulation with increase in T-suppressor cells [60,61]. Abramson and coworkers concluded from a meta-analysis of 24 double-blind, placebo-controlled studies that immunotherapy might be efficacious in selected patients with mild to moderate, non-steroid-dependent asthma [61]. The literature is, however, equivocal, with enthusiastic supporters [62], as well as defeatist opposers [63]. A major drawback for immunotherapy is the potentially lethal anaphylaxis. If there is any indication for immunotherapy, it seems to be restricted to young patients with a mono-allergy in whom allergen avoidance cannot be achieved [61,64].

Hyposensitization by oral immunotherapy has been introduced recently, which obviously does not require subcutaneous injections. Side effects still seem to occur whilst efficacy is disappointing [65–68]. Possibly, future immunotherapy should also be focused on novel techniques, like DNA vaccination or immunization early in life, all based on an improved understanding of allergic disease [69].

Allergen–antibody complexes

Allergen–antibody complexes derived from allergens and autologous specific antibodies from the serum of allergic patients might modulate the allergic immune response possibly by interfering with allergen presentation and processing.

Machiels *et al.* showed an improvement in symptoms, corticosteroid medication requirements and aspecific bronchial hyperresponsiveness in patients with severe atopic asthma by treatment with allergen–antibody complexes in a controlled design [70–72]. The value of this therapy still has to be established and the results need to be confirmed by other groups.

Plasmapheresis

Several anecdotal reports suggest a possible role for plasmapheresis in the treatment of therapy-resistant asthma [73–75] by elimination of antibodies or immunocomplexes. To our knowledge, there are no controlled trials in English literature that support the use of plasma exchange in asthma therapy.

Intravenous immunoglobulins

Administration of intravenous immunoglobulins (IVIG) has been proven to be successful in the management of various immunodeficiency as well as auto-immune disorders [76]. Therefore, IVIG might be effective in asthma that is related to recurrent airway infections with associated immunodeficiency syndromes [77,78]. In addition, IVIG could modify noninfectious asthma by inhibition of mononuclear cell proliferation and B-cell differentiation, IgG-Fc-receptor blockage, modification of complement activation or reduction of IgE synthesis by anti-idiotypic antibodies [76,79]. IVIG is rather expensive, but side effects are mild and include headache and pyrexia. Prevention of transmission of viral infections, however, remains of concern.

Mazer and Gelfand performed an open study with high dose IVIG (2 g/kg every 4 weeks) in eight children with severe atopic steroid-dependent asthma without a humoral immunodeficiency [80]. After 6 months of therapy, IVIG resulted in an improvement in symptoms, lung function and corticosteroid requirement. In addition, a reduced skin reactivity to specific allergens supported the immunomodulatory effect of IVIG. Results of other open studies by, respectively, Jakobsson *et al.* and Landwehr *et al.* were in line with the findings of Mazer and Gelfand [81,82]. Recently, however, neither Valacer *et al.* nor Niggemann *et al.* could confirm this beneficial effect of IVIG (1–2 g/kg every 4 weeks) in two double-blind, placebo-controlled trials in severe asthma [83,84].

Conclusion

At present allergen hyposensitization seems the only immunotherapeutic option being additive to pharmacotherapy in asthma management. Unfortunately, patients with severe, long-standing, steroid-dependent asthma do not seem to benefit from hyposensitization. Therefore, immunotherapy does not seem to be indicated in the management of severe asthma. Future developments, such as DNA vaccination or immunization early in life, might, however, alter the scope of this therapy.

Macrolide antibiotics

For many years it has been thought that bacterial infections played an important role in the pathophysiology of asthma, and antibiotics were prescribed routinely during exacerbations. Nowadays, antibiotics do not have a central place in asthma therapy. Nonetheless, several macrolide antibiotics appear to possess anti-inflammatory properties and might therefore be used in asthma control.

Troleandomycin

The efficacy of troleandomycin (TAO) as a steroid-sparing drug in severe corticosteroid-dependent asthma has been suggested in several open studies [85–89]. This effect cannot be contributed to the antibiotic properties of TAO [90], but may be explained at least in part by a two- to threefold reduction of methylprednisolone (but not prednisolone) clearance [91]. This explains the superiority of TAO-methylprednisolone over TAO-prednisolone combinations. Other therapeutic properties include inhibition of neutrophil chemotaxis *in vitro* [92] and normalization of inhibition of the phytohaemagglutinin-driven proliferation of peripheral blood mononuclear cells from patients with steroid-resistant asthma *in vitro* [93].

Kamada and coworkers performed a randomized, double-blind, parallel tapering of methylprednisolone with and without TAO (250 mg once daily) for 3 months in 18 children with severe steroid-dependent asthma [94]. The TAO-methylprednisolone regimen allowed tapering of steroids considerably as compared with the placebo-methylprednisolone strategy, without deterioration of symptoms or lung function parameters. Nelson *et al.*, however, could not confirm this steroid-saving effect in 57 asthmatics in a study with similar design for 1 year [95]. More importantly, even if it would be possible to reduce the daily dose of methylprednisolone as a result of a reduced clearance, steroid-related side effects thus would remain unchanged. Indeed, Harris and German demonstrated an increase in side effects in TAO-methylprednisolone regimens despite reduction of the steroid dose [96]. Prominent side effects include

cataract, hypertension, diabetes mellitus, hepatitis, hypercholesterolemia and cushingoid appearance [96,97], and consequently limit therapeutic properties of TAO.

Erythromycin

Erythromycin, like TAO and possibly other macrolide antimicrobial agents, might have anti-inflammatory effects beneficial in asthma therapy. Erythromycin interferes with methylprednisolone metabolism, reduces oxygen radical production by neutrophils [98,99], affects neutrophil migration and chemotaxis [100], and has antimicrobial properties potentially useful in 'chlamydia pneumoniae-induced' bronchial asthma [101].

Miyatake and colleagues showed a small but significant reduction in airway responsiveness, however, without improving symptoms or lung function, after 10 weeks of treatment with erythromycin (600 mg daily) in an open design [102].

Conclusion

Efficacy of macrolides has been studied extensively in the management of steroid-dependent asthma. Troleandomycin allows reduction of daily corticosteroid dosage, but there is no substantial reduction of steroid-related side effects. Hence, macrolide antibiotics should not be regarded as steroid-sparing agents.

Immunosuppressants and antimetabolites

Immunosuppressants might dampen the asthmatic immune response by affecting inflammatory cell numbers and function. These drugs already have been shown to be efficacious in rheumatoid arthritis and other inflammatory diseases.

Methotrexate

Methotrexate (MTX) is a folic acid antagonist, being used for more than 40 years in cancer treatment. In lower dosage, it has anti-inflammatory properties beneficial in psoriasis and rheumatoid arthritis [103]. The mode of action in modulating immune response remains speculative, although inhibition of neutrophil recruitment and adherence, monocyte chemotaxis, B-cell differentiation, cytokine and histamine release have all been suggested [103]. From 1988, MTX (15 mg weekly) has been studied extensively as a non-steroidal anti-inflammatory agent in asthma. Results were contradictory, as several controlled studies showed a steroid-sparing effect [104–108] while in others benefit was lacking [109–114].

Marin performed a meta-analysis of all these studies,

reviewing a total number of 199 patients with steroid-dependent asthma [115]. MTX resulted in an almost 25% reduction in daily steroid dose. Patients with low dosage of steroids seemed to profit most from methotrexate, especially when methotrexate was prescribed for at least 6 months. Yet, it is not feasible to discriminate between responders and non-responders to MTX.

In the 11 reviews studied, no life-threatening side effects were reported. Adverse events are reported in other studies in up to 60% of cases, and are dose-dependent [103]. Hepatotoxicity is the most troublesome complication, although also gastrointestinal toxicity, haematological abnormalities, and pulmonary toxicity are described. Hence, methotrexate has modest but significant steroid-saving effects in steroid-dependent asthma. More information is required about what subgroup of asthmatics will benefit most of MTX.

Azathioprine

Azathioprine, a purine analogon, is an immunosuppressive drug that inhibits monocyte function and is therefore used in diverse autoimmune disorders like rheumatoid arthritis, inflammatory bowel disease and systemic vasculitis [103,116].

Two placebo-controlled studies were unable to demonstrate a beneficial effect of azathioprine (2–5 mg/kg daily) in asthma [117,118]. These studies can be criticized, however, for the short duration of azathioprine therapy of maximal 4 weeks [116]. Azathioprine requires at least 8 weeks of treatment in diseases like rheumatoid arthritis to exert a clinical significant effect. This might explain the more encouraging results of Irwin and associates in an open study after 3 months of azathioprine in severe steroid-dependent asthma [119]. They encountered, however, serious complications like haematological disorders, liver failure, meningitis and viral and fungal infections, making azathioprine therapy unacceptable in asthma.

Cyclosporin A

Cyclosporin A is an immunosuppressive drug with proven value in organ transplantation, and has been used in a number of inflammatory diseases like psoriasis, rheumatoid arthritis and Crohn's colitis. Cyclosporin A inhibits T-lymphocyte proliferation *in vitro* from peripheral blood mononuclear cells from patients with corticosteroid-sensitive as well as corticosteroid-resistant asthma, with subsequent decrease in cytokine release [120,121]. Furthermore, cyclosporin A suppresses eosinophil proliferation [122] and interferes with mast cell function [123]. It has been shown to reduce the allergen-induced late allergic reaction [124] and might reduce bronchial hyperresponsiveness [125].

Alexander and coworkers were the first to assess efficacy of cyclosporin A (initial dose 5 mg/kg daily) for 12 weeks in 33 patients with steroid-dependent asthma in a double-blind, placebo-controlled, crossover fashion [126]. Results were encouraging, and demonstrated an increase in lung function parameters with amelioration of diurnal peak flow variation, and reduction in number of exacerbations during cyclosporin A treatment vs placebo. In addition to improving lung function, the paper by Lock and associates seemed to extend these findings by allowing a significant reduction in the daily dose of oral corticosteroids over a 9-month period [127]. On the other hand, Nizankowska *et al.* could not demonstrate an improved lung function to cyclosporin in a parallel design, although they noticed a slight but significant reduction in symptoms [128]. In addition, cyclosporin was more efficacious than placebo in tapering systemic corticosteroid dose.

Nephrotoxicity is the most worrying adverse event: though basic functional changes always occur during cyclosporin treatment, the superimposed tubular and vascular toxicity leading to chronic renal failure is dose-dependent and demands frequent monitoring of blood levels and renal function [103,129]. Other important side effects include hypertension, hepatotoxicity, peripheral neuropathy and hypertrichosis [103]. Thus, cyclosporin A might have its merits in treatment of intractable, especially steroid-resistant asthma, although side effects will limit widespread use.

Conclusion

Methotrexate and cyclosporin A, both immunosuppressive drugs, might be of value in the control of asthma. In view of the potential deleterious side effects, these strategies should only be used in selected patients with severe, steroid-dependent asthma in whom the therapeutic effect outweighs these adverse events.

Other drugs with anti-inflammatory properties

Several drugs might affect the asthmatic immune response without cytotoxic properties. These agents are, from a pathophysiological point of view, potentially the most successful approach in asthma treatment. Therefore, many trials have been performed to assess the additional value, especially in the management of moderate to severe asthma.

Antihistamines

Allergic rhinitis and allergic bronchial asthma are related diseases in which histamine is an important mediator. Although the use of antihistamines in treatment of allergic rhinitis is more than established, its role in asthma remains

controversial. Effects of ketotifen, a first generation H_1 -specific receptor antagonist, seemed to be promising because of possible intrinsic anti-inflammatory properties resulting in reduction of eosinophilic activation and migration, and normalization of β -receptor expression thus preventing tachyphylaxis [130,131]. Since then, many double-blind, placebo-controlled studies estimating clinical efficacy of ketotifen in asthma have been performed [131–151]. Overall, ketotifen (1 mg bid) seems to ameliorate asthma severity slightly (especially in children), with improvement of symptoms, rescue medication use and number of exacerbations. Ketotifen does not improve lung function or reduce corticosteroid requirements. Side effects are marked and include weight gain and sedation [130].

With the introduction of the more potent and highly specific non-sedating second generation H_1 -antihistamines, the use of this class of medication in asthma has been reassessed and recently reviewed by Malick and Grant [152]. Cetirizine is possibly the most potent antihistamine: cetirizine (10 mg bid) improved asthma symptoms, rescue medication use and peak flow significantly in atopic asthmatics in a double-blind, placebo-controlled trial, even when comparing it with another antihistamine (terfenadine) [153,154]. Aaronson demonstrated a reduction in asthma symptoms, albuterol use, and airflow obstruction as measured by peak flow when comparing cetirizine (20 mg daily) with placebo in 28 patients with mild to moderate perennial asthma [155]. These effects are, however, marginal. In addition, cetirizine does not seem to affect early and late asthmatic reactions [156,157]. In conclusion, although histamine is an important mediator in the pathogenesis of asthma, histamine blockage does not seem to contribute significantly to asthma therapy. Recently, interest has been raised in the use of cetirizine in the prevention of development of allergic airways disease in early childhood [158].

Gold

Treatment with gold salts, so-called chrysotherapy, appeared to be effective in patients with rheumatoid arthritis, with immunomodulatory effects and steroid-sparing properties. The mechanisms by which gold acts are unravelled, but might include inhibition of T-lymphocyte function, inhibition of histamine release from basophils, and decrease in IgE production [159–161].

After a few promising studies [162–164], Nierop and colleagues performed a randomized, double-blind, parallel study in 32 patients with corticosteroid-dependent asthma, comparing auranofin (3 mg bid), an oral gold compound, and placebo for 26 weeks [165]. In the auranofin group FEV_1 increased significantly, whilst oral corticosteroids could be reduced. Bernstein *et al.*'s results were in keeping with these findings in a similar design in 279 patients with

steroid-dependent asthma during an 8-month trial [160]. Oral corticosteroids could be reduced significantly (at least 50% from baseline) in 60% of the patients in the auranofin-treated group, vs 32% of the patients in the placebo group.

Rash, pruritus, exacerbations of eczema, and diarrhoea are most noted, however, mild side effects, and result only occasionally in discontinuation of treatment [161,165]. Proteinuria is a rare side effect, but requires urinalysis during treatment. Therefore, auranofin should be regarded as a relatively safe, steroid-sparing drug in asthma.

Dapsone

Dapsone, a sulphone used in the treatment of leprosy and rheumatic disorders, inhibits neutrophil function by decreasing reactive oxygen radical production as well as by inhibition of neutrophil chemotaxis [166,167].

Berlow and coworkers examined the effects of dapsone in asthma in an open trial: seven out of 10 patients with steroid-dependent asthma were able to withdraw systemic corticosteroids completely after 7 months of treatment with dapsone (100 mg bid) [167]. Corticosteroids could be reduced by 75% in two other patients. The reduction of corticosteroids did not result in increase in symptoms or deterioration of lung function. Side effects are rare, but include neurological reactions (neuropathy, psychosis), hepatitis, and haematological abnormalities (agranulocytosis, haemolysis). Only the latter side effect appears to be common, and dose dependent. Albeit the results of Berlow's study were promising, up to now no other studies have been published concerning the possible steroid-sparing properties of dapsone.

Hydroxychloroquine

Hydroxychloroquine (HCQ) is an antimalarial agent with immunomodulatory properties, and is therefore prescribed as second line therapy in connective tissue diseases, like rheumatoid arthritis and lupus erythematosus. HCQ interferes with arachidonic acid metabolism by inhibition of the phospholipase- A_2 enzyme, thus resulting in a reduced production of leukotrienes, prostaglandins and platelet-activating factor [168]. In addition, HCQ inhibits histamine production. Retinal toxicity is the only potential, but rare (1%) serious side-effect, and requires a periodic ophthalmologic check.

Roberts and associates compared HCQ (400 mg daily) and placebo for 8 weeks in nine adults with steroid-dependent asthma in a crossover fashion and could not demonstrate a significant difference in symptoms, rescue medication use, lung function or corticosteroid requirements between the two groups [169]. In contrast, Charous claimed in an open label of HCQ (300–400 mg daily, maximum 6.5 mg/kg/day)

for 28 weeks in 11 patients with moderate to severe asthma (of which seven were steroid dependent) an improvement in asthma symptoms, with concomitant increase in lung function and reduction of corticosteroid dosage [168,170]. Of note, serum IgE levels showed a significant reduction during HCQ treatment.

Colchicine

Colchicine is a drug with immunomodulatory properties, that has been used in the treatment of gout, psoriatic arthritis, M. Behçet, familial Mediterranean fever, and primary biliary cirrhosis [171]. An aetiological mechanism in the latter two diseases, as well in bronchial asthma, might be a disorder in the suppressor T-cell function, which is, at least in part, corrected by colchicine *in vitro* [172–174]. The combination of colchicine and theophylline is synergistic in normalizing the T-cell imbalance [175]. Furthermore, colchicine inhibits LTB₄ release from neutrophils [176,177], and reduces the early and late phase airway reactions to allergen [177].

Schwarz and colleagues demonstrated immunomodulatory effects of 4 weeks' colchicine (0.5 mg bid) in combination with oral theophylline vs placebo and theophylline in a double-blind, randomized trial in mild to moderate perennial asthma by reduction of symptoms, rescue medication use, and serum IgE [171]. Lung function characteristics were unaffected. More recently, however, several clinical studies on the efficacy of colchicine were unable to demonstrate a relevant beneficial effect in the treatment of asthma [178–180]: colchicine treatment (0.6 mg/bid) was not superior to placebo in preventing asthma deterioration after withdrawal of inhaled corticosteroids in 71 adult patients with moderate asthma in a multicentre, randomized, controlled trial by Fish *et al.* [180]. Theoretically, the latter studies can be criticized by omitting the possible superior combination of colchicine with theophylline [171,175].

Anti-CD4 monoclonal antibodies

A monoclonal antibody directed against a CD4 epitope of T lymphocytes is currently being investigated as a treatment for asthma and rheumatoid arthritis. A recent double-blind, placebo-controlled parallel trial examined the effect of a specific anti-CD4 monoclonal antibody, given as a single intravenous infusion to five patients with severe corticosteroid-dependent asthma. The results demonstrated that anti-CD4 (3 mg/kg) increased peak flow significantly for at least 3 weeks [181]. There were no serious adverse events, however, worsening of eczema and a rash were noted. Further studies with this class of drugs in severe chronic asthma are warranted.

Lidocaine

Lidocaine has been used for many years now to achieve topical anaesthesia of the airways for bronchoscopy by suppressing irritant-induced cough. Early studies [182] demonstrated an inhibition of exercise-induced bronchoconstriction after inhalation of nebulized lidocaine (1 mg/kg), although data are conflicting [183,184]. In addition, inhaled lidocaine affects airway hyperresponsiveness to hypertonic saline [185] as well as to histamine [186]. Groeben *et al.* demonstrated a similar effect on airway hyperresponsiveness to histamine after intravenous as well as inhaled lidocaine as compared with placebo [187].

Recently, Hunt and coworkers conducted prospectively an open study of the steroid-sparing effects of inhaled lidocaine (40–160 mg qid) in 20 adult patients with corticosteroid-dependent asthma [188]. Prednisone could be reduced in 17 out of 20 patients after a mean treatment period of 12.2 months. Strikingly, 13 of them were able to discontinue oral use of glucocorticoids entirely. Three recent studies are in line with these observations [189,190,191]. Lidocaine might act by dampening neurogenic reflexes [185,186]. Furthermore, lidocaine has anti-inflammatory properties, since it inhibits cytokine-induced eosinophil survival [192]. Hypothetically, lidocaine might improve asthma symptoms merely by abolishing dyspnea sensations through vagal blockage [186], without reduction of inflammation.

Anti-leukotrienes

Leukotrienes are products of the 5-lipoxygenase pathway of the arachidonic acid metabolism [193]. Cysteinyl-leukotrienes (LTC₄, LTD₄, LTE₄) are potent contractors of airway smooth muscle, and have pro-inflammatory properties. Blockage of these mediators might therefore be of value in asthma. Indeed, cysteinyl-leukotriene receptor antagonists and biosynthesis inhibitors possess both bronchodilatory [194–196] and anti-inflammatory qualities [193,197]. They protect against dry air hyperventilation-induced [198,199], exercise-induced [200–203], aspirin-induced [204,205], and allergen-induced bronchoconstriction [206–210], and inhibit the increase in eosinophil and lymphocyte numbers in bronchoalveolar lavage fluid after allergen challenge [211–213]. Peripheral blood eosinophilia are reduced by leukotriene antagonists further suggesting anti-inflammatory properties [214–216]. Recently, Leff *et al.* demonstrated that leukotriene antagonists dampen eosinophilic airway inflammation by showing a reduction in sputum eosinophils after 4 weeks treatment with a cysteinyl leukotriene antagonist as compared with placebo [217].

In clinical trials in patients with mild to moderate asthma,

these drugs have shown efficacy on asthma symptoms, morning and evening peak flow, FEV₁ and rescue medication use [200,214–216,218–220]. Leukotriene antagonist therapy also resulted in a reduced number of exacerbations [215,218]. Tachyphylaxis or rebound phenomena could not be identified in these studies [200,215,221]. In some studies, the most severe asthma patients showed the best response to treatment. Recent results of two randomized, double-blind, placebo-controlled trials in 79 and 226 patients with moderate to severe asthma on high doses of inhaled corticosteroids, suggest that oral pranlukast (450 mg bid) as well as montelukast (10 mg daily) — both specific cysteinyl leukotriene antagonists — have steroid-sparing effects [222,223]. Results obtained with zafirlukast (20 mg daily) seemed to confirm the steroid-saving effects of this new class of drugs [224]. Adverse events were, if present, mild, of which reversible liver function tests were reported most often. Hence, cysteinyl leukotriene receptor antagonists and biosynthesis inhibitors are a potential first-line treatment modality in certain subgroups of asthma, and might be additive in the treatment of more severe asthma. To that end, it now becomes mandatory to assess the effects of this group of drugs in a large number of oral corticosteroid-dependent asthma.

Conclusion

Although the above-mentioned drugs have some potential in asthma therapy, none of them can compete with corticosteroids. Nonetheless, leukotriene receptor antagonists might be used as monotherapy in mild asthma as well as add-on therapy in the management of severe, steroid-dependent asthma. Also gold therapy has been proven to be efficacious as a steroid-sparing agent in severe asthma. More controlled trials are needed to value other immunomodulatory drugs.

Drugs affecting ion and water transport

An alternative approach in modifying bronchoconstriction and airway inflammation might be by direct interaction with ion transport that is essential for smooth muscle contraction or neural transmission.

Calcium channel blockers

Cellular influx of calcium ions plays a key role in the pathophysiological mechanism of bronchial smooth muscle contraction, secretion of mast cell mediators, mucus secretion and vagal neurotransmission [225,226]. Therefore, after the introduction of calcium channel blockers (like verapamil, nifedipine and diltiazem) in treatment of hypertension and ischemic heart disease, interest has been raised for these drugs in asthma. Unfortunately, none of the calcium antagonists came up to these high expectations [227].

Despite the reduction in spontaneous and laboratory-induced bronchoconstriction by calcium channel blockage [228–235], in clinical studies no relevant improvement in asthma control could be demonstrated [227,235–237]. This lack of benefit might be explained by the pharmacological mode of action: the available calcium antagonists interact mainly with the so-called ‘voltage-dependent’ channels, whilst cellular calcium transport in asthma is mediated by ‘receptor-operated’ channels [226,227]. Thus, the only positive implication about calcium antagonists and asthma is that these drugs are not potentially harmful in contrast with other antihypertensive agents like β -blockers and angiotensin-converting enzyme inhibitors [1,238].

Potassium channel openers

Cellular hyperpolarization by potassium efflux induces smooth muscle relaxation [239]. This phenomenon became of particular interest after the discovery that potassium channel activation mediates the effect of β_2 -agonists [240]. Potassium channel openers, like cromakalim, bimakalim, pinacidil and lemakalim, indeed result in spontaneous bronchodilation, or after induced bronchoconstriction in animal studies [239,241]. In addition, potassium channel openers seem to attenuate neurogenic inflammation, possibly through interaction with the nonadrenergic, non-cholinergic transmission.

Williams *et al.* demonstrated a significant alleviation of nocturnal asthma by oral cromakalim (0.5 mg daily) as compared with placebo as shown by improving early morning FEV₁ in eight patients with mild to moderate asthma [242]. On the other hand, Kidney and associates could not demonstrate any effect on airway narrowing or airway hyperresponsiveness when comparing cromakalim (0.5 mg daily) and placebo in 17 patients with mild to moderate severe asthma in a controlled fashion [243]. The use of potassium channel activators is hampered by side effects such as headache and hypotension [242–244]. These adverse events can be avoided when delivered by inhaled route [245]. Unfortunately, these drugs, when inhaled, seem to lose their possible therapeutic abilities as well [245].

Inhaled frusemide

Bianco and colleagues were the first to show that nebulized frusemide attenuates exercise-induced bronchoconstriction [246]. Since then the inhibitory effect of nebulized frusemide has been shown in a number of indirect bronchial provocation tests [247–256]. In addition, inhaled frusemide might reduce bronchoconstriction during allergen-induced early- and late-phase reactions [257,258]. Inhaled frusemide has no, or very little protective effect on so-called direct challenges [248,254–256]. In addition, inhaled frusemide

has no direct bronchodilatory properties [255,256], although data are conflicting [249,259]. The profile of effects are quite similar to that of cromones, suggesting a common mechanism of action [260]. Frusemide has inhibitory effects on histamine release *in vitro* [261], and reduces mediator release from eosinophils *in vitro* [262]. Alternatively, frusemide might counterbalance ion and water movement across airway epithelium [246,253,260].

Bianco *et al.* compared inhaled frusemide (40 mg bid) combined with inhaled lysine acetylsalicylate (which has been shown to potentiate effects of frusemide) and placebo in nine inhaled corticosteroid dependent asthmatics during a 10-week randomized, double-blind, crossover trial [263]. As compared with placebo, inhaled steroids could be withdrawn completely in two patients, and in the remaining seven patients a steroid reduction could be achieved in 71% without deterioration of symptoms or lung function. Ono as well as Pendino and colleagues assessed the potential role of inhaled frusemide in 40 and 42 asthma exacerbations, respectively, and showed that frusemide significantly improved peak flow and FEV₁ as compared with placebo in a controlled, parallel design [264,265]. In contrast, in a study from Karpel *et al.* frusemide did not alleviate asthma exacerbations [266]. Altogether, the role of nebulized frusemide still remains unclear, and more studies, especially in severe asthma, are required.

Conclusion

Calcium channel blockers and potassium channel openers do not appear to be useful in asthma due to lack of efficacy or induction of side effects, respectively. Although inhaled frusemide has been suggested to be efficacious in clinical studies in severe asthma, its additional therapeutic value remains to be determined in large controlled trials.

Alternative medicine

Alternative remedies, as reviewed by Lane and Lane [267], are gaining popularity in the treatment of bronchial asthma, although scientific proof of their efficacy is usually inadequate. Assessment of efficacy of acupuncture, hypnosis and yoga is hampered by difficulties in designing double-blind, placebo-controlled trials. Kleijnen and Knipschild [268] and later Jobst [269] reviewed the methodological reliable studies evaluating the role acupuncture, and showed that results were contradictory. Several mostly uncontrolled studies insinuate a beneficial effect of hypnosis on asthma severity in susceptible individuals [270–274]. Lane and Lane therefore questioned whether the response to hypnosis is a good placebo response in selected individuals [267]. Recently, a controlled study was unable to prove chiropractic

manipulation to be efficacious in the adjunctive treatment of children with mild or moderate asthma [275].

In contrast with acupuncture and hypnosis, homeopathic medicine easily allows double-blind, placebo-controlled evaluation. Despite this, there is a paucity of large randomized, controlled trials in asthma. Reilly and associates randomly allocated 28 patients with allergic asthma to receive oral homeopathic therapy or placebo and showed after 8 weeks a relief in symptoms [276]. In addition, lung function and airway hyperresponsiveness tended to improve.

In conclusion, the use of unconventional or complementary therapies remains debatable. However, in view of the increasing popularity, there is a need for research determining the status of alternative remedies in asthma therapy.

Surgery

Surgical division of sympathetic and parasympathetic pulmonary plexus as treatment for severe asthma has been advocated in the first half of this century, lastly reviewed by Belcher [277]. Though some authors claimed improvement of disease control, no long-term reports concerning long-term effects are published. The search for surgical options has been abandoned with the introduction of more efficacious drugs, like inhaled corticosteroids. With the introduction of lung transplantation, a rather radical but possibly permanent solution came within reach. Corris and Dark published a case report in which two patients with severe intractable asthma were free of disease after lung transplantation with normal lungs [278]. In follow-up, corticosteroids could be tapered, airway hyperresponsiveness normalized and transbronchial biopsies could not identify characteristics of asthma. Of interest, they also reported two nonasthmatic recipients of asthmatic lungs who consequently developed asthma.

Future developments

With the recognition that asthma is an inflammatory process and with increased understanding of the pathophysiology of asthma, novel therapeutic strategies can be developed. 'Old' molecules such as heparin are demonstrating new beneficial activities [279–282]. More specific compounds of non-selective anti-inflammatory agents, like selective phosphodiesterase inhibitors [283–287], should be developed. The recent discovery of nitric oxide as a mediator in asthma implies a role for selective inducible nitric oxide synthase inhibitors [286]. Finally, inhibitors of T-cell function [285,286,288], cytokines (like interferon- γ , interleukin-10 and interleukin-12) [289–291], as well as selective cytokine-antagonists (e.g. interleukin-5 and chemokine receptor (CCR3) antagonists) [292–294], and even gene therapy

[280,295] may offer novel immunomodulatory approaches to treat asthmatic airways inflammation.

General conclusions

Many alternative approaches in the treatment of asthma have been proposed. The reviewed strategies cannot replace current standard asthma therapy with inhaled corticosteroids and bronchodilators [1]. Although not relevant in asthma therapy, nutritional factors (e.g. sodium chloride, oily fish and selenium) and antihistamines (cetirizine) might play a role in asthma prevention. Young patients with mild to moderate asthma sensitized to a single inhaled allergen might benefit from allergen hyposensitization. Leukotriene receptor antagonists and biosynthesis inhibitors might alleviate mild asthma, even without the need for other drugs. These drugs, as well as some anti-inflammatory agents (like methotrexate, cyclosporin A and gold) might also be used as steroid-sparing drugs in the management of patients with severe oral steroid-dependent asthma. These patients should be monitored carefully in view of the many possible harmful side effects. Intravenous magnesium sulphate and inhaled halothane or heliox are likely to be beneficial in the management of and uncontrollable exacerbation with severe, therapy-resistant airflow obstruction.

In conclusion, none of the reviewed strategies identifies a breakthrough in asthma management. The additive and steroid-sparing effects of most of the proposed strategies are disappointing. In addition, unacceptable side effects often do not outweigh the amelioration of the disease. Controlled trials are warranted to validate the most promising of the above reviewed therapies, and research into novel management strategies, including (anti) cytokine therapies, for severe, steroid-dependent asthma is urgently needed.

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