Against expectations, genetic variation does not alter asthma treatment response

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(PhysOrg.com) -- Studies have suggested that asthma patients with a specific genetic variation might not respond as well to certain treatments as those with a different variation. But a new study in this week's edition of The Lancet shows that patients with either variation respond to combination treatment, and that this treatment should be continued, School of Medicine researchers report.

Studies have suggested that asthma patients with a specific genetic variation might not respond as well to certain treatments as those with a different variation. But an article published in this week's edition of The Lancet shows that patients with either variation respond to combination treatment, and that this treatment should be continued for these patients.

The study, called the Long-Acting Beta Agonist Response by Genotype (LARGE) trial was conducted by the Asthma Clinical Research Network established by the National Institutes of Health. Mario Castro, M.D., professor of medicine in the Division of Pulmonary and Critical Care Medicine and of pediatrics at Washington University School of Medicine in St. Louis, is one of the study authors.

"This study is important as it provides reassurance that the use of combination medications, inhaled steroids and long-acting beta-agonists (tradenames Advair or Symbicort), which are widely prescribed for asthma, are safe in patients that have this genetic variation," he says.

The genetic variation relates to the beta-2-adrenergic receptor, the receptor that asthma bronchodilators bind to in order to exert their effects. Some studies suggest that patients with two genes coding for the amino-acid arginine at a certain position in this receptor (termed B16 Arg/Arg) benefit less from treatment with long-acting beta-2 agonists such as salmeterol and inhaled corticosteroids than do those with two genes coding for amino acid glycine (termed B16 Gly/Gly) at this position. The authors investigated whether there is a genotype-specific response to treatment with a long-acting beta-2 agonist in combination with an inhaled corticosteroid.

In this randomized controlled trial, adult patients with moderate asthma were enrolled in pairs of similar lung capacity and ethnic origin according to whether they had the B16 Arg/Arg genotype (42 patients) or B16 Gly/Gly genotype (45 patients). Individuals in a matched pair were assigned to receive inhaled long-acting beta-2 agonist (salmeterol 50 ?g twice a day) or placebo for two 18-week periods. An inhaled corticosteroid (hydrofluoroalkane beclometasone 240 ?g twice a day) was given to all participants during the treatment periods. For each study participant, doctors monitored morning peak expiratory flow (PEF), a standard measure of lung function.

The team found that PEF did not differ between treatment groups, with both recording very similar lung function. However, airway constriction in response to methacholine administration was also assessed, which is a common method for testing for an asthmatic response. The test revealed that B16 Arg/Arg genotype patients did not benefit from the addition of salmeterol in response to the methacholine challenge.

Another interesting finding was that the lung function of African-Americans with the B16 Arg/Arg genotype did not improve with the long-acting beta-2-agonist the way African-American B16 Gly/Gly patients did. This may modify the risk-benefit ratio of long-acting beta agonists in this population. Twenty percent of African-Americans have the B16 Arg/Arg genotype.

The authors conclude: "The LARGE study showed that B16 Arg/Arg and B16 Gly/Gly patients with asthma had similar and substantial improvements

in airway function when salmeterol was added to inhaled corticosteroid therapy. These findings provide reassurance that in the general population, patients should continue to be treated with long-acting beta-2 agonists plus moderate-dose inhaled corticosteroids irrespective of B16 genotype. However, we need to further investigate the importance of the genotype-differentiated response in airway reactivity favoring Gly/Gly participants, as well as the finding that African-Americans with the Arg/Arg genotype might not benefit from treatment with salmeterol."

More information: Effect of beta-2-adrenergic receptor polymorphism on response to longacting beta-2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled crossover trial. *The Lancet*. November 21, 2009: 1754-1764.

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