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Review article

Why choose tiotropium for my patient? A comprehensive review of actions and outcomes versus other bronchodilators

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ABSTRACT

Purpose: Chronic obstructive pulmonary disease (COPD) and asthma are leading causes of morbidity and mortality. This narrative review provides an appraisal of the pharmacological and clinical characteristics of tiotropium in COPD and asthma, and examines how these compare with other long-acting bronchodilators. The evidence base is placed into context by relating it to factors affecting clinicians' choice of therapy.

Main findings: Desirable attributes of a long-acting muscarinic antagonist (LAMA) maintenance therapy include effective pharmacological bronchodilation, improved lung function, exacerbation efficacy, and positive effects on symptom control, exercise capacity and quality of life across a broad patient population. Tolerability and convenience of use are also important for patient well-being and treatment adherence. Tiotropium shows higher affinity for muscarinic receptors than ipratropium, and prolonged binding to the M_3 receptor compared with other LAMAs. In COPD, tiotropium has demonstrated improved lung function and exacerbation prevention compared with placebo or long-acting β_2-agonists, similar exacerbation efficacy to other LAMAs, and enhanced symptom control and health status versus placebo. UniTinA-asthma® showed the benefits of add-on tiotropium in patients with uncontrolled mild to moderate and severe asthma. Tiotropium is well tolerated, with an incidence of adverse events similar to placebo, except for known infrequent side effects of anticholinergics. Tiotropium HandiHaler® and Respimat® augment inhaler choice in COPD.

Principal conclusions: With over 10 years' prescribing history and 50 million patient-years of use, tiotropium has the benefit of a more extensive clinical evidence base than other long-acting bronchodilators, with demonstrated efficacy and safety in COPD and symptomatic asthma.

Contents

Non-standard abbreviations: INSPIRE, Investigating New Standards for Prophylaxis in Reduction of Exacerbations; POET-COPD®, Prevention of Exacerbations with Tiotropium in COPD; TIOSPIR®, TIOtropium Safety and Performance in Respimat®; UPLIFT®, Understanding Potential Long-term Impacts on Function with Tiotropium; WISDOM, Withdrawal of Inhaled Steroids During Optimised bronchodilator Management.

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1. Introduction

Chronic respiratory diseases represent an increasing public health concern. Globally, more than 200 million people suffer from chronic obstructive pulmonary disease (COPD) [1], resulting in approximately 3 million deaths per year [2]. The World Health Organization predicts that by 2030, COPD will be the third-leading cause of mortality worldwide [3]. Asthma, which affects approximately 235 million people of all ages, is also of major importance, being the most common noncommunicable disease among children [4].

Long-acting bronchodilators play an important role in reducing symptoms in patients with uncontrolled asthma [5] and are the mainstay of treatment for COPD [6]. Tiotropium bromide (SPIRIVA® [Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany]) was the first long-acting muscarinic antagonist (LAMA) to be approved for maintenance treatment of COPD [7]. It is available in two formulations: dry powder (18 μg once daily) delivered via the breath-actuated HandiHaler®, and aqueous solution (5 μg, two puffs 2.5 μg once daily) delivered via the Respimat® Soft Mist™ Inhaler. In 2014, tiotropium Respimat® became the first LAMA to receive EU approval for add-on maintenance treatment of adults with symptomatic asthma [8], which was followed in 2015 by approval in Canada in adults [9], and in the United States for treatment of asthma in patients aged $\geq$ 12 years [10].

Several other LAMAs have since been developed, each demonstrating lung function and exacerbation benefits, together with good tolerability profiles [11–13]. New therapies have given patients and clinicians a greater choice of which drug and inhaler device to use; however, there is the potential for prescribing confusion and a possible assumption that all drugs within a class are the same.

Numerous systematic reviews and critical appraisals of the efficacy and safety of tiotropium have been published [14–16], and it is not our intention to provide a further review of already extensively discussed studies. Instead, the purpose of this article is to help clarify the treatment decision-making process by providing a review of how the unique pharmacological and clinical properties of tiotropium meet the guideline-defined treatment goals for all types of patients with COPD seen in primary care and in patients with symptomatic asthma. Included in this discussion is an appraisal of how these characteristics compare with other long-acting bronchodilators, with a specific focus on other LAMAs.

2. Methods

In this narrative review, we provide an objective appraisal of the pharmacological and clinical characteristics that, when considered as a whole, set tiotropium apart from other long-acting bronchodilators for the maintenance treatment of COPD and symptomatic asthma. While reference is made to pivotal clinical trials and meta-analyses of tiotropium versus newer LAMAs and other long-acting bronchodilators, we do not provide a formal systematic review of evidence, as this has been extensively covered in previous publications [17–19]. Instead, the authors' approach was to place this evidence base into context by relating it to the key factors that affect the clinician's choice of therapy (e.g. mechanism of action, impact on clinical outcomes of lung function, exacerbation reduction, quality of life [QoL] improvement, safety, clinical experience) and to illustrate how tiotropium meets these needs.

Comparative pharmacological and clinical data were selected from the prescribing information of LAMAs and other long-acting bronchodilators, as well as from all randomised clinical trials comparing tiotropium versus other LAMAs and landmark COPD and asthma studies, and were related to the key choice factors highlighted. In addition, evidence is provided on the applicability of the data to all clinical settings, including primary care.

3. What do clinicians want of a LAMA?

The goal of COPD therapy is to obtain maximal control over symptoms and minimise or prevent disease exacerbations, with minimal adverse events, by delivering the optimal inhaled drug dose to the lungs [6]. With the growing array of therapies now available for treatment of both COPD and asthma, clinicians are faced with a wide-ranging choice of treatment options for their patients. Ideally, these treatments will demonstrate a good safety profile with limited systemic adverse events, effective and sustained bronchodilation and proven efficacy in relevant patient populations on relevant outcomes.

In addition, desirable attributes will include once-daily dosing and administration via an easy-to-use inhaler, both of which help to