Aclidinium

As maintenance therapy in the management of COPD (▼Bretaris Genuair®, ▼Eklira Genuair®)

Besides an anticholinergic agent, what else do we know about this drug?

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ABSTRACT

There is no head-to-head trial comparing aclidinium vs other long-acting bronchodilators.

Compared to placebo, aclidinium 400 mcg/12h improves spirometry parameters although the clinical relevance of this improvement is modest.

Adverse effects related to heart conduction have been reported, and the EMA has requested a post-approval study to monitor cardiovascular events.

It should be employed with precaution in patients with heart disease.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	NO THERAPEUTIC INNOVATION
0	**INSUFFICIENT EVIDENCE**

Indications[1]

Aclidinium is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

Mechanism of action[1]

Aclidinium is a selective competitive antagonist of muscarinic receptors. The activation of these cholinergic receptors produces smooth muscle contraction in the respiratory tract and its antagonism produces bronchodilation.

Posology and administration[1]

The commercialised dose is 322 mcg aclidinium, which is equivalent to the recommended inhalation of 400 mcg/12h of aclidinium bromide. It is administered through a dry powder multidose inhaler Genuair®.

Clinical efficacy

Three double-blind, randomized clinical trials comparing the drug to placebo have been carried out to establish the efficacy and safety profile of aclidinium.[4] The 24-week pivotal study ATTAIN[5] (n=828) and supporting trials ACCORD I[6] (n=561) and ACCORD II[4] (n=544) which lasted 12 weeks. The trials included patients ≥ 40 years, who were smokers or had a history of smoking and diagnosed with moderate to severe COPD (according to the GOLD classification: FEV_1/ FVC <0,7 and FEV_1 <80%). Patients suffering from asthma, respiratory tract infection, a COPD exacerbation during the 6 week interval before the screening visit (3 months in cases of hospital admission) and cardiovascular disease were excluded.

The primary efficacy endpoint in the three studies was the change in FEV_1 with respect to baseline values in the morning pre-dose (trough FEV_1). Although there is controversy, a variation in FEV_1 >100 mL[4] can be considered clinically relevant.

The result was a trough FEV_1=128 mL (95%CI, 85-170; p<0.0001) in the ATTAIN trial[5] (24 weeks) and 124 mL (95%CI, 83–164; p<0.0001) in the ACCORD I[6] (12 weeks) favourable for aclidinium vs placebo. The results of the ACCORD II (not published) showed lower differences while not reaching clinical relevance: trough FEV_1=72 mL (95%CI, 29-115; p<0.05).[4]

An extension was carried out in the ACCORD I and ACCORD II to obtain results on long-term efficacy. These results suggest that the benefits are maintained up to week 52.[7]

Later on, a phase III trial was published (LAS 9) carried out on patients with moderate- severe COPD with the objective of showing superiority compared to placebo. This trial included three arms, aclidinium 400 mcg/12h, tiotropium 18 mcg/d, and placebo (2:2:1). The endpoint was change in $FEV_{1\ 0\text{-}24}$ from baseline up to 6 weeks of therapy. No significant differences were found between aclidinium and tiotropium, in any of the variables under study ($FEV_{1\ 0\text{-}24}$, 150 mL *vs* 140 mL in the case of aclidinium and tiotropium respectively; difference between groups, 10 mL; 95%CI -36 to 56).[1,8]

There is no evidence of any added value in the management of COPD compared to other long-acting bronchodilators.

Despite the lower incidence of moderate or severe exacerbations in the aclidinium group, the difference compared to placebo was not statistically significant in any of the trials.

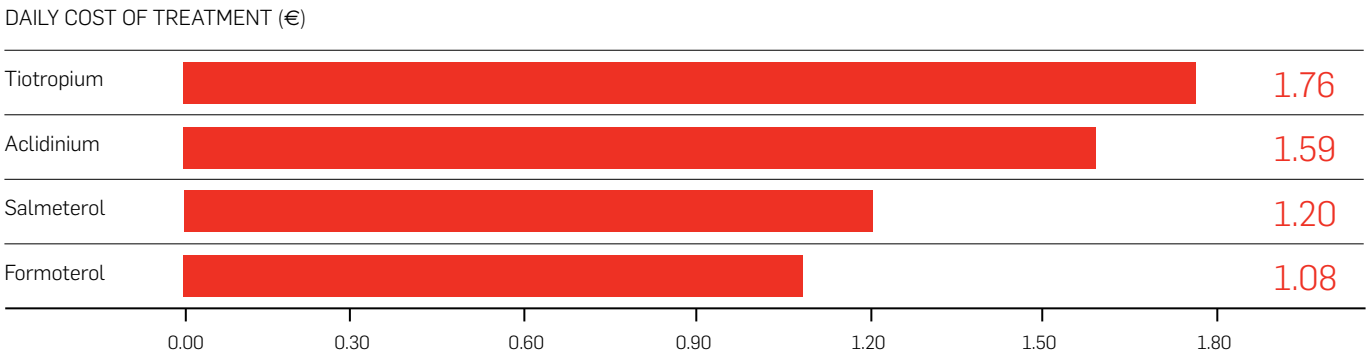
Safety

Adverse reactions[1]

The incidence of overall adverse effects was similar between aclidinium (50.2%) and placebo (53.7%). The most frequent adverse reactions (excluding exacerbations) were headache (6.6% vs 5%) and nasopharyngitis (5.5% vs 3.9%), respectively.

Urinary tract infections were more frequent with aclidinium, and in the ATTAIN trial, differences were observed between both groups: 2.2% (aclidinium) *vs* placebo 0.7% (placebo).

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.



Patients abandoned treatment in 15% of the cases under placebo and 6.3% in the group under aclidinium. Dropouts due to adverse effects were 4% and 3% (placebo and aclidinium, respectively).

Based on long-term data, the EMA reviewers suspected an apparent relationship between the administration of aclidinium and abnormalities in atrioventricular conduction and requested a study to monitor cardiovascular events.

Contraindications

Hypersensitivity to aclidinium, atropine or derivatives, including ipratropium, oxytropium, tiotropium or any of its excipients (contains lactose).

Warnings and precautions

· It should not be employed in asthma, due to lack of information.
· As in the case of other inhaled treatments, it could cause paradoxical bronchospasm
· As a maintenance bronchodilator, it should not be employed as rescue medication.
· Given it anticholinergic effects, precaution should be taken in patients with a history of myocardial infarction, unstable angina, newly diagnosed arrhythmia, or hospital admission due to NYHA type II and IV heart failure.
· Precaution in patients with symptomatic prostate hyperplasia, bladder neck obstruction or narrow-angle glaucoma.

Use in special situations

Elderly patients: No dose adjustments are necessary. **Children:** no specific recommendation in children or adolescents. **Renal and liver impairment:** no dose adjustments are necessary. **Pregnancy:** no data available. It should only be employed when the expected benefits are greater than the possible risks. **Breastfeeding:** no data in humans. **Fertility:** it is considered improbable that it may cause any effects on fertility when employed at therapeutic doses.

Interactions with food and medication

Its use is not recommended with other anticholinergic drugs, as no studies have been carried out. According to in vitro studies, no interactions are foreseen between aclidinium and glycoprotein (P-gp) substrate drugs or drugs metabolised by the cytochrome CYP450 and esterases.

EMA Risk Management Plan

The EMA has requested a cohort study to evaluate the cardiovascular safety profile of aclidinium.

Place in therapeutics

Chronic obstructive pulmonary disease (COPD) is a preventable, chronic, progressive disease with important comorbidity associated. The natural course of the disease gives place to a progressive reduction of airflow and a deficient exchange of gases provoking hypoxia, cardiovascular and multiorgan affectation.

The most important intervention in the management of COPD is to promote smoking cessation. The goals of treatment are to maintain the airflow through bronchodilators in combination with a multidisciplinar intervention that includes the prevention and treatment of exacerbations (respiratory infections) and antiinflammatory therapy.[1,2]

Management of stable COPD is based on long-acting bronchodilators to which other drugs may be added (inhaled corticosteroids, theophylline, phosphodiestarase IV inhibitors, or mucolytics) according to the severity, frequency of exacerbations and symptoms. The long-acting bronchodilators may include beta-adrenergic agents (LABA) such as salmeterol, formoterol and indacaterol or anticholinergic agents (LAMA) such as tiotropium bromide.[1,2]

In symptomatic patients, despite monotherapy with long-acting bronchodilators, double therapy with LAMA+LABA bronchodilators is recommended. Long-term management with inhaled corticoids is reserved to patients with severe or very severe limitation in airflow and frequent exacerbations that are not adequately controlled with long-acting bronchodilators LABD.[1,2]

Aclidinium is another long-acting anticholinergic drug that has not been compared to any of the other recommended treatments (LABA or LAMA).

The safety profile of aclidinium shows that in general it is well tolerated. However, a series of adverse events related to heart conduction were detected leading to a request for a post-marketing study by the EMA.

The Spanish Medicines Agency has published a report regarding its stance on aclidinium in which it points out that "the data available do not allow for a conclusion to be made on the existence of clinically relevant differences or treatment compliance vs other approved inhaled anticholinergic drugs such as Spiriva® (tiotropium bromide), while no comparative data vs Atrovent® (ipratropium bromide) are available".[12]

Presentations

Bretaris Genuair® (Menarini) 322 mcg/dose, 60 doses (47.61 €) and Eklira Genuair® (Almirall) 322 mcg/dose, 60 doses (47.61 €)

References

A full report on Aclidinium is available at: http://www.bit.navarra.es

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