Inhaled steroids in COPD

So inhaled steroids slow the rate of decline of FEV_1 in patients with COPD after all?

P S Burge, S A Lewis

Meta-analyses show that inhaled steroids are helpful in COPD

The medical community has made up its mind that, although inhaled corticosteroids reduce exacerbations in patients with chronic obstructive pulmonary disease (COPD),[1] they do not affect disease progression.[2] Despite measurement of forced expiratory volume in one second (FEV_1) being widely available and a strong predictor of mortality,[3] the emphasis has moved to softer outcome measures which do show changes with available treatments. Ten years ago many of us had different beliefs—several small studies using simple statistics suggested that the rate of decline in FEV_1 could be reduced by about 20 ml a year by inhaled corticosteroids.[4–6] This led to several large studies, the primary outcome of which was decline in FEV_1 and which were powered to detect a 20 ml/year difference between active and placebo treatments.[7–10] All failed to show significant differences in their primary outcome of FEV_1 decline between various inhaled corticosteroids and placebo.

In this issue Sutherland and colleagues have done a meta-analysis of those trials, and have shown that inhaled corticosteroids do slow the decline in FEV_1 significantly.[11] How should we respond to this meta-analysis? Are the differences found clinically meaningful? Was there anything wrong with our original hypotheses or analyses? And what should we make of a similar meta-analysis that appeared to come to opposite conclusions?[12]

Despite the lack of clinical licences, inhaled corticosteroids have been widely prescribed for patients with COPD. In some parts of the world more that 50% of patients were receiving these drugs "off licence" by the mid 1990s.[8 13] This has allowed various database studies to estimate the effect on mortality of prescribing inhaled corticosteroids.

There are problems in adequately controlling for confounders in non-randomised studies; despite this, the extent of the reduction in mortality seen in some of these studies was much larger than expected,[13–15] and the study showing the largest reduction in mortality comparing the regularity of inhaled corticosteroid prescription would appear free of immortal time bias.[14] Could mortality be reduced by so much if inhaled corticosteroids were not altering disease progression? The problems of unknown confounding can be overcome with randomised trials, giving added importance to the current meta-analysis, which shows a mean reduction of 7.7 ml/year FEV_1 decline with inhaled corticosteroids. Is this enough to explain the mortality reduction suggested by the database studies?

The meta-analysis used the estimates of FEV_1 decline derived from mixed effects models used in the original trial analyses.[16 17] There are unexplained differences in the estimates of FEV_1 decline using these models and those observed using linear regression before study entry. For instance the EUROSCOP study had a six month run-in with no active treatment. In individuals who had not previously taken inhaled steroids the mean FEV_1 declined by 113 ml/year in those subsequently randomised to placebo. The mixed effects model for the three years on placebo gave an estimate of 69 ml/year.[7] In contrast, the Copenhagen City lung study, where the patients had much less advanced COPD, had similar rates of decline during a 13 year pretrial period and in the three year placebo treatment period, at 52 and 49.6 ml/year, respectively.[9]

The best explanation at present divides those seen cross sectionally into two groups. In one the FEV_1 is declining rapidly—these patients preferentially drop out of long term studies; they show a meaningful reduction in the rate of FEV_1 decline with inhaled corticosteroids, but their failure to complete studies means that they are underrepresented in the mixed effects analysis. The second group have arrived at similarly low values of FEV_1 but now have stable disease and no room for an FEV_1 response from treatment. The Isolde study supports this model,[18] where those withdrawn from the study randomised to placebo started with a higher FEV_1 than those randomised to fluticasone; their FEV_1 declined by 95.3 ml/year compared with 74.4 ml/year in the fluticasone group. Those who completed the three years of the trial declined at 50.7 and 46.4 ml/year, respectively. The message appears to be in those dropping out of the study after randomisation to fluticasone propionate, rather than those completing it. Mixed effects models are conservative when, as here, those who drop out have a larger treatment benefit than those completing the trial, as they only contribute data up to the point of withdrawal, minimising the overall estimates of change.

Attempts have been made to identify those who will and will not benefit from inhaled corticosteroid treatment. Neither short term response to bronchodilator nor oral corticosteroid use predicts long term response.[19–21] The presence or absence of emphysema is also not related to short term corticosteroid response.[22] Whether pathology is related to long term inhaled corticosteroid response is unknown, and needs investigation.

The optimal dose of inhaled corticosteroids in COPD is still unknown. None of the large randomised trials used more than one dose. The reanalysis of smaller studies showed some evidence that beclomethasone dipropionate 800 μg/day was less effective than ⩾1500 μg/day.[4] The observational studies also show less efficacy with doses of <500 μg/day compared with larger doses,[15] and less effect when fluticasone prescriptions were repeated less regularly compared with 12 times a year.[14] In the current meta-analysis, the lung health study—using triamcinolone 1.2 mg daily (equivalent to about 600 μg beclomethasone dipropionate)—showed less effect on FEV_1 decline, at 2.8 ml/year *v* 9.9 ml/year for the studies using budesonide 800 μg/day or fluticasone propionate 1 mg/day. Ten millilitres a year is still a small effect. However, it could be interpreted as reducing the excess FEV_1 decline caused by COPD (over and above the 30 ml/year caused by healthy aging) by about 30%, from 30 to 20 ml a year for the higher dose studies. There is a proportionally bigger effect for those who have stopped smoking, as the absolute change in FEV_1 decline seems to be reduced similarly in those who continue to smoke and in those who have stopped completely.[9] On current evidence doses of beclomethasone dipropionate or equivalents of ⩾800 μg/day should be used; any increased benefit for higher doses remains to be proven.

The reduction in exacerbations of COPD with inhaled corticosteroids is more impressive in those with FEV_1 <50% of predicted.[1] The current meta-analysis also shows a greater effect on FEV_1 decline in this group, the mean reduction being 18.3 ml/year, close to the 20 ml/year suggested by the preliminary studies.[11]

Meta-analyses are only as good as the studies included, and any selection bias from publication or inclusion bias. The studies in this analysis were regarded as high quality. There was no evidence of significant statistical heterogeneity in the higher dose studies, nor in the studies that enrolled subjects with an FEV_1 <50% of predicted. There was evidence of publication bias, with a lack of small negative studies identified from the funnel plot. The authors comment that this is unlikely to have influenced the results because of the number of large negative studies included.[11] Meta-analyses are also reliant on the quality of the numerical information that can be extracted from the studies on which they are based; where the original studies do not present all the required data—that being the mean annual decline in lung function and its standard error in this case—meta-analyses include a degree of subjective guesswork.

The problems that this can introduce are well demonstrated if one compares the results of the present (Sutherland) study[11] with those of a previous meta-analysis undertaken by Highland *et al*,[12] which sought to answer the same question and arrived at a different conclusion. Highland found a reduction of 5 ml per year in the decline in FEV_1 in the inhaled steroid group compared with placebo, which was not statistically significant ($p = 0.11$). The two meta-analyses used data from an almost identical set of studies, five of six being common to both, and the sixth comprising overlapping data. The differences partly depend on the results of the study of early COPD, which most agree genuinely shows no benefit from inhaled budesonide in a mainly asymptomatic group.[9] Highland presumed a 3.1 ml/year greater rate of FEV_1 decline in the budesonide group in their analyses, while Sutherland correctly interpreted the data as showing a 3.1 ml/year benefit in the budesonide group.

Sutherland and Highland also arrived at different approximations to the standard error (using information such as the p value) for some of the remaining studies. If Highland *et al* had used the results as extracted by Sutherland (the latter seeming to correspond more closely in most instances to those shown in the original papers), their findings would have been more equivocal (with a difference of 5.5 ml/year and a p value of 0.07). In the EUROSCOP study,[7] which was included in both meta-analyses, two versions of the effect of inhaled steroid on lung function decline were presented, one based on the three year decline in FEV_1 in those who completed the study, used by Sutherland *et al* in their meta-analysis, and the other from a mixed effects model including all study subjects from nine months of treatment onwards, used by Highland. This, together with the one differing study, explain any residual discrepancy between the two meta-analyses. Their findings are therefore more consistent with respect to the size of effect of inhaled steroid in COPD than appears at first sight—their differing messages to some extent serve to demonstrate what can happen when one draws different conclusions depending on whether a p value is to the right or left of 0.05.

The differences in the meta-analyses raise the question of a separation of the short term improvement in FEV_1 from any effect on subsequent FEV_1 decline. The short term effect had been missed in the initial smaller and shorter studies.[4–6] It was the size and duration of the four main studies[7–10] which allowed the short term effect to be separately identified. It was also the cause of these studies' reduced power to identify any long term effect, as the first 6–9 months' data were excluded from the calculation of long term decline. It is possible that the effect on exacerbation reduction is related to a one-off improvement in FEV_1 from inhaled corticosteroids, which is maintained for as long as they are taken and accounts for relapses once they are stopped.[23 24] However, the increasing benefit of treatment on health related quality of life over time[8] would favour a long term disease modifying effect over and above any one-off effect.

This meta-analysis is a welcome addition to the work on inhaled corticosteroids in patients with COPD. It is no longer ethical to do more long term placebo controlled studies in this condition. New studies should concentrate of the optimal dose, the optimal stage of the disease for starting regular treatment with inhaled corticosteroids, and the optimal combinations of long acting bronchodilators, inhaled corticosteroids, and other treatments. FEV_1 decline remains a valid but difficult endpoint; validation of the existing mixed effects models is required for studies with differential dropouts of patients with the most rapidly progressing disease.

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Lung biopsy

Lung biopsy guidelines—for the obedience of fools and guidance of wise men

A R Manhire, C M Richardson, F V Gleeson

Lung biopsy is not without morbidity and occasionally mortality

Percutaneous transthoracic lung biopsy is thought to have been developed by Leyden in 1883 in order to diagnose pneumonia. The technique was extended to the diagnosis of cancer from the 1930s onwards, but at that time there was a significant complication rate, primarily associated with the use of large bore needles. The more widespread use of the technique in the 1960s and 1970s was heralded by the development of high resolution image intensification and improved cytological techniques, which permitted the use of smaller needles and reduced complications. One hundred and twenty years after its inception, percutaneous lung biopsy is now a generally accepted and widely used method of establishing the aetiology of lung masses.

Despite its usefulness, the procedure is not without its morbidity and rarely mortality. It was one of these rare deaths that prompted a search for current standards of good practice. A survey published in 2002 by Richardson *et al*,[1] in which all known centres performing lung biopsy in the United Kingdom were invited to participate, showed that practice varied greatly across the country. Some centres reported undertaking as few as three biopsies a year and others over 200. There appeared to be a general lack of consensus about most aspects of the procedure, and this was reflected in confusion over whether patients needed to be admitted overnight, the range of prebiopsy tests required, and the timing of follow up chest radiographs. This was the first national study of percutaneous lung biopsy in the United Kingdom and it concluded that national guidelines were needed to ensure consistency of standards. The guidelines published in *Thorax* this month have been with this aim.

Any guidelines will generate objections to at least some of their recommendations and for that reason the current paper has been reviewed by various groups and societies who can be regarded has having an interest in the topic. As the title of the article suggests, they are intended to offer guidance based on evidence to those with experience and to help those who have a more limited practice.

One of the main developments in the management of lung cancer has been the formalisation of the multidisciplinary team, which is now the cornerstone of clinical practice in this disease. These guidelines encourage the use of the same concept in the process of deciding in whom and how to biopsy lung lesions. The term ''multidisciplinary meeting'' (MDM) has been used partly to avoid confusion with the cancer group, but also to make clear that the decision making group is not as large and is less rigid in its structure. Despite this the MDM, consisting of at least a radiologist and a respiratory physician, or a clinician with an interest in respiratory medicine, is recommended as the way in which decisions about whether to undertake a lung biopsy should be organised. This practice should ensure a proper preprocedure assessment, both of the need for biopsy and of patient suitability.

There is controversy over the role of percutaneous biopsy in the diagnosis of potentially resectable lung masses in patients considered operable. Some units prefer to proceed straight to surgery in this situation, arguing that a percutaneous biopsy rarely changes the need for surgery in these patients. Others feel that patients should have a histologically confirmed malignancy before proceeding to surgery, to avoid doing unnecessary operations in those who have benign disease. This difficult issue has not been addressed in these guidelines, but it serves to emphasise the importance of multidisciplinary decision making before biopsy.

These guidelines do not seek to be prescriptive. Some operators may have a preference for a particular type of needle or means of imaging. This often depends on the local circumstances or external factors. Where evidence is available, the most appropriate method has been advised. For instance, if a lesion is suspected to be benign the yield in these circumstances is favoured by the use of a cutting needle. However, in certain centres where there is a confident cytopathologist, fine needle aspiration may achieve similar accuracy of sampling for benign lesions. Similarly, having a cytologist present at the time of biopsy to review the sample reduces morbidity and increases yield but has significant resource implications.

Recently there has been a move to do lung biopsies as day case procedures, and this practice has been implemented successfully in many centres. Published reports indicate that this can lead to better use of hospital beds without an increase in the risk to the patients if they are selected appropriately. It does, however, depend on instructing the patient carefully and giving written and verbal instructions should their condition deteriorate on leaving hospital.

It is worth remembering that guidelines are only as good as the evidence they are based upon. One of the main problems in establishing procedural guidelines is the lack of grade A, or even grade B, evidence to support particular practices. The published morbidity and the mortality rates associated with percutaneous lung biopsy vary widely. The quoted pneumothorax rate post-biopsy ranges from 0% to 61%, although in the UK survey[1] the range was between 14% and 20%. Clearly practitioners should aspire to the lowest figure, but centres should audit their own practice in order to inform patients of local complication rates.

Furthermore, to ensure that normal clotting studies are available before a biopsy would seem prudent, but no randomised controlled trials have ever been done to assess this. Similarly the safe cut off values for FEV_1 are difficult to establish but for obvious ethical reasons no grade A evidence exists. In cases where the evidence base is weak, common sense and consensus have been used. Additionally good practice has been derived in some areas by looking at the advice given by other groups such as the BTS guidelines on diagnostic flexible bronchoscopy.[2]

In conclusion, although a few of the recommendations may go against some practitioners' cherished practices, they are intended to offer food for thought for the experienced and guidance for the less experienced—*they are for the obedience of fools and the guidance of wise men*.

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Inpatient management of acute COPD

Inpatient management of acute COPD: a cause for concern?

M Rudolf

Inpatient mortality rates for patients with COPD vary with the type of hospital

British guidelines for the management of chronic obstructive pulmonary disease (COPD) were first published in 1997.[1] Over the subsequent 6 years there has been an enormous increase in our understanding of the underlying causes and mechanisms of acute exacerbations of COPD,[2–4] as well as the realisation that, in addition to being a major cause of morbidity and mortality, acute exacerbations place an enormous burden on healthcare resources.

COPD is the third largest cause of respiratory death in the UK after pneumonia and cancer, causing over 30 000 deaths per year. Age adjusted emergency admission rates for COPD in the UK rose by more than 50% between 1991 and 2000, and about one quarter of all hospital inpatient bed days used for treating acute respiratory disease are for COPD,[5] amounting to nearly one million hospital bed days per year.[6]

With such a significant proportion of inpatient resources being consumed by acute exacerbations of COPD, understanding how well and effectively they are managed in hospital becomes a matter of much more than academic interest. In order to obtain information on this, the British Thoracic Society (BTS) and the Clinical Effectiveness and Evaluation Unit (CEEU) of the Royal College of Physicians undertook a national audit in 1997.[7 8]

Data were collected from 38 acute hospitals across the UK on the management of 1400 acute admissions with COPD. The main findings were that 14% of cases died within 3 months of admission, the median length of stay was 8 days, and 34% of the patients were readmitted within 3 months of the initial inpatient episode. There were, not surprisingly, large variations between hospitals for many of the outcome measures studied and, disappointingly, the median standards of care observed in routine clinical practice fell below those recommended by the BTS guidelines.[7 8]

An important conclusion from this audit was that the wide variations observed in both process of care and in outcomes could not be accounted for by case mix alone, and that resource and organisational factors might be relevant. In this issue of *Thorax* Roberts *et al*[9] report the results of a further audit designed to test the hypothesis that death from acute COPD might be related to the size and type of hospital to which patients are admitted—for example, teaching hospital or large or small district general hospital (DGH)—and to factors such as medical staffing ratios and the availability of non-invasive ventilation (NIV).

The authors obtained information from 30 units in England and Wales using prospective case ascertainment with retrospective case note audit of consecutive cases admitted over an 8 week period for each hospital. Despite the limitations of the study which the authors freely acknowledge (it was only a pilot study, small number of hospitals, some data collection may have been incomplete and/or inaccurate), the results are of extreme importance. Mortality was highest in the small DGHs and lowest in the teaching hospitals. Although the performance status of patients being admitted to small DGHs was worse, this did not account for the higher mortality observed. Small DGHs also had the lowest medical staffing ratios and were less likely to offer an NIV service.

It is imperative that these findings are verified in a much larger national audit which is currently being conducted by the BTS and CEEU. This should allow for a far more detailed analysis and, in addition to accurate data collection on individual patients, participating hospitals must provide comprehensive information on their local resources for the management of acute COPD, including

details of clinical staffing (medical and nursing, specialist and non-specialist, routine and out of hours), workload figures, provision of NIV service, availability of high dependency and intensive care beds. Only by the rigorous interrogation of a much larger data base will it be possible to take account of various confounding factors and decide whether or not resource and organisational issues are, indeed, responsible for differences in outcome.

New British guidelines for the management of COPD, produced under the auspices of the National Institute of Clinical Excellence (NICE), will be published early in 2004. Many clinicians are already anticipating the new evidence based recommendations on the hospital management of acute exacerbations. But it is essential that the new guidelines are not regarded as aspirational and unachievable in the real world at a time when, for example, the majority of patients who need NIV do not actually receive it despite its proven benefit and cost effectiveness.[7 10 11]

The conclusions of Roberts *et al*[9] should be of great interest to all those who wish to optimise patient care, and the results of the audit currently being undertaken will be eagerly awaited. The strength of national comparative audits such as those conducted by the BTS and CEEU is that they allow teams and hospitals to compare themselves with the results being achieved by their peers and which therefore are, by definition, achievable. If variations in mortality rates between hospitals are, indeed, due to organisational and resource factors, then much more must be done to address these. The lack of a national service framework for respiratory disease must not be allowed to become an excuse for not making COPD a local priority where audit data clearly show this to be necessary.[12]

In a recent editorial in *Thorax*, Partridge[13] highlighted a number of key areas where we currently fail to provide adequately for people with COPD, and pointed out that we all have an obligation to raise the profile of this common disease. Admission to hospital for an acute exacerbation is when our patients are most vulnerable; ensuring that appropriate standards of care are provided is the responsibility of every respiratory physician.

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Images in *Thorax*

Images in *Thorax*

J M FitzGerald, N Müller, J Hogg

Introducing a new series, ''Images in *Thorax*''

With the exponential increase in medical knowledge there is a constant flow of new data. Parallel with the rapid expansion of knowledge has been the development of many new and exciting imaging and diagnostic techniques. At a cellular level, newer molecular techniques have allowed us to describe and display normal as well as pathological processes at a level unimaginable in the recent past.

We would like to build on the recent advances in imaging and in techniques available to process pathological specimens in a new series in *Thorax*. This new series will be called ''Images in *Thorax*''. Submissions should normally consist of an interesting radiological image, photograph, and/or pathological specimen. In addition to radiological or pathological images, there will also be an opportunity to submit interesting photographs from diagnostic procedures. The ability to correlate anatomical and pathological images has been a cornerstone of medical education for centuries. Priority will be given to images that incorporate newer technologies which provide original insights into pulmonary disease.

The images should be submitted with a 100–150 word commentary and, at most, one or two key references. It is anticipated that a maximum of two images will be displayed but, in most cases, one image should suffice. Ideally, the commentary should emphasise some key learning points which have a practical impact on pulmonary medicine.

These submissions will be reviewed by the series editors but will not be externally reviewed and, although included in the table of contents, will not be cited on Medline. We look forward to seeing these submissions. It is intended that they will be posted on the *Thorax* website and, in time, will become a valuable educational resource, especially for physicians and other healthcare workers in training.

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ELISPOT

Spotting latent infection: the path to better tuberculosis control

A Lalvani

The new ELISPOT assay will help control tuberculosis

Tuberculosis (TB) control is based on prevention as well as prompt diagnosis and treatment of active TB. Since the latter is usually accomplished quite effectively in developed countries, and since BCG vaccination is of limited effectiveness, better TB control will require improved diagnosis and preventative treatment of latent tuberculosis infection (LTBI).[1–3] The reservoir of latently infected individuals is much larger than the number of active TB cases, and includes recently infected contacts of pulmonary TB cases and immigrants from high prevalence regions who acquired infection in their country of origin. This latter group is becoming increasingly important because over half the burden of TB in many low prevalence countries is carried by immigrants,[3–5] and because several higher prevalence countries will soon join the European Union.

Prophylactic treatment of LTBI is highly effective in preventing the subsequent development of active TB;[1] the difficulty lies in identifying who is harbouring latent bacilli. TB control programmes rely exclusively on the century old tuberculin skin test (TST) for diagnosing LTBI in asymptomatic individuals with known or suspected TB exposure.[1 3] The success or otherwise of TB control and elimination in the developed world thus hinges on the oldest diagnostic test in medicine, and the multiple limitations of the TST constitute a major roadblock to better TB control.

The main drawback of the TST is its poor specificity because of false positive results in BCG vaccinated individuals caused by antigenic cross reactivity of purified protein derivative (PPD) with BCG;[6] this confounding effect persists for as long as 15 years after vaccination.[7] This is a widespread problem as most of the world's population is BCG vaccinated and, even in low prevalence countries that have ceased BCG vaccination, most TB cases and their contacts are BCG vaccinated immigrants. The problem is so significant that the British Thoracic Society Code of Practice for Control and Prevention of TB no longer recommends performing the TST on BCG vaccinated adults with recent TB exposure.[8]

The recent identification of genes present in *Mycobacterium tuberculosis* but absent from BCG raises the possibility of developing a more specific diagnostic test.[9 10] Detecting an immune response to one of these gene products could, in theory, indicate *M tuberculosis* infection as distinct from BCG vaccination.[11] However, humoral immune responses in LTBI are generally weak, and this has proved to be an insurmountable barrier to the development of a useful serological test.[11] Individuals with LTBI (and most patients with active TB) do, however, mount a strong cellular immune response to *M tuberculosis*. Fortunately, two of the proteins that are absent from BCG are major targets of the T cell response to *M tuberculosis*—early secretory antigenic target 6 (ESAT-6)[12] and culture filtrate protein 10 (CFP10).[13]

ENZYME LINKED IMMUNOSPOT (ELISPOT)

Measurement of T cell responses has traditionally been confined to the research laboratory as it required specialised sterile tissue culture facilities, technical expertise, and radioisotopes. However, the most sensitive assay for detecting antigen specific T cells was recently modified to enable rapid and convenient detection of T cells directly from a blood sample.[14] The rapid ex vivo enzyme linked immunospot (ELISPOT) assay counts individual antigen specific T cells. T cells from individuals infected with *M tuberculosis* become sensitised to ESAT-6 or CFP10 in vivo; when the T cells re-encounter these antigens ex vivo in the overnight ELISPOT assay they release the cytokine interferon-γ.[15] By the next morning each such T cell gives rise to a dark spot which is the ''footprint'' of an individual *M tuberculosis* specific T cell. The read out is thus the number of spots, which are counted using a magnifying lens or automated reader. The principle that underpins ELISPOT is that a highly sensitive T cell assay using highly specific *M tuberculosis* antigens should result in a test with high diagnostic sensitivity and specificity. So what happens in the clinic?

Clinical studies

ELISPOT was first validated and compared with TST in patients with culture confirmed active TB and control patients with non-tuberculous illnesses; its sensitivity was 96%, significantly higher than the 69% for TST.[16] Importantly, non-tuberculous illnesses did not cause false positive results. Unlike TST, ELISPOT is not susceptible to false negative results in patients with disseminated TB and it maintains its high sensitivity it HIV infected TB patients.[17] ELISPOT may thus prove clinically useful in the diagnostic assessment of patients with suspected active TB in low prevalence regions; in particular, its high sensitivity could help clinicians to rule out a diagnosis of TB.[18]

Demonstrating superiority of a new test for LTBI is more difficult than for active TB because there is no gold standard reference test. Thus, it is not possible to measure directly the sensitivity and specificity of a new test for LTBI. However, as airborne transmission of *M tuberculosis* is promoted by increasing duration and proximity of contact with an infectious case, a key determinant of infection is the amount of time spent sharing room air with the source case. If ELISPOT is indeed a more sensitive and specific test, it should therefore correlate more closely with the level of exposure to *M tuberculosis* than the TST, and should be independent of BCG vaccination status.

A community study of 50 recent TB contacts at risk of LTBI found that ELISPOT correlated with the extent of recent exposure to cases of pulmonary TB, as judged by exposure history, whereas unexposed people were uniformly ELISPOT negative.[19] Unlike TST, ELISPOT was not confounded by BCG vaccination status.[19] However, proving a statistically significant better correlation with exposure is a major challenge, as it would require simultaneous screening by ELISPOT and TST of large numbers of people with a wide range of precisely quantified exposure to *M tuberculosis*. In 2001 the UK suffered its largest outbreak of TB since the Second World War. It occurred in a secondary school and resulted from a single infectious source case with several hundred contacts; school timetables permitted precise quantification of the amount of time each child spent sharing room air with the source case. 535 students were tested by ELISPOT and TST in a blinded, prospective study, and correlation of each test with degree of exposure to the source case and BCG vaccination status was compared. Although agreement bet-

ween the tests was high (89% concordance), ELISPOT correlated significantly more closely with *M tuberculosis* exposure than TST, based on predefined measures of proximity and duration of exposure to the source case.[20] TST was significantly more likely to be positive in BCG vaccinated students whereas ELISPOT was independent of BCG vaccination. Thus, although direct quantification of sensitivity and specificity of ELISPOT or TST for LTBI is not possible in the absence of a gold standard, the unique circumstances of this outbreak made it possible to rank the tests according to their diagnostic accuracy.[20]

What more do we need to know?

Three thousand individuals in seven countries have been tested by ELISPOT to date; the results from the first 1000 have already been published[16 17 19–21] and indicate that ELISPOT is a more accurate marker of LTBI than TST. What more do we need to know before we can use ELISPOT to guide the management of LTBI? Notwithstanding the numerous limitations of the TST, several decades of long term follow up studies have shown that a strongly positive TST in exposed asymptomatic individuals has some predictive value for subsequent development of active TB. Thus, the cross sectional data indicating that ELISPOT is more accurate than TST should be supplemented by some longitudinal data to confirm that exposed individuals with a positive ELISPOT result really are at risk of subsequent active TB. Despite the long incubation period of TB, clinical outcome data of this sort are already beginning to emerge from several ongoing longitudinal studies around the world. In addition, we need to know how reliably ELISPOT performs in high throughput routine hospital laboratories. ELISPOT only requires a centrifuge, incubator and microscope and has been successfully transferred to several rudimentary laboratories in resource poor settings; thus, we already know that it is simple and robust. Nonetheless, commercial development of the assay through to regulatory approval, which is already underway, is making ELISPOT even faster and better suited to high throughput laboratories.

IMPACT OF ELISPOT

Once ELISPOT enters routine practice, how will it impact on TB control? We can try to predict this on the basis of its three key attributes:

- high specificity;
- high sensitivity;
- it is an ex vivo blood test rather than an in vivo skin test.

High specificity

The improved specificity of ELISPOT will mean that, in BCG vaccinated populations, targeted screening and treatment for LTBI could be performed more widely and vigorously without anxiety about false positive results due to prior BCG vaccination. It would also avoid unnecessary chemoprophylaxis and its attendant toxicity. This ability to screen out false positive TST results will become increasingly important as the prevalence of LTBI falls in low prevalence countries. This is likely to be an enabling step for control programmes that aim to eliminate TB, such as those of the United States Centers for Disease Control[1 2] and the European Working Group on Control and Elimination of TB.[3]

High sensitivity

Although the sensitivity of TST for LTBI cannot be directly quantified, we know that false negative results are common in at least two important groups: HIV infected individuals and those on immunosuppressive drugs.[1 6] This is a significant problem because it is precisely these people who, once infected, are at highest risk of progression to active TB.[1] Comparative studies to date indicate that ELISPOT has a higher sensitivity than TST in people with HIV induced[17] or iatrogenic immunosuppression (L Richeldi and A Lalvani, unpublished observations). False negative TST results also occur in contacts who already have active TB at the time of screening. The higher sensitivity of ELISPOT for active TB will help to minimise this problem.[16] Thus, the improved sensitivity of ELISPOT over TST in these groups should help to reduce the burden of active TB.

Blood test rather than skin test

The fact that ELISPOT is a blood test will have three major consequences: (1) the problem of people not returning to have their skin tests read will be circumvented and this should increase the yield of contact investigations and screening for LTBI; (2) repeated testing of high risk individuals such as healthcare workers would not be confounded by the booster phenomenon where repeated skin testing eventually induces false positive TST results[1 6]; and (3) test results will be issued by hospital laboratories instead of being read by contact clinic nurses, thus increasing the workload in laboratories while decreasing the workload in contact clinics. The operational consequences of this are hard to predict, but it could allow overburdened contact clinic personnel to focus on contact tracing and adherence with preventative treatment rather than administering and reading TST results.

Since the TST is cheap, the introduction of ELISPOT would initially increase the cost of TB control. However, the cost savings that would follow from avoiding unnecessary chemoprophylaxis and from reducing the number of cases of active TB could make ELISPOT very cost effective in the long term. The World Health Organisation is undertaking a quantitative cost-benefit health economic analysis of the recent use of ELISPOT to prevent a potential outbreak of multidrug resistant TB in northern Italy.

For high burden countries, improving prompt diagnosis and treatment of active disease remain the immediate priorities. However, better diagnosis of TB infection by ELISPOT could help TB control in high burden countries in three ways: (1) by improving diagnosis of asymptomatic infection (and active TB) in children; (2) by improving diagnosis in HIV infected individuals;[17] and (3) by enhancing epidemiological surveys to assess the effect of TB control measures.[21] Thus, although the greatest impact of ELISPOT will initially be on TB control in the developed world, it is likely that countries with a high burden of TB and HIV will also stand to benefit from this new approach to spotting TB infection.

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