Prevalence of asthma

Asthma prevalence in adults: good news?

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Time trends in asthma prevalence may have levelled off

Few diseases have a relation to age which is as fascinating and complex as for asthma. It is a chronic but not necessarily lifelong condition. The incidence of asthma and wheezing illness peaks in very early childhood, but new incident cases occur throughout life.[1–4] In many affected subjects, particularly children, it disappears after some time.[2–4] However, in a substantial proportion of cases which have apparently lost the disease it will come back, often after many years.[3 4] Another intriguing feature is that the sex ratio changes with age. Most studies show that boys are affected more often by wheezing illnesses than girls, but this sex ratio usually reverses during or shortly after puberty, partly due to a higher incidence in females.[5–9]

Most studies investigating the relationship between age and asthma have been performed in infants and children and, in fact, different age related phenotypes in childhood have been described which seem to have distinct causes and consequences.[2 10] Information on the relation to age in adults is scarce and has often been based on routine data or cross sectional studies.[1 6]

In this issue of *Thorax* Chinn and colleagues report the findings of phase II of the European Community Respiratory Health Survey (ECRHS) which involved following more than 11 000 randomly selected adults (participants in ECRHS phase I stage 2 at which time they were aged 20–44 years) for a period of 5–11 years.[11] The investigators used the same standardised questionnaires at the start and end of the observation period, asking about the occurrence and severity of respiratory symptoms in the 12 months before the survey. The study is unique because of its international approach which included 29 study centres from 14 countries. Consistency of findings across countries argues strongly for the validity of the results.

Nevertheless, there are several methodological issues that should be considered before accepting the findings as valid. In particular, measuring asthma in populations is no easy task.[12] There is no single simple instrument by which cases can be identified. Instead, there is a whole battery of different measures, all of which have advantages and disadvantages. Chinn *et al*[11] report data collected by standardised symptom based questionnaires which are considered to be the standard method for measuring the prevalence of asthma in epidemiological studies.[12] However, since these do not measure the prevalence of asthma in individuals with complete accuracy, changes within individuals between repeated surveys may reflect measurement error rather than genuine changes in morbidity. Chinn *et al* therefore report the "net change" in symptom status for each centre rather than reporting separately the rate at which previously disease free subjects became symptomatic (incidence) and the rate at which previously diseased subjects became asymptomatic (remission). While this approach is perhaps regrettable from a clinical point of view, it is methodologically valid and provides findings that are of considerable interest.

The study showed no increase in the 12 month period prevalence of wheeze and more severe asthma symptoms during the follow up period which averaged about 8 years. However, there was a significant increase in the reported 12 month period prevalence of attacks, labelled as "asthma attacks", and in the point prevalence of asthma medication use and nasal allergies.

How can these apparently contradictory patterns be reconciled? An increased prevalence of asthma attacks and medication use could be due to an increase in the prevalence of severe asthma, in recognition of symptoms by patients, in diagnostic labelling of wheezing illness by physicians, or in medical treatment of the condition. Each of these, in turn, could reflect temporal trends (changes over time) or age effects (changes with increasing age). However, Chinn *et al* also measured the prevalence of wheeze and severe asthma symptoms and these did not increase. It is therefore most likely that the observed increases reflect changes in diagnostic labelling and/or medical treatment for mild and/or moderate asthma.

Although the study by Chinn *et al* does not allow to disentangle potential age and period effects, it is interesting to review the current evidence for time trends in asthma prevalence. An increase in the prevalence of asthma and allergies in the late 20th century is generally accepted. While most studies reported increases in the prevalence of symptoms and diagnoses (and these are mostly in children), these observations are supported by studies which also included physiological markers.[13] Recently, however, several studies have suggested that this increase may have come to an end—at least in some areas.

A study in adults over the period from 1972 to 1998 still observed increases in the prevalence of asthma symptoms and diagnoses which was more pronounced among those aged less than 40 years.[14] Two other studies on adults examining time trends during the 1990s, however, found no increase in the prevalence of either asthma symptoms[15] or bronchial hyperresponsiveness,[16] but an increase in the prevalence of reported asthma diagnoses. An investigation of Swiss adolescents observed no further increase in the prevalence of asthma symptoms and allergic sensitisation in the late 1990s.[17] Finally, Anderson *et al*,[18] in a large survey in the UK, actually found a decrease in the prevalence of symptoms of asthma, hay fever, and eczema in 12–14 year olds between 1995 and 2002. During the same period there was an increase in the lifetime prevalence of diagnoses of the three disease entities under investigation. Robertson *et al*[19] reported a similar reduction in the prevalence of asthma in children in Melbourne during 1993–2004. Thus, there is evidence from several countries that time trends in the burden from asthma may have levelled off—in some countries even reversed—while the rate of reported diagnoses continued to increase. It is important to note, however, that these reports come mostly from high income countries with prevalence rates ranking among the highest in the world.[20] The global burden of asthma, however, will be determined to a large extent also by what happens in low income countries. In this respect, the upcoming results of phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), which has studied recent time trends in about 100 centres worldwide (including those of Anderson *et al*[18] and Robertson *et al*[19]), will be of particular interest.[21]

If, in fact, time trends in asthma prevalence have levelled off, it is not clear which factors have determined this change. It is possible that the increase in asthma prevalence has reached a natural plateau in English speaking countries in which virtually all the "susceptibles" may have developed the

condition. However, this speculation would not explain the apparent decrease in some countries. In this regard, it is likely that improved medical treatment, especially the use of inhaled steroids, has contributed.[16] It has been argued that many patients do not benefit from new treatment because their disease is not diagnosed and/or treated adequately.[22 23] In this sense, the increased prevalence of diagnosed asthma reported by Chinn *et al*, in the absence of an increased symptom prevalence, could also be a reflection that medical care of asthma patients has changed for the better. Whatever the explanation, the findings of Chinn *et al* are in line with those of other recent studies and may, in fact, be good news.

Thorax 2004;**59**:637–638.
doi: 10.1136/thx.2004.026302

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The Centre for Public Health Research is supported by a Programme Grant from the Health Research Council of New Zealand.

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Oxygen in COPD

Short burst oxygen therapy for relief of breathlessness in COPD

C M Roberts

More evidence against the effect of short burst oxygen therapy, but doubts remain

In this issue of *Thorax* Stevenson and Calverley[1] provide more evidence for a lack of effect of short burst oxygen therapy in the relief of dyspnoea following exercise in patients with chronic obstructive pulmonary disease (COPD). This study follows other recent publications that appear to draw the same conclusion. Despite this mounting evidence, oxygen cylinders for "as needed" use are still frequently prescribed at great cost.[2 3] Oxygen used in this way is often perceived as life saving by patients, but can this continuing practice of short burst oxygen use for COPD patients be justified in the light of the emerging evidence?

Oxygen therapy for the management of chronic COPD comes in various forms. Long term oxygen therapy (LTOT) prescribing has an accepted evidence base and any patient considered for short burst treatment should first have undergone an assessment for LTOT. Ambulatory oxygen has been shown to have some beneficial effect in some patients researched in a number of studies that demonstrate some concordance. It is a continuing challenge to the respiratory establishment, however, that the form of oxygen most commonly prescribed in the UK lacks such an agreed evidence base. Short burst oxygen use for the palliation of dyspnoea is fairly widespread among patients with severe COPD.[2] Anecdotally, it is beloved by them and often given at their request by respiratory specialists and general practitioners when other options have been exhausted. When it is given there is some evidence that it is used inconsistently[4]—either before or after exercise—and that the delivery mode is non-standardised with both face masks and nasal cannulae being used with flow rates set usually at 2 or 4 l/min, but often left to the discretion of the non-specialist or patient to determine.

This sounds like a mess that needs sorting out and it is notable that the initial British Thoracic Society,[5] American Thoracic Society,[6] and European Respiratory Society[7] management guidelines for COPD had little to say on this subject. More disappointingly, the contemporary GOLD[8] document virtually ignores short burst oxygen and recommendations from the 2004 NICE guideline[9] consist of rather vague statements based on levels C and D evidence. Although this

perceived paucity of an historical evidence base has previously precluded authoritative guidance, a number of contemporary studies examining the effectiveness of short burst oxygen therapy are now available for us to analyse. The problem for the jobbing clinician is that the available evidence has yet to be synthesised into a whole and, practically, this is a challenging exercise for a number of reasons evident on review of the literature.

REVIEW OF THE EVIDENCE

Perhaps the best evidence for a positive effect of short burst oxygen therapy in exercise for subjects with COPD comes from a single paper published some years ago. Woodcock *et al*[10] showed that pre-dosing with oxygen for as little as 5 minutes at a rate of 4 l/min using nasal cannulae before both a submaximal treadmill test and a 6 minute walk test increased walking distance compared with administered air in COPD subjects. Dyspnoea, however, was reduced only for the shorter treadmill test and not for the 6 minute test. The subjects were not severely hypoxic at rest and real time oxygen saturation was not measured.

Two further papers provide borderline positive findings. Evans *et al*[11] studied 19 hypoxic subjects with severe COPD of mean age 65 years. Subjects undertook three simulated step tests breathing via a face mask, 67% oxygen, 10 l/min compressed air, or room air with no mask. Breathing oxygen after exercise was associated with a shortened dyspnoea recovery time from 3.6 minutes to 3.0 minutes. This study is remarkable because it is one of only two cited in the literature that has specifically tested the reproducibility of patient discrimination between oxygen and air. Little consistency was found after a time interval and the authors concluded that, despite the reduction in recovery time observed in the first part of the trial, the poor reproducibility of this finding cast doubt on the justification for short burst therapy following exercise.

Most recently, Killen and Corris[12] reported in this journal the use of short burst oxygen given either before or after stair climbing in 18 subjects with COPD. Air or oxygen was delivered for 5 minutes at a rate of 2 l/min via a face mask before and after ascending stairs in subjects who desaturated on exercise. Three combinations were provided of air and air, air then oxygen, or oxygen then air. Although there was no statistical difference in dyspnoea scores between these three groups, a statistically significant difference in dyspnoea was seen (visual analogue score of 7 mm) when the oxygen subgroups were combined compared with those breathing air. Recovery times were not measured. The authors suggest that this level of dyspnoea reduction represented a significant benefit of short burst oxygen therapy.

One further paper which deserves comment is that of Swinburn *et al*.[13] This study also found a reduction in the dyspnoea score in 12 subjects with severe COPD at rest breathing 28% oxygen via a face mask compared with compressed air at the same flow rate. Visual analogue scores reduced from 46 mm on air to 30 mm on oxygen. The subjects were asked repeatedly when blinded if they felt better breathing air or oxygen by mask compared with room air; compressed air helped in 15 of 24 occasions tested and oxygen in 22 of 24. Although often quoted as a study supporting short burst oxygen therapy, it must be noted that the subjects were tested at rest and the effects of exertion were not studied.

While these studies at best provide evidence of partial benefit, there is inconsistency in the subject groups, exercise performed, and outcome measures. Moreover, there are other studies with distinctly negative results. McKeon *et al*[14] examined the effect of predosing with air or oxygen at a rate of 2.5 l/min via nasal cannulae prior to a treadmill exercise test in 20 subjects with COPD (mean FEV_1 31% predicted). No effect was observed on the dyspnoea score during exercise. Rhind *et al*[15] presented similar findings in 12 subjects with COPD.

More recently, Nandi *et al*[16] reported the effect of both predosing for 10 minutes with either 28% oxygen by face mask or compressed air at a rate of 4 l/min and also post exercise dosing with similarly blinded gas mixtures. Six minute walk tests were undertaken and oxygen was found to have no benefit compared with compressed air in terms of relief of dyspnoea in either arm of the study in the 34 subjects included (mean FEV_1 34% predicted). All of these subjects had significant oxygen desaturation. In a not dissimilar study Lewis *et al*[17] also used the 6 minute walk test to study 22 patients with COPD (mean FEV_1 34% predicted) without resting hypoxia but most of whom desaturated on exercise. In this study the gas mixture was administered for 5 minutes at a flow rate of 2 l/min via nasal cannulae. No effect was observed on the dyspnoea score with either pre or post dosing with oxygen compared with compressed air.

In contrast to these at best equivocal and conflicting results, there is a clearer—although by no means perfect—consensus on the use of ambulatory oxygen therapy as an adjunct to reducing dyspnoea and improving exercise tolerance. A number of studies have reported benefits,[18–20] although not in all subjects.[21] The mechanism for this apparent reduction in dyspnoea is postulated as the reduced work of breathing when hypoxaemia is prevented or reduced in severity.[22] So why is oxygen helpful in the ambulatory setting but of less value following exercise? One key element of the increased work of breathing in patients with limited expiratory flow is the development of dynamic hyperinflation.

STUDY BY STEVENSON AND CALVERLEY

It is argued by Stevenson and Calverley[1] in this issue of *Thorax* that a reduction in dynamic hyperinflation may hold the key to the successful identification of those subjects who will benefit from oxygen and, specifically in this study, those using it as a short burst dosing intervention following exercise.

Stevenson and Calverley administered oxygen at an inspired oxygen fraction of 0.4 or air at a similar flow rate (10 l/min) to 18 moderately severe COPD patients (FEV_1 40% predicted) after standardised exercise. In this study subjects exercised both ''instrumented'' in a full cardiorespiratory exercise test breathing via a mouthpiece and ''non-instrumented'' breathing from a face mask. The hypothesis tested was that oxygen administration should reduce the work of breathing and aid resolution of dynamic hyperinflation by reducing tidal volume breathing and allowing an increased expiratory time. Administration of oxygen after exercise was associated with a reduced ventilatory effort and more rapid resolution of dynamic hyperinflation but no significant reduction in dyspnoea. The findings were essentially negative in that, although observed changes occurred, these did not produce a significant reduction in breathlessness as measured by a Borg scale when oxygen administration was compared with that of air. A significant difference in recovery time of dyspnoea was noted, however, between the instrumented mouthpiece tests (11.38 (1.49) minutes) and those when face masks alone were used (7.94 (1.12) minutes).

The study by Stevenson and Calverley adds to the evidence that there is no single easily measured mechanism by which oxygen reduces dyspnoea after exercise, and that the mechanisms which may operate to prevent dyspnoea when oxygen is administered during exercise may not be the same as those which may operate in influencing dyspnoea after exercise. The authors point out that the reduced recovery time observed in the subjects when receiving

oxygen by face mask may reflect stimulation of facial receptors that could reduce dyspnoea perception.[23] Even this suggestion is contentious in the context of clinical use of short burst oxygen after exercise. The best evidence for a positive effect of oxygen was derived from a study using nasal cannulae rather than masks,[10] and a recent study examining the effect of mask versus room air breathing concluded that any apparent benefit is an order effect of exercise rather than a result of either oxygen or delivery apparatus.[24]

CLINICAL IMPLICATIONS

The difficulty for those trying to develop guidelines in this arena is the disparate nature of these studies. In some the study end points were dyspnoea and in others exercise tolerance; the nature and duration of exercise was different; the inspired oxygen tensions, flow rates and delivery systems were not standardised; and perhaps most challenging of all were the settings for the studies. Finally, as clinicians we must ask practical questions—are the study subjects included the ones we would consider recommending for short burst oxygen therapy and are the study circumstances those in which patients commonly use this form of oxygen?

What we may deduce so far is that short burst oxygen therapy either before or after exercise probably does not benefit the majority of patients with moderately severe COPD who exercise for more than a very short period of time. Before comprehensive recommendations can be made we still require specific studies to re-evaluate the work of Swinburn[13] and Killen[12] in subjects at rest and after very short episodes of exertion set in the circumstances of everyday living.

Thorax 2004;**59**:638–640.
doi: 10.1136/thx.2003.017301

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Regulatory T cells and asthma and allergy

Regulation: the art of control? Regulatory T cells and asthma and allergy

D S Robinson

A better understanding of the immunology of regulation may allow preventive or disease modifying treatment for asthma and other respiratory diseases

Much is currently made of the control of asthma in therapeutic guidelines. Both the British guidelines and the Global Initiative for Asthma (GINA) define measures of control of the disease, and recent studies have defined strategies for control using available anti-inflammatory and bronchodilator therapy such as inhaled steroids and long acting β_2 agonists.[1 2] However, currently available treatments suppress inflammation but do not modify the underlying immunological predisposition to the disease.

Asthma is widely recognised as an inflammatory airway disease driven by activation of Th2-type T lymphocytes in both atopic allergic and intrinsic or non-allergic forms.[3–5] Recent advances in our understanding of the control of the immunological process have identified regulatory suppressive T cells which can prevent activation of self-reactive or pathological T cells in autoimmune or infectious disease models.[6–8] Does this understanding of immune regulation hold the prospect of disease control or even prevention for asthma?

MECHANISM OF ACTION

The interest of immunologists in actively suppressive T cells was re-awoken by the finding by Sakaguchi and co-workers that depletion of CD4+CD25+ T lymphocytes from mice led to development of autoimmune

pathology which could be prevented by re-introduction of these cells.[9] Such CD4+CD25+ regulatory T cells were active in many disease models and could reverse established inflammatory diseases such as colitis.[10] These cells were shown to arise by high affinity selection in the thymus and are thought to form a ''naturally occurring'' regulatory population that is an important part of maintenance of tolerance or non-reactivity of the immune system against itself.[11 12] Shevach and co-workers established an in vitro system and showed that CD4+CD25+ T cells failed to proliferate to polyclonal or antigenic stimulation in culture; furthermore, they could suppress proliferation and cytokine production by CD4+CD25− T cells.[13] This system showed that human peripheral blood CD4+CD25+ T cells also represent a non-proliferating suppressive T cell population.[14–19] The mechanism of suppression by CD4+CD25+ regulatory T cells remains unclear: in some in vivo models suppression is dependent on the immunosuppressive cytokines interleukin 10 (IL-10) and transforming growth factor β (TGFβ), whereas suppressive activity in vitro is not affected by the absence or neutralisation of these factors.[7 8] In vitro suppression by both mouse and human CD4+CD25+ T cells requires contact between regulating and responding cells and is partly dependent on negative co-stimulatory signals including CTLA4 and PD-1.[7] As CD25 is the alpha chain of the IL-2 receptor and these cells do not make their own IL-2, one possibility is that regulation occurs through competition for this and other T cell growth factors as well as by competition for ''space'' in repopulation experiments in lymphopenic mice.[20] Since CD4+CD25+ T cells could regulate non-T cell dependent colitis in a mouse model, such interactions with responder T cells cannot be the sole mode of suppression and regulatory T cells are likely to influence cells of the innate immune system including dendritic cells.[21] Can CD4+CD25+ T cells inhibit activation of Th2 cells in animal models or in vitro?

Animal models

Animal models of allergic airway sensitisation have been useful in defining potential immunological mechanisms in asthma and allergic disease.[22] However, there are few data on CD4+CD25+ T cell regulation of mouse Th2 airway inflammation and airway hyperresponsiveness. When CD4+CD25+ T cells were depleted in one model airway, inflammation actually decreased.[23] This may be because CD25 is also a marker of recently activated T cells or memory effector cells, so both regulators and effectors had been removed. However, co-transfer of ex vivo expanded CD4+CD25+ ovalbumin specific T cells together with Th2 cells had no effect on subsequent inhaled ovalbumin challenge in another mouse model,[24] and ovalbumin specific airway CD4+CD25+ T cells in another complex double transgenic model reduced airway inflammation but not airway hyperresponsiveness in response to inhaled challenge.[25]

In vitro experiments

Human peripheral blood CD4+CD25+ T cells were shown to be suppressive in allergen stimulated cultures.[26–28] We recently compared such suppressive activity in allergen stimulated in vitro cultures of CD4+CD25− and CD4+CD25+ T cells from non-atopic and atopic volunteers. CD4+CD25+ T cells suppressed proliferation and cytokine production by CD4+CD25− from non-atopic subjects almost completely, but this suppressive activity was significantly reduced in cultures from atopic volunteers, particularly when blood was taken from hay fever sufferers during the height of the pollen season.[28] Interestingly, removal of CD4+CD25+ T cells from peripheral blood of non-atopic individuals revealed proliferation and Th2 cytokine production to allergen stimulation which was similar to that from atopic volunteers. These data led to the suggestion that Th2 responses to allergen in non-atopic subjects may be actively suppressed by CD4+CD25+ T cells, and that this regulation is either deficient in atopic subjects or overcome by allergen exposure. Clearly, further work is required to determine whether such regulatory cells occur in the airway or are reduced in asthma.

Although CD4+CD25+ regulatory T cells have been isolated from lung tissue around lung cancers,[29] phenotypic identification of regulatory T cells is hampered by the lack of a specific cell marker. One important advance in understanding the regulatory function of these cells came from studies of a rare human immunodefiency (IPEX) which results in autoimmune and allergic disease and its murine counterpart, the ''scurfy'' mouse strain: both were shown to result from mutation of a transcription factor termed FoxP3.[30 31] Furthermore, in elegant experiments FoxP3 knockout mice were shown to lack CD4+CD25+ regulatory T cells, whereas ectopic expression of the transcription factor by retroviral transfer into CD4+CD25− T cells rendered these regulatory.[32–34] How FoxP3 influences suppression is unclear, and although we and others have confirmed relative overexpression of mRNA for FoxP3 by human CD4+CD25+ T cells,[28] this may not represent a specific marker for this cell type[35] nor does it appear to be active in suppression by other regulatory T cell subtypes. Recently, neuropilin-1 was identified as a potential surface marker for mouse CD4+CD25+ T cells.[36]

It is therefore possible that atopy (and asthma) result from a failure to suppress inappropriate Th2 responses to environmental allergens. What factors determine the balance between regulatory and potentially immunopathogical Th2 responses to allergen exposure in the developing (or mature) immune system? Increasing interest has focused on the mode of activation of the innate immune system (including airway dendritic cells) as a major determinant of the type of T cell response to antigen exposure. As well as the route, dose and frequency of antigen exposure, co-activation of pattern recognition receptors such as Toll-like receptors (TLR) or co-stimulatory molecules act as important determinants of T cell activation.[37] It is possible that relative levels of activation of these receptors may be relevant—for example, low dose bacterial lipopolysaccharide (LPS) acting through TLR4 favours Th2 development[38] whereas higher doses drive Th1 development and exposure of dendritic cells to LPS can overcome regulation by CD4+CD25+ T cells.[39 40] Similarly, the balance of co-stimulation may be important as ICOS co-stimulation is active in supporting Th2 responses but can also drive development of IL-10 producing regulatory T cells in the mouse lung.[41] Such considerations may provide an immunological basis for the hygiene hypothesis for the increasing prevalence of asthma and allergic disease: this may represent a failure of development of appropriate regulatory responses due to lack of appropriate TLR or co-stimulator activation at the time of allergen exposure.[42] It may also underlie some of the genetic associations of asthma as with TLR2 or CD14 (an LPS receptor) polymorphisms.[43 44] It is noteworthy that high exposure to cat allergen reduces the risk of IgE sensitisation and induces an IL-10 predominant ''modified Th2'' response which may represent regulation.[45] However, such a protective effect of high level allergen exposure is not reported for house dust mite. Much more work is required before exposure to allergen or other factors can be manipulated to prevent allergic sensitisation.

CLINICAL IMPLICATIONS

How might regulatory T cells be manipulated or induced for treatment or prevention of asthma? Although CD4+CD25+ T cells do not proliferate in vitro in many systems, it has recently been shown that human cells can be

expanded in response to antigen[46] and CD4+CD25+ T cells do proliferate upon in vivo transfer to mice.[47] It is suggested that suppression by CD4+CD25+ T cells is not antigen specific once these cells are activated, and it might be feasible to transfer cells expanded ex vivo. However, such cell therapy would be complex and potentially hazardous. Another approach is to induce a regulatory population in vivo. Such "adaptive" regulatory T cells have been described in vivo in mice and in vitro in mice and humans and include a range of subtypes that are distinct from the "naturally occurring" CD4+CD25+ T cells.[12] For example, IL-10 producing regulatory T cells were derived in vitro from both human and mouse T cells by activation in the presence of dexamethasone and vitamin D3 (which inhibit development of Th2 and Th1 cells, respectively).[48] This raises the possibility of inducing similar cells by in vivo allergen exposure in the face of immunosuppressive agents. We recently showed that in vitro exposure of CD4+CD25+ T cells to corticosteroids increased their suppressive activity in subsequent allergen stimulated cultures through increased IL-10 production.[49] IL-10 producing regulatory T cell clones were produced by activation in the presence of IL-10: these Tr1 cells prevented IgE and Th2 expansion in a mouse model of allergic airways disease but also produced both IL-5 and interferon γ.[50 51] Animal models of tolerance involving nasal or oral delivery of protein or peptide also induce regulatory T cell populations—either IL-10 producing T cells or Th3 cells making TGFβ.[52 53] For many years allergen injection immunotherapy has been used to control allergic diseases including rhinitis and seasonal asthma,[54 55] and this treatment produces long lasting clinical effects and a reduction in Th2 responses to allergen exposure. Allergen immunotherapy also induces a predominant IL-10 response to allergen, and this may be associated with development of regulatory T cells which were CD4+CD25+.[56 57] Whether this phenotype relates to CD4+CD25+ regulatory T cells or represents activation by allergen remains to be determined, although no difference was found in the suppressive activity of peripheral blood CD4+CD25+ T cells from hay fever patients who had or had not been treated with immunotherapy.[58] Allergen immunotherapy is not used for asthma treatment in the UK because of the risk of anaphylaxis,[59] but a number of modifications may allow its development for asthma. One approach is to break the allergen into short peptides which retain T cell reactivity but which no longer crosslink IgE (so it will not trigger anaphylaxis).[60] This approach shows some efficacy in reducing airway hyperresponsiveness and reduced peripheral blood Th2 responses to allergen, again with an increase in IL-10 production.[61 62] We recently showed that reduced CD4+ T cell responses to cat allergen following peptide therapy were not associated with changes in suppression by blood CD4+CD25+ T cells,[63] so this type of immunotherapy may induce other regulatory T cell subtypes (or work in another fashion). Other approaches are a combination of immunotherapy with adjuvants such as CpG oligonucleotides (which activate TLR9) or mycobacterial products.[64 65] Clearly, it will be important to establish both safety and bystander suppression of other allergens or antigens before these approaches can be used clinically. However, it is interesting that allergen immunotherapy reduced the development of both new allergen sensitisation and of asthma in trials in children with allergic rhinitis, which suggests that immune modulation may hold the potential to prevent asthma.[66 67]

CONCLUSIONS

Current data support the suggestion that regulatory T cells may be important in preventing allergic sensitisation in non-allergic individuals. If the balance between regulation and activation of Th2 T cells can be manipulated, this holds great promise for treatment and prevention of asthma. Regulatory T cells may also be important for a number of other lung diseases: CD4+CD25+ T cells isolated from lung tissue around lung cancers suppressed anti-tumour responses and temporary inactivation of such suppression may be useful for treatment.[29] It is also possible that airway inflammation in chronic obstructive pulmonary disease results from a failure to suppress T cell responses to host antigens revealed or altered by smoking or infection. Understanding and manipulation of immune regulation will form a key part in the development of new treatments in coming years.

Thorax 2004;**59**:640–643.
doi: 10.1136/thx.2003.019166

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DSR is supported in part by a Research Leave Award for Clinical Academics from the Wellcome Trust, UK.

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Treatment of SARS

Antiviral agents and corticosteroids in the treatment of severe acute respiratory syndrome (SARS)

W C Yu, D S C Hui, M Chan-Yeung

Systematic evaluation of treatment modalities for SARS is still needed

The epidemic of severe acute respiratory syndrome (SARS) of 2003 caught the medical profession by surprise. The accumulated global total number of cases was 8098 with 774 deaths, a case-fatality ratio of 9.6%.[1] Although the novel coronavirus (SARS-CoV) was discovered within weeks,[2] treatment was inevitably empirical as controlled clinical trials were not possible during the epidemic of this new and serious illness. Many antiviral and immunomodulatory drugs, as well as other treatments such as convalescent patient plasma and traditional Chinese medicines, have been tried. Ribavirin and corticosteroids are by far the most widely used treatments for SARS. In the later phase of the epidemic lopinavir and ritonavir in combination were also used in Hong Kong.

ANTIVIRAL AGENTS

Ribavirin

Ribavirin is used extensively for the treatment of SARS and was given to over 90% of patients in Hong Kong. It is a nucleoside analogue that has activity against a number of DNA and RNA

viruses in vitro.[3] The mechanism of action of ribavirin has been studied for decades and is still under active debate.[4] In early March 2003, before the isolation of the SARS-CoV, many experts believed that the mysterious severe illness was due to an unknown virus and ribavirin was empirically given because of its broad spectrum antiviral activity. Furthermore, corticosteroids were increasingly prescribed for the treatment of SARS and some believed that such treatment would be dangerous if not covered with an antiviral agent. The published reports on the effectiveness of ribavirin were mostly retrospective case series with intrinsic methodological issues and it is difficult to draw conclusions. The major side effect of ribavirin is anaemia which occurs in 27–59% of patients.[5–9] Anaemia reduces oxygen transport and potentiates the existing problem of oxygenation and tissue hypoxia. Other significant side effects include raised transaminases and bradycardia,[5] as well as hypocalcaemia, hypomagnesaemia, and risk of teratogenicity.[10] In a detailed study on the clinical course and viral load, Peiris *et al*[11] reported that 14 patients given a standard regimen of ribavirin and steroids showed a peak viral load at day 10 from onset of illness. This study, although involving a small number of subjects, clearly indicated the inability of ribavirin to clear SARS-CoV from patients with SARS. The result of this study also explained why patients treated with ribavirin early in the illness were able to infect healthcare workers when they subsequently required endotracheal intubation. The lack of in vitro activity of the drug against SARS-CoV[12–14] cast further doubts on the usefulness of ribavirin in SARS. The use of ribavirin in SARS has been reviewed elsewhere.[15 16]

Lopinavir and ritonavir

Lopinavir and ritonavir (LPV/r) are protease inhibitors which, in combination, have been licensed for the treatment of HIV disease. Ritonavir has little antiviral activity and its role is to inhibit CYP3A mediated metabolism of lopinavir, thus increasing the serum concentration of lopinavir. In the laboratory lopinavir and ribavirin have significant synergism in inhibiting SARS-CoV[6] and, on that basis, this combination—together with steroids—have been used in some centres in Hong Kong since mid April 2003. In this retrospective study the authors found that the 12 patients who received early treatment with LPV/r together with ribavirin and steroids had significantly fewer 21 day adverse clinical outcomes (acute respiratory distress syndrome or death) than 111 historical controls receiving ribavirin and steroids. Other benefits of the LPV/r group included favourable viral load profiles (in six patients), early rise of lymphocyte counts, and a reduced need for ''rescue'' pulse steroid doses. Adverse events attributable to LPV/r were minimal. Similar findings were reported in a case controlled study involving more patients from Hong Kong.[17] Randomised controlled trials are being planned in Hong Kong to confirm these results should SARS re-emerge.

CORTICOSTEROIDS

Corticosteroids have been used widely to treat SARS, first in mainland China and then in Hong Kong. The main rationale for their use in SARS is that, in acute viral respiratory infections, early response cytokines such as interferon gamma (IFN-γ), tumour necrosis factor, interleukin 1 (IL-1), and interleukin 6 (IL-6) contribute to tissue injury,[18 19] and corticosteroid treatment may suppress the ''cytokine storm''.[20] Peiris *et al* hypothesised that the clinical worsening often observed during the second phase of illness is the result of immunopathological damage from an overexuberant host response.[13] In a newly published report Wong *et al*[21] showed in 20 consecutive adults with SARS that there was a marked increase in the Th1 cytokine IFN-γ, inflammatory cytokines IL-1, IL-6, and IL-12 for at least 2 weeks after disease onset. The chemokine profile showed a significant increase in IL-8, monocyte chemoattractant protein-1 (MCP-1), and IFN-γ inducible protein-10 (IP-10). Corticosteroids significantly reduce IL-8, MCP-1, and IP-10 concentrations 5–8 days after treatment. The data confirmed the Th1 cell mediated immunity and hyperinnate inflammatory response in SARS through the accumulation of monocytes/macrophages and neutrophils. Another rationale for use of steroids in SARS is the necroscopic finding of features of acute respiratory distress syndrome (ARDS),[22 23] and there have been reports of successful use of steroids in the treatment of ARDS[24] and septic shock.[25] In addition, systemic steroids have been used in the treatment of some infections with variable success.[26–29] On the other hand, the potential for corticosteroids to suppress the innate host defence against SARS-CoV resulting in increased viral replication has to be considered. Chu *et al* reported an increase in viral load in one patient following pulse methylprednisolone therapy.[6] Increased replication of other respiratory viruses has also been reported following steroid therapy.[26 30–32]

Whereas ''low dose'' steroids at 0.5–1.0 mg/kg/day prednisolone (or equivalent) have been used in infections, ARDS and septic shock, ''pulse doses'' at 0.5–1.0 g/day methylprednisolone have generally not been recommended for these conditions but were used extensively in SARS, particularly in the second week of illness when patients often show acute clinical deterioration. The efficacy of pulse steroids in SARS remains to be determined, but it is conceivable that higher steroid doses will result in a higher incidence and severity of side effects.

Published case series examining the clinical efficacy of steroid treatment in SARS[7 9 33–40] suffer the same methodological problems as those of ribavirin. In addition, there is a wide variety of steroid dosing schedules making retrospective analysis of steroid efficacy exceptionally difficult. There is so far no systematic review of the efficacy of corticosteroid treatment in SARS based on the numerous published studies. Some investigators do feel that judicious use of corticosteroids is beneficial, but randomised controlled studies are needed to confirm the beneficial effects as well as to give insight into the optimal regimen. The possible beneficial effects, however, have to be balanced against the significant side effects including nosocomial infections,[7 9 40 41] hyperglycaemia, hypokalaemia, hypertension, and gastrointestinal haemorrhage.[7–9] Avascular necrosis of bone (AVN) is perhaps the most distressing medium term side effect of steroids in patients with SARS. Preliminary data on a cohort of 330 adult patients from Princess Margaret Hospital, Hong Kong who received various doses of steroids and in whom magnetic resonance imaging was performed at an average of 7.5 months from illness onset showed that AVN was present in 48 of them (14.5%, (unpublished data). Of the 48, 16 (33%) had unilateral involvement of the femoral head and 19 (40%) had bilateral involvement of the femoral head. Univariate analysis showed that the total steroid dose was significantly associated with development of AVN (unpublished data).

CONCLUSIONS

As SARS has only recently appeared and a limited number of patients have been managed in different locations, it is understandable that there has been a lack of systematic and critical evaluation of treatment in the form of randomised controlled trials. Nonetheless, the enormous effort that researchers put into looking for effective treatments for SARS is highly commended. The recent re-emergence of SARS did not result in secondary spread, but is nevertheless a reminder that it could strike again. What may be even more threatening

is the deadly avian influenza A (H5N1) which has repeatedly demonstrated its ability to infect humans, and may acquire the ability for efficient human to human transmission in the future. It is hoped that, when epidemics of new disease strikes, a systematic way of evaluating treatment modalities would be in place to provide answers to important questions in the shortest possible time.

Thorax 2004;**59**:643–645.
doi: 10.1136/thx.2003.017665

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