New Tests on the Horizon to Detect Latent TB

BY BRUCE K. DIXON Chicago Bureau

KEYSTONE, COLO. — New tests that detect latent tuberculosis infection by quantifying interferon-y released from sensitized lymphocytes in whole blood may be a big step toward the elimination of TB, Dr. Charles Daley said at a meeting on allergy/clinical immunology, asthma, and pulmonary medicine.

This class of tests, called in vitro T-

cell-based interferon-y release assays (IGRAs), is the first replacement for the flawed tuberculin skin test, which has been in use in one form or another for a century.

'We absolutely can and must replace the tuberculin skin test, and the reason we can is because of these specific mycobacterium tuberculosis antigens, ESAT-6 and CFP-10," Dr. Daley said at the meeting, sponsored by the National Jewish Medical and Research Center.

The first replacement for the tuberculin skin test in a century, Quantiferon-TB (Cellestis), was approved by the Food and Drug Administration in 2001.

A version called Quantiferon-TB Gold In-Tube, which should be available this summer, will allow the drawing of blood directly into tubes containing the antigens, said Dr. Daley, who is head of mycobacterial and respiratory infections at National Jewish, Denver.

Another impending test is T-Spot.TB

PULMICORT FLEXHALER™ (budesonde inhalation powder, 90 mcg & 180 mcg) PULMICORT FLEXHALER™ (budesonide inhalation powder, 90 mcg & 180 mcg)

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advised that increments and use advised t orally inhaled conficosteroids, including PULMICORT FLEXHALER, should be monitored routinely (eg., via stadiometry). The potential growth effects of prolonged treatment should be weighed against incircue benefits obtained and the resists and benefits associated with alternative therapies. To minimize the systemic effects of inhaled conficosteroids, including PULMICORT FLEXHALER, each patient should be titrated to his/her lowest effective does. **Ceriotric Use** Of the total number of patients in controlled clinica studies receiving inhaled budesonide, 153 (n=11 treated with PULMCORT FLEXHALER) were 65 years of age or older and one was age 75 years or older. No overall differences in stately were observed between these patients and younger patients. Clinical studies due not include sufficient numbers of patients aged 65 years and over to determine differences in efficacy between elderly patient souther spectrated and younger patients. In general, does alcohor to an alcerly patient souther exported clinical or medical surveillance experience has not identif-ted differences in responses between the eldrify and younger patients. In general, does alcohor to an alcerly patient should be cautious, usually starting at the low end of the dosing range, reflecting the retrater with PULMICORT FLEXHALER 181 at of more in the double-lining pleach-controlled (linical trials in which 226 patients age 6-80 years, previously receiving bronchodilators, inhaled cortico-steroids, or toth, were treated with PULMICORT FLEXHALER, administered as 380 mg twice duly for 2 weeks. The Holiving Lable stores the incidence on adverse vense (identer considered durg-ted with set to holiving lable stores the incidence on adverse vense (identer considered durg-ticals in which 226 patients age 6-80 years, previously receiving bronchodilators, inhaled cortico-steroids, or toth, were treated with PULMICORT FLEXHALER. Adverse Event M = 21% Indexe and Windows Prevention States and Public Preventions Public Public Preventions Public Publi

reported by patients on PULMICORT FLEXHALER 180 or 90 mcg		
Adverse Event	PULMICORT FLEXHALER 360 mcg twice daily	Placebo N=230
	N=226 %	%
Nasopharyngitis	9.3	8.3
Nasal congestion	2.7	0.4
Pharyngitis	2.7	1.7
Rhinitis allergic	22	1.3
Viral upper respiratory tract infection	2.2	1.3
Nausea	1.8	0.9
Viral gastroenteritis	1.8	0.4
Otitis media	1.3	0.9
Oral candidiasis	1.3	0.4

1.3 0.4 Average exposure duration (days) 76.2 68.2 Long-Term Sofety Non-placeb controlled long-term studies in children (at dosse up to 960 mcg daily, and addesernia adult studiests (at dosse up 120 mcg daily, traded for up to one year with PULMCORT FLDHALER, revealed a similar pattern and incidence of adverse events. Adverse Event Reports from Other Sources The following other adverse events courter (in placebo-controlled dimatria with similar to over budesonic does with PULMCORT THEUHALER with an incidence of =1% in the budesonide group and were more common than in the placebo proup =3%: respiratory interion, simults, headache, pain, back pain, feyer, 2-1%, neck pain, syncope, abdominal pain, dry mouth, vomiting, veight gain, fracture, myalgia, hypertonia, migraine, eccty-mosis, insomina, infection, taste perversion, voice alteration. Higher doses of PLUMCORT TUBRUHALER wild astimutities veituelle run increased incidence of voise alteration, the syndrome, dyspepsia, gastroenteritis, nausea, and back pain, pompared with doses of 400 mcg twice daily. In a 60-week trial mal attamatics were even veituelle main increase incidence of voise daily. Net Solvees trial mal astimatics were deviced and controstentism, the direst daily (N=53) were compared with placebo (N=53) on the frequency of reporter adverse events. In consid-ening thes data, the increased verse que duration of exposure for inhabit budesonide paintes (78 days) Average exposure duration (days) (uesa) view compared with placebu (vesa) on the neglency of replaced advesse events. In closure and the increased average duration of exposure for inhaled buddeschilde platents (78 days for inhaled buddeschilde vestens), which was a straight of the placebu should be taken into account. Advesse events, whether considered drug-related or non-drug-related by the investigators, reported in more than five platents in the buddeschild puddeschilde taken into account. Advesse events, whether the buddeschild prug and which occurred more frequentity with buddeschilde that placebo are given (% inhaled buddeschilde) (28, and (24), placebic) (28, a the budesonce group and which occurred more frequently with budesonde than placebo are given (% inhaled budesonike and % placeboti schemic (% and 2%), budesolce (2% and 2%), buji (10% and 2%), dyspepsia (4% and 0%), nausea (6% and 0%), oral candidicais (10% and 3%), othring (and 0%), cough increased (6% and 2%), respiratory infection (32% and 13%), thinki (6% and 2%), simislis (16% and 1%), hare adverse events reported in the published literature or from wolfdwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including sah, contrad fermatiks, uriticain, angiedeman ad bronchospasm; symptoms of hyperorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms induiting depression, aggressive reactions, inritability anviety and psychosis. **OVENDOSAGE** The potential for caute toxice flasts following overdose of PUMICNDRT FLEXHALER is low. If used at excessive doese for prolonged periods, systemic corticosteroid effects such as hyperonricism may occur (see PRECAUTIONS), nother budesonide containing by provider inhaler at 200 mcg dai/a dynimistered for & weeks caused a significant reduction (2%) in the glasma cortisol response to a 6-hour infusion of ACTH compared with placebo (4%). The corresponding effect of 10 mg predinsione cataly was a 35% reduction in the glasma cortisol response to ACTH. The minimal inhalation lotase in adults and agrorxi-to gaproximately 300 lines the maximum recommended daily inhalation dose in adults and agrorxi-tably 300 lines the maximum recommended daily inhalation dose in adults and agrorxi-tably 300 lines the maximum recommended daily inhalation dose in adults and agrorxi-mately 300 lines the maximum recommended daily inhalation dose in adults and agrorxi-mately 300 lines the maximum recommended daily inhalation dose in adults and agrorxi-mately 450 lines the maximum recommended daily inhalation dose in children on a mcg/m² basis). There were no deatts tollowing the administration of an inhala The minimal oral leftal does was 200 mg/kg in mice (approximately 600 times the maximum ecom-mended daily indiation does in adults and approximately 670 times the maximum recommended daily initiation does in children on a mcgnire basis and less than 100 mg/kg in rats (approximately 670 times the maximum recommended daily initiation does in adults and approximately 670 times the maximum recommended daily initiation does in children based on a mcgnire basis). Post-marketing experience showed that acute overdose of initiate budesconde commonly remained asymptomate. The use of excessive coses (up to 8400 mg/daily for protonged periods showed systemic corticosteroid effects such as hypercorticism. **Potients Maintained on Chronic Oral Cortico-steroids**. Clinical studies with PULMICORT ILCR/INLER did not evaluate patients on oral controsteroids. Novere, clinical studies with Papagent does of PULMICORT IURB/INLER haud be used concurrently with the patients usual maintaneo dose of systemic corticosteroids. The aptients integrate and systemic controsteroids resolutions to retrosteroids. The patients activity and the systemic corticosteroids approximately on a systemic controsteroids resolutions controsteroids resolutions to retrosteroids. The patients activity does. The next reduction is made after an interval of one two weeks, depending on the response of the patient. Generally, these decrements should not exceed 2.5 mg of predinsion or tisse patients usual is stongly recommended 2.5 mg of predinsione or its quivalent. A sitow rate of within avail is stongly recommended 2.5 mg of predinsione or its quivalent. Show rate of within avail is stongly commended 2.5 mg of predinsione or its quivalent. Show rate of within avail is stongly recommended. During reduction sito on al corticosteroids, patients should be carelily mantored for adama instability, including objective is hearing the decorgoine determination relative availy resonamented. During reduction given to relative may experience syndrams of systemic corticoster measures of airway function, and for adrenal insufficiency (see WARINIGS). During withdrawal, see patients may experience symptoms of systemic conticosteroid withdrawal, eq. joint and/or muscular patients may experience symptoms of systemic conticosteroid withdrawal, eq. joint and/or muscular patients should be encouraged to continue with PULMICORT FLEXHALER but should be moni-tread for objective signs of adversarial insufficiency. Periadence of adversal insufficiency cocurs, the systemic conticoderoid doess should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may paquire supplementary treatment with systemic conducationis. **Directions for Use:** Illustrate Patient's *Instructions for use* accompany each package of PULMICORT FLEXHALER. Patients should be instructed to prime PULMICORT FLEXHALER. Prior to Isinal use, and instructed to invite deeply and forcefully each time the unit is used. Rinsing the mouth after inhibition is also recommended (see further instructions in PECAUTIONS, Information for Patients).

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(Oxford Immunotec Ltd.), which detects or spots individual T cells, and can be used for the diagnosis of latent disease simply by detecting the presence of an effector Tcell response.

A major advantage of these new tests is that they avoid false-positive results caused by previous inoculation with the BCG vaccine, which is widely used outside the United States and is a critical factor in the screening of foreign-born individuals.

"Over time, this cross reactivity has led to a distrust of the skin test in vaccinated people, many of whom can't remember when or even if they received BCG," Dr. Daley explained.

Dr. Daley, who consults for both companies, said that IGRAs are more sensitive



Both new tests correlate with exposure better than does the tuberculin skin test.

DR. DALEY

and specific than the tuberculin skin test, and that the T.Spot-TB is more sensitive than Quantiferon-TB while Quantiferon-TB is more specific.

Both IGRAs correlate with exposure better than does the tuberculin skin test, and may be more cost effective as well, he explained.

In addition, IRGAs require only one patient visit, assess responses to multiple antigens simultaneously, do not boost anamnestic immune responses, provide results within a day, and greatly reduce interreader variability.

A prospective study of 393 consecutively enrolled patients with latent tuberculosis infection or suspected TB looked at agreement between the tuberculin skin test and both interferon-y release assays, and found that indeterminate results were more common with Quantiferon-TB than with T-Spot.TB, particularly in young children and those who were immunocompromised (Lancet 2006;367:1328-34).

We still need to study more populations to optimize sensitivity and specificity in these IRGA tests. I'm not convinced that the cut-points currently recommended by the companies are appropriate, and we need to know how these are going to work in the immunocompromised and in young children.

There aren't enough data to guide us in these areas, so most people are kind of holding off on using these new assays," Dr. Daley said.

In addition, more needs to be learned about using IRGAs for serial testing. To that end, Dr. Daley and others are launching a four-center U.S. study of 3,000 health care workers who will be tested every 6 months with skin tests and both IRGAs.

Meanwhile, Dr. Daley and his colleagues at National Jewish are using Quantiferon-TB Gold and will begin using T-Spot.TB this summer.

Pulmicort 90 Flexhaler 180 mg (budesonide inhalation powder, 90 mcg & 180 mcg) For Oral Inhalation Only

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PROFESSIONAL INFORMA-TION BROCHUNE) INDICATIONS AND USAGE PULMICORT FLEXHALER is indicated for the maintenance treat-

INDICATIONS AND USAGE PULMICORT FLEXHALER is indicated for the mainterance treat-ment of astima as prophylactic therapy in abult and pediatric patients skycars of age or older. It is also indicated for patients requiring not abult and pediatric patients skycars of age or older. It is also indicated for patients requiring not abult and pediatric patients skycars of age or older. It is also indicated for patients requiring not abult and pediatric patients skycars of age or older. It is also indicated for patients requiring not abult and pediatric patients skycars of age or older. It is also able to return compared in astima control following initiation of undeconde can EVENALER is not indicated for the relief of auch benchospasm. CONTRAINDICATIONE VULMCORT FLEXHALER is contraindicated in the primary treatment of status astimatious or other acute episodes of astima where intensive measures are required. PULMICORT FLEXHALER patient should be divised in the information of undeconde can is contraindicated in patients which are patients who are transferred from systemically acute in astimatic patients who are transferred from systemically acute able to reclosseroids have been reduced or withdrawn should be instructed to a rord esciption of astistes or and inabinatic patients who are transferred from systemic controsteroids to state that they may are expresely, to consist their physicians who are transferred from systemic controsteroids to avoid exposure to chicken able intelled corticosteroids. After withdrawal from systemic controsteroids to any a empresed, to consult their physicians who are dearged from more inabination applies who are transferred from systemic controsteroids to avoid exposure to chicken able intelled corticosteroids. After withdrawal from systemic controsteroids to a need the systemic controsteroid to systemic controsteroids to evolue the expense the rok sogne able intelled corticostero required for recovery of HPA function. Patients who have been previously maintained on 20 mg or more reguited for recovery of HPA function. Haterist who have been previously maintained on 20 mg or more per day of prefinitione (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adremal insufficiency when exposed to trauma, surgery, or indiction (particularly gastroenterist) or other conditions associated with severe electrolyte loss. Although PULMICORT FLEXHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocriticoid systemi-cally and does ND provide the mineralocotticicid activity that is necessary for coping with these emergencies. During periods of stress or a severe asthma attack, patients who have been withfrawn from systemic contendential to instrument the instrument to resume and anticortenties fulls have to near dosen. emergercies: During periods of stress or a severe asthma attack, patients who have been withdrawn trom systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a metical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack. Patients requiring oral cortico-steroids should be weaned slowly from systemic corticosteroid use after transferring to PLUMCOBT FLEXNALER. Lung function (FEV, or AM PEF), beta-agoinst use, and sattma symptoms should be carefully monitored during withdrawail do rait corticosteroids. In addition to monitoring sattma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotersion. Transfer of patients from systemic corticosteroid the systemic corticosteroid therapy, e.g., rithitis, contunctivitis, arthritis, essinophilic conditions, and ecerma (see OOSAGE AND AMDINISTRATION in Full Prescribing Information). Patients who are on drugs which suggeres the immune system are more susceptible to intection.

use of YULMICUN HEXHALLH abrupty, e relatints should be varied to avoid exposure to chicken poor or meastes and if they are exposed, to consult their physicians without delay. • Long-term use of inhaled corticosteroids, including budesonide, may increase the risk of some eye problems (cataracts or glucorna). Regular eye evanimations should be considered. • Women considering the use of PULMICORT FLEXHALER should consult with their physician withy thore program for rithen to become pregnant, or if they are breast-freeding a baby. • Patients considering use of PULMICORT FLEXHALES should consult with their physician if they are relegic to budesonide or any other orally inhaled corticos sterid. • Patients should inform their physician of other medications they are taking as PULMICORT FLEXHALES. Revised constants should inform their physician of other medication of budesonide on the precision. I the precedence is the prior to the precision of the precedence is the precedence is chicked and the precedence is the prior to the precision of the precedence. Hundy PM 0025: 11 00161 He graphs during dama particle dama parts during head with the particle state of the particle state state FLEARALET may not be studied in some originisations and the physician may wish to use a different reficience. **Drug Intercritions**: It indical studies concurrent administration of budgesonde and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budgesonide, as well as other corticosteroids, is often stylchrome P450 (CPP) scienzyme 344 (CPR344). After oral administration of Metoconarole, a potent other drugs cor