Questions and answers

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Received 12 April 2015
Accepted 14 April 2015

The Egyptian Society of Internal Medicine
2015, 27:80–86

Egypt J Intern Med 27:80–86

1110-7782

Q1: Discuss the new approaches in the management of severe bronchial asthma

The preferred controller medication is a high-dose inhaled corticosteroid plus a leukotriene receptor antagonist plus an oral corticosteroid. Consider omalizumab for patients who have allergies.

Quick relief medication can be used for all patients and severities listed above. A short-acting β-agonist, as needed for symptoms, can be used. The intensity of treatment depends on the severity of symptoms. Up to three treatments at 20-min intervals as needed can be administered. A short course of oral systemic corticosteroids may be needed. The use of a short-acting β-agonist more than 2 days a week for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment. The 2009 VA/DoD guideline emphasizes that patients with persistent asthma should never be treated exclusively with long-acting β2 agonists.

In patients with exercise-induced bronchospasm, the primary aim of therapy is prophylaxis to prevent acute episodes. A warm-up period of 15 min is recommended before a scheduled exercise event and has been shown to have a duration of effect as long as 40 min. This approach is not helpful for unscheduled events, prolonged exercise, or elite athletes.

With exercise-induced bronchospasm, one of the primary treatments is to ensure good control of the underlying asthma. Regularly scheduled medications are generally not indicated for persons with isolated exercise-induced bronchospasm without underlying asthma. Prophylaxis in the form of inhaled medications administered 15–30 min before exercise is usually required. The most commonly used medications are short-acting β-agonists such as albuterol. Sodium cromolyn and nedocromil used 30 min before exercise have also been effective.

The use of long-acting beta agonists such as salmeterol (at least 90 min before exercise) can be effective for repetitive exercise. Newer agents such as the leukotriene antagonists, inhaled heparin, and inhaled furosemide have demonstrated an ability to prevent exercise-induced bronchospasm. Inhaled corticosteroids have a limited role in the treatment of exercise-induced bronchospasm, except to control underlying asthma [1].

Treatment updates [2]

Monotherapy with an intermittent corticosteroid (ICS)

ICSs leucotrien antagonists are the first line of therapy for control of persistent asthma in adults and older children and are considered the most effective form of anti-inflammatory treatment [3].

Monotherapy or add-on therapy with a leukotriene modifier

Leukotriene modifiers include two types of agents, the LTRAs, which are antagonists of cysteinyl leukotriene 1 [e.g. montelukast (Singulair; Merck and Co. Inc., West Point, Pennsylvania, USA)], zafirlukast (Accolate; AstraZeneca LP; Wilmington, Delaware, USA), and agents that block the synthesis of 5-lipoxygenase from arachidonic acid [zileuton (Zyflo; Critical Therapeutics Inc., Lexington, Massachusetts, USA)]. Although a new formulation was launched in 2005, zileuton has been available since 1997 as a 600 mg oral tablet that is administered four times daily in adults and children aged older than 12 years. A sustained-release formulation was approved for twice-daily administration in May 2007.

The LTMs leucotriene modifiers (including LTRAs and zileuton) were more effective than placebo

 DOI: 10.4103/1110-7782.159479

in preventing asthma exacerbations, but were less effective than ICS [4].

ICS/ long acting beta agonists (LABA) combination therapy

The ICSs are considered the most effective anti-inflammatory treatment strategy for control of persistent asthma, and inhaled β_2-adrenergic agonists are the most effective bronchodilators [3]. The ICSs inhibit eosinophils, macrophages, T-lymphocytes, mast cells, and other markers of inflammation. LABAs may possess anti-inflammatory properties or other beneficial pharmacologic effects that complement ICSs, such as inhibiting the release of inflammatory mediators from mast cells, blocking plasma exudates and reducing airway edema, and modulating airway sensory nerves that mediate airway hyper-responsiveness.

Anti-IgE therapy

Omalizumab (Xolair; Genentech Inc., San Francisco, California, USA) is a relatively new addition to the asthma treatment armamentarium. This agent is a humanized monoclonal antibody that binds to the Fc portion of circulating IgE antibody on mast cells and basophils, desensitizing mast cells to allergens. The mast cell-stabilizing effect of omalizumab blocks the release of inflammatory mediators in the lung and reduces IgE levels in response to allergen exposure [5].

Immunotherapy

Immunotherapies target specific elements of asthma pathophysiology.

The role of allergen-specific immunotherapy in the treatment of asthma has been extensively studied. A systematic review of 75 trials demonstrated that allergen-specific intradermal or subcutaneous immunotherapy for asthma reduced asthma symptoms and medication use and improved bronchial hyper-reactivity [6]. Moreover, a recent long-term trial demonstrated that a 3-year course of subcutaneous immunotherapy given to children and adolescents with grass and/or birch pollen allergy resulted in clinical benefit and possible prevention of the development of asthma 7 years after therapy [7].

Sublingual immunotherapy is being considered as a possible alternative to the subcutaneous route of administration [8].

Rush immunotherapy is a procedure that enables rapid desensitization of allergic patients through repeated injections of allergenic extract over a short time period. Using this technique, the therapeutic maintenance dose can be achieved in as little as 1–3 days compared with 3–6 months using conventional immunotherapy [9].

Biologic modifiers

Tumor necrosis factor-α (TNF-α) is an inflammatory cytokine produced by mast cells and found in the airways of patients with asthma. Several small pilot studies suggest a possible role for blocking the effects of TNF-α in patients with severe, refractory asthma. The TNF-α antagonist, etanercept (Enbrel; Immunex Corporation, Thousand Oaks, California, USA), administered 25 mg subcutaneously twice weekly for 2 weeks, was evaluated in a randomized, placebo-controlled trial of patients with mild to moderate allergic asthma (n = 26) [10]. No appreciable clinical effect on measures of airway hyper-responsiveness was demonstrated, and the trial was stopped early.

In contrast, a placebo-controlled crossover study of patients with refractory asthma (n = 10) demonstrated that a twice-weekly course of etanercept 25 mg for 10 weeks was significantly more effective than placebo in improving pulmonary function, asthma symptoms, and quality of life [11]. The humanized monoclonal antibody against TNF-α, infliximab (Remicade; Centocor, Malvern, Pennsylvania, USA), was evaluated in a placebo-controlled trial of patients with moderately severe asthma (n = 38) [12]. Infliximab was administered as a 5 mg/kg intravenous infusion at weeks 0, 2, and 6. No significant differences were observed between infliximab and placebo in the change from baseline for morning PEF (primary endpoint). However, infliximab treatment resulted in significantly greater improvements in the diurnal variation in PEF and reduced rates of exacerbations compared with placebo.

Tacrolimus is a calcineurin inhibitor used orally as an immunosuppressive agent in organ transplantation (Prograf; Astellas Pharma US Inc., Deerfield, Illinois, USA) and topically (Protopic; Astellas Pharma US Inc.) in dermatologic conditions, such as psoriasis. The putative mechanism of action of tacrolimus in asthma is inhibition of type 2 T helper (Th2) cytokines and subsequent improvement in airway inflammation [13]. Anti-interleukin-5 (IL-5) is another biologic modifier under investigation in clinical trials. Mepolizumab is one monoclonal antibody against IL-5 that reduces eosinophils in the airways and periphery [14].

Pharmacogenetics

In the future, pharmacogenetics may offer the opportunity to individualize asthma treatment based on associations between a particular genetic

polymorphism and a predicted response to treatment [15].

Gene therapy

Gene-based vaccines may have a role in immunomodulation for patients who have corticosteroid-resistant asthma or severe asthma requiring systemic corticosteroid therapy [16]. It has been postulated that gene therapies targeting the Th2 cell pathway involved in chronic airway inflammation may be beneficial in the treatment of asthma [17].

Bronchial thermoplasty

A new therapeutic option for the treatment of severe, uncontrolled asthma in adults

Bronchial thermoplasty is an interventional bronchoscopic procedure for the treatment of severe, uncontrolled asthma patients.

Performing bronchial thermoplasty requires bronchoscopic rigor, dexterity, and a thorough knowledge of the airway anatomy. Three treatment sessions at ~3-week intervals are recommended; full recovery of the patient between treatments is necessary in order to proceed. The sequence of treatments involves the right lower lobe (first session), the left lower lobe (second session), and then both upper lobes (third session). The right middle lobe is not treated, as the clinical program excluded this area based on the theoretical possibility of obstruction and right middle lobe syndrome. Each bronchial thermoplasty session takes ~30–45 min. Each bronchus is treated along its entire visible length, with each activation targeting a 5 mm section of bronchus between 3 and 10 mm in diameter, beginning at the periphery and moving proximally. Areas should not be retreated. A full treatment consists of ~30–70 activations per lobe (depending on the specific anatomy); on average, 44 for the right lower lobe, 47 for the left lower lobe, and 60 for the upper lobes are performed [9]. The effectiveness of the treatment may depend on how thoroughly the procedure is performed; if a segment is left untreated it may theoretically continue to constrict when stimulated, potentially negating the benefits of the treatment [18].

The use of magnesium in bronchial asthma: a new approach to an old problem

Magnesium deficiency is a common electrolyte disorder in patients with acute severe asthma, but intracellular magnesium content better reflects its homeostasis than does its serum concentration. Magnesium takes part in many metabolic processes in the organism, including energy metabolism, protein and nucleic acid synthesis, cell cycle, the binding of substances to the plasma membrane, and maintenance of cytoskeletal and mitochondrial integrity. It also modulates ion transport and influences intracellular calcium concentration. Maintenance of the cells' transmembrane gradient depends on the presence of magnesium, and hypomagnesemia may result in an increase in neuromuscular cell excitability. Magnesium is a cation modulating the smooth muscle contractility of different tissues: hypomagnesemia causes their contraction and hypermagnesemia their relaxation. Suggestions of a positive influence of magnesium in the treatment of asthma exacerbation have been known for a long time, but research results differ. A single dose of intravenous magnesium sulfate given to patients with acute asthma exacerbation has been shown to be safe, but its efficiency is still under discussion. According to the Global Initiative for Asthma GINA-2005, magnesium sulfate administration is not recommended for routine treatment, but it is permitted in patients with severe asthma exacerbation not responding to treatment (evidence category A). Recommendations of the British Thoracic Society allow one dose of magnesium sulfate to patients with acute severe asthma exacerbation and inadequate initial response to broncho-dilating inhalation treatment (evidence category A). Future investigations should help to establish the indications for magnesium use in the treatment of acute asthma exacerbations as well as the magnesium dose and the scheme of its administration [19].

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Q2: Give an account of the important recommendations of the ACCORD study for diabetic patients

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study according to National Health Institute was a large clinical trial of adults with established type 2 diabetes who were at especially high risk for cardiovascular disease (CVD).

Type 2 diabetes increases the risk of a number of complications, especially CVD, which is the leading cause of early death in people with diabetes. Many people with diabetes are overweight and have high blood pressure (BP) and lipid or cholesterol problems – conditions that further add to their CVD risk. Adults with type 2 diabetes are two to four times more likely to die of heart disease and stroke than are adults without diabetes, and about 65% of people with diabetes die from heart disease or stroke.

The ACCORD study was primarily composed of three clinical trials, which tested treatment approaches to determine the best ways to decrease the high rate of major CVD events – heart attack, stroke, or death from CVD – among people with type 2 diabetes who are at especially high risk of having a CVD event, such as a heart attack or stroke. These three treatment approaches were as follows: intensive lowering of blood sugar levels compared with a more standard blood sugar treatment; intensive lowering of BP compared with standard BP treatment; and treatment of multiple blood lipids with two drugs – a fibrate plus a statin – compared with one drug, a statin alone.

All three ACCORD clinical trials have ended. The National Heart, Lung, and Blood Institute stopped the intensive blood sugar-lowering strategy on 6 February 2008 because of safety concerns. Participants in the intensive blood sugar treatment strategy group were transitioned to the standard treatment strategy. The BP and lipid treatment trials continued until the planned end of the study in June 2009.

The results of ACCORD apply only to patients at particularly high risk for CVD and established diabetes. ACCORD participants had diabetes on average for 10 years; over a third had existing CVD; and the rest had at least two additional risk factors (such as high BP, high blood cholesterol, or obesity). Different levels of risk factor control may be recommended depending on each patient's individual risk profile [1].

The prevalence of diabetes increased with age and peaked at 60–74 years (crude prevalence 17.6%) [2].

Older adults with diabetes are at risk of developing a similar spectrum of macrovascular and microvascular complications as their younger counterparts with diabetes. However, their absolute risk for CVD is much higher than that of younger adults. Older adults with diabetes suffer excess morbidity and mortality compared with older individuals without diabetes [3]. In addition, they are at high risk for polypharmacy, functional disabilities, and common geriatric syndromes that include cognitive impairment, depression, urinary incontinence, falls, and persistent pain [4].

Recommendations of the ACCORD study:

(1) Concerning control of blood sugar:

As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with type 2 diabetes [5].

The results of the ACCORD trial suggest that a target A1C of 7.0–7.9% (achieving a median of 7.5%) may be safer than a lower target for patients with long-standing type 2 diabetes who are at high risk for CVD [6].

(2) Concerning control of BP:

The message from ACCORD pertaining to guidelines and clinical practice is that in diabetic patients it is not necessary to adopt an aggressive BP-lowering strategy because a systolic blood pressure (SBP) reduction to the 130–140 mmHg range (for which the beneficial effects are documented) appears to suffice. Indeed, a more aggressive BP-lowering strategy may be detrimental because the ACCORD patients in whom in-treatment SBP was less than 120 mmHg had an incidence of serious side effects that was almost three

times as frequent as that of patients with SBP greater than 130 mmHg [5].

(3) Concerning control of lipids:

The ACCORD lipid trial tested the hypothesis that treatment of patients with type 2 diabetes with fenofibrate to increase plasma HDL cholesterol levels and reduce plasma triglyceride concentrations, on the background of simvastatin therapy, would result in additional cardiovascular benefit compared with simvastatin therapy alone [7].

The ACCORD lipid trial was negative. There is no evidence from this trial to indicate that fenofibrate should be routinely added to a statin for the treatment of lipids in patients with type 2 diabetes. Indeed, routine addition of fenofibrate might be harmful for women with type 2 diabetes. However, the ACCORD data, together with post-hoc analyses of three other fibrate trials, suggest that, when triglycerides is more than 200 mg/dl and HDL is less than 35 mg/dl after statin therapy has significantly reduced LDL cholesterol levels, fibrate treatment can be considered, at least in men [8].

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Q3: Give an account of Iron homeostasis

According to [1], iron is an essential nutrient required for a variety of biochemical processes. It is a vital component of the heme in hemoglobin, myoglobin, and cytochromes and is also an essential cofactor for nonheme enzymes such as ribonucleotide reductase, the limiting enzyme for DNA synthesis. When in excess, iron is toxic because it generates superoxide anions and hydroxyl radicals that react readily with biological molecules, including proteins, lipids, and DNA. As a result, humans possess elegant control mechanisms to maintain iron homeostasis by coordinately regulating iron absorption, iron recycling, and mobilization of stored iron. Disruption of these processes causes either iron-deficient anemia or iron overload disorders.

Iron absorption: Adults absorb ~1–2 mg of iron/day from the diet to compensate for daily iron loss due to the sloughing of epithelial cells, blood loss, and sweat. Most diets contain two different forms of iron, inorganic nonheme iron in vegetables and grains and heme iron (ferrous iron protoporphyrin IX) in red meat. Iron traverses both the apical and basolateral membranes of absorptive epithelial cells to reach the blood, where it is incorporated into Tf [3], the major iron transport protein. At least two different sets of transporters are used in this process. Nonheme iron is transported by DMT1 (divalent metal transporter 1), the intestinal iron importer. Dietary nonheme iron exists mainly as Fe^{3+} and has to be reduced before transport. DcytB, a reductase whose expression is induced by iron deficiency, is localized in the apical membrane of intestinal enterocytes and is a major but most likely not the only reductase. The transporter responsible for heme uptake remains controversial [2–4].

Iron distribution in the body: Adults have a total of 3–5 g of iron. Approximately 65–75% is found in the hemoglobin of erythrocytes in the form of heme. The liver stores 10–20% in the form of ferritin, which can be mobilized easily when needed. About 3–4% of the body's iron is in heme-bound myoglobin in striated muscle. The rest is distributed in other tissues. Under physiological conditions, ~25 mg of iron/day is consumed by immature erythrocytes in the bone marrow for heme biosynthesis.

Iron recycling within the body: Macrophages in the liver and spleen are responsible for the recycling of heme iron from senescent erythrocytes. The hemoglobin-derived heme is catabolized by the cytosolic heme oxygenase-1 to release iron, and the iron is subsequently exported into the circulation by FPN. In addition, heme can also be exported directly into the circulation through the heme exporter FLVCR (feline leukemia virus subgroup C receptor) on macrophage plasma membranes. A recent study demonstrated that FLVCR also plays a critical role in the export of excess heme from immature erythrocytes and hepatocytes [5]. Plasma heme is scavenged and transported by hemopexin to hepatocytes for degradation. Iron recycling from senescent erythrocytes in macrophages constitutes the major iron supply for hemoglobin synthesis.

Cellular iron sensing and regulation

The majority of cells obtain their iron requirements by Tf-mediated iron uptake through TfR1. TfR1

is internalized into endosomes that are acidified, facilitating the release of iron from Tf [6,7]. The iron is reduced by a recently identified ferrireductase, Steap3, and transported across the vesicle membrane for utilization within the cell and/or storage [8]. DMT1 is the transporter in immature red blood cells [9]. Iron uptake is roughly proportional to the number of TfRs on the cell surface. Regulation of TfR1 is achieved through IRPs and mRNA stem-loop structures, IREs, which have been reviewed extensively [10,11]. The IREs in mRNA of TfR1 negatively regulate the stability of TfR1 mRNA when cytosolic iron levels are high. Under low iron conditions, the IRPs bind to the IREs, where they stabilize TfR1 mRNA. The double knockout of IRP1 and IRP2 is embryonic lethal. The double knockout of these genes in the intestine results in the death of intestinal epithelial cells, presumably by iron depletion [12], underscoring the importance of these proteins.

Liver as the central iron regulatory organ

Hepcidin, a peptide synthesized by liver hepatocytes, plays a major role in regulating iron homeostasis in the body [10,11]. The mature form is 25 amino acids with four intersubunit disulfide bonds. The massive iron overload found in hepcidin knockout mice suggests that hepcidin is an iron stores regulator involved in communication of body iron status to the intestine [13]. In contrast, mice engineered to overproduce hepcidin are severely anemic [14]. The discovery that a hepatic adenoma overexpressing hepcidin results in anemia and that the anemia is resolved upon removal of the tumor confirms the relationship between hepcidin expression and inhibition of iron uptake by the intestine [15]. Studies have demonstrated that hepcidin binds FPN, which results in the internalization and degradation of FPN [16]. Hepcidin therefore functions to decrease serum iron levels by blocking iron absorption from the intestine, iron recycling from macrophages, and mobilization of stored iron from liver hepatocytes.

The liver plays a major role in iron homeostasis in the body in addition to secreting hepcidin. Liver macrophages take up senescent red blood cells and hemoglobin through the hemoglobin-haptoglobin receptor (CD163), salvage the iron released from hemoglobin, and secrete the iron as Fe^{2+} through FPN. Hepatocytes synthesize both Tf and Cp. Cp facilitates the efflux of iron from cells as well as the loading of iron into Tf [17,18]. Hepatocytes take up Tf through TfR1 and the more recently identified TfR2 [19]. They also take up other forms of non-Tf-bound iron, including heme through the heme hemopexin receptor [20], and are capable of storing large quantities of iron in ferritin and hemosiderin, a breakdown product of ferritin. Thus, the liver and, in particular, the hepatocyte are thought to sense and reflect body iron stores [21].

Iron sensing and regulation of hepcidin expression

Humans possess elegant mechanisms to maintain iron homeostasis by modulating the expression of hepatic hepcidin. HJV, BMPs, TfR2, HFE, and Tf are critical to this process. Hepcidin expression is also regulated by erythroid factors, hypoxia, and inflammation, regardless of body iron levels.

Other regulators of hepcidin

Erythroid factor: The sensors for communicating body iron stores and the erythropoietic state are only beginning to be understood. Early physiological studies demonstrated that soluble factor(s) in the blood are involved. Iron-loaded Tf, ferritin, serum TfR1 generated from the proteolytic cleavage of full-length transmembrane TfR1, and hepcidin have been proposed as candidate factors [22–28]. Tf, ferritin, and serum TfR1 are found in serum and fluctuate with the iron status of the individual. The amount of serum ferritin increases in iron-overloaded individuals.

Hypoxia: Hypoxia is another suppressor of hepatic hepcidin expression independent of body iron levels.

Under hypoxia or following iron chelation, the prolyl hydroxylase activity is inhibited, resulting in the accumulation and translocation of hypoxia inducible factor into the nucleus. Hypoxia inducible factor (HIF) binding to the promoter of hepcidin leads to the suppression of hepcidin expression in hepatocytes [29] and increased iron uptake to meet the erythropoietic demand.

Inflammation: Inflammation is a dominant and robust inducer of hepcidin gene transcription regardless of body iron levels. IL-6 and possibly other inflammatory cytokines are the major players in this process.

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