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Antileukotrienes and asthma: Alternative or adjunct to inhaled steroids?

■ ABSTRACT

Antileukotriene agents may be reasonable and safe alternatives or adjuncts to inhaled steroid therapy in chronic asthma, as they act at sites further down in the inflammatory cascade. This article reviews the clinical experience with three antileukotriene agents and discusses their role in the management of asthma.

■ KEY POINTS

Inhaled corticosteroids are very effective and quite safe when used appropriately, but compliance with inhaler therapy is poor, and concerns remain about their long-term safety, especially at higher doses, durations greater than 5 years, and in children.

Leukotriene antagonists inhibit asthmatic responses to a variety of stimuli, including allergens, exercise, aspirin, and cold, dry air.

In a given patient, it is not known how much of the inflammation of asthma is due to leukotrienes and how much is due to other factors. Therefore, short of an empiric trial, there is no way to know which patients will respond well to antileukotriene drugs.

INHALED CORTICOSTEROIDS remain the standard therapy for patients with chronic asthma, but concern about toxicity and poor compliance often limit their effectiveness. In such cases, oral therapy with an antileukotriene, a new type of anti-inflammatory drug, may be a reasonable alternative. In addition, in patients who remain symptomatic despite high doses of inhaled corticosteroids, an antileukotriene drug may be a reasonable adjunctive therapy.

This article summarizes the clinical experience to date with the three antileukotriene drugs approved for treating mild to moderate asthma: zileuton, zafirlukast, and montelukast. It also compares them with inhaled corticosteroid therapy and discusses recommendations for their use as alternatives or adjuncts to inhaled corticosteroid therapy for asthma.

■ ASTHMA'S INFLAMMATORY COMPONENT

Asthma is characterized by episodic respiratory symptoms related to:

- Variable airflow obstruction, which is often reversible
- Airway hyperresponsiveness to a variety of stimuli
- Chronic airway inflammation.

The critical steps of the inflammatory cascade of asthma are poorly understood, although a variety of inflammatory cellular, epithelial, neurogenic, and biochemical mediators appear to be important.

Drawbacks of inhaled corticosteroid therapy

The emphasis of maintenance therapy for asthma has been on anti-inflammatory agents, most often inhaled corticosteroids.¹ Controlled

studies and anecdotal experience show that inhaled corticosteroids are very effective and quite safe when used appropriately.

But 20 years of experience have not eliminated serious problems with this therapy. Studies show that patients do not comply well with inhaler therapy,² and concerns remain about the long-term safety of inhaled steroids, especially at higher doses, for durations greater than 5 years, and in children.³ Studies have demonstrated the systemic effect of inhaled steroids by a variety of biochemical markers (eg, adrenal function, bone metabolism), as well as by clinical toxicity (eg, impaired growth, cataracts). Furthermore, although inhaled steroids ameliorate the cellular inflammation in the airways, this effect is short-lived, and certain features (airway hyperresponsiveness, basement membrane thickening, airway remodeling) persist even after 10 years of steroid therapy.⁴

Leukotrienes and airway inflammation

Since the 1970s, experts have known of a link between leukotrienes and the airway inflammation typical of asthma. Leukotrienes, a product of the metabolism of arachidonic acid, are produced by a variety of tissues and cells in the lungs (eg, mast cells, eosinophils, macrophages). Research has shown that, when leukotrienes interact with specific airway receptors, symptoms of asthmatic airway inflammation result. As a result, in the last few years leukotrienes have become the target of pharmacologic antagonism by a new class of agents, antileukotrienes (FIGURE 1).⁵

The lipoxygenase pathway of arachidonic acid metabolism is responsible for the production of the cysteinyl leukotrienes (leukotrienes C₄, D₄, and E₄) and leukotriene B₄. The strong asthma-related effects of these leukotrienes occur when they interact with specific receptors on the surface of airway cells. Cysteinyl leukotrienes and leukotriene B₄ interact with different receptors.

Several lines of evidence indicate that leukotrienes play an important role in asthma.⁶

- Leukotrienes stimulate airway smooth muscle contraction, mucosal edema, mucus secretion, and chemotactic activity for a variety of cells, including eosinophils and neu-

trophils. All of these features are important in asthma.

- Giving aerosolized leukotrienes can produce the typical physiologic and symptomatic changes characteristic of asthma.

- Leukotriene antagonists inhibit asthmatic responses to a variety of stimuli, including allergens, exercise, aspirin, and cold, dry air.

- Recent placebo-controlled clinical trials^{7,8} show that leukotriene blockade has beneficial effects on chronic, spontaneously occurring asthma (ie, without experimental provocation or challenge) in both adults and children.

Several issues remain poorly understood, however. Asthma has a variety of triggers, and it varies in its clinical expression in adults and children. In any patient, we do not know how much of the inflammation of asthma is due to leukotrienes and how much is due to other factors. Therefore, short of an empiric trial, there is no way to know which patients will respond well to antileukotriene drugs. We also do not know whether antileukotriene drugs merely lessen the symptoms of asthma, or if they fundamentally affect critical aspects of airway inflammation and forestall long-term airway damage or airway remodeling.

■ ANTILEUKOTRIENES CLASSIFIED BY ACTION

Three antileukotriene agents have been approved in the United States for maintenance therapy of persistent asthma: zileuton, zafirlukast, and montelukast. These agents have different mechanisms of action: zileuton blocks a critical step in leukotriene production, whereas zafirlukast and montelukast prevent leukotrienes from binding to their receptors (FIGURE 1). It is still not known which is the better strategy for asthma therapy.

The following sections review the clinical experience with these agents. TABLE 1 compares various characteristics of the three antileukotrienes.

■ ZILEUTON

Zileuton is approved for use as 600-mg tablets four times a day. It can be taken with food.

**Inhaled
steroids remain
the gold
standard of
asthma
management**

■ How antileukotriene drugs treat asthma

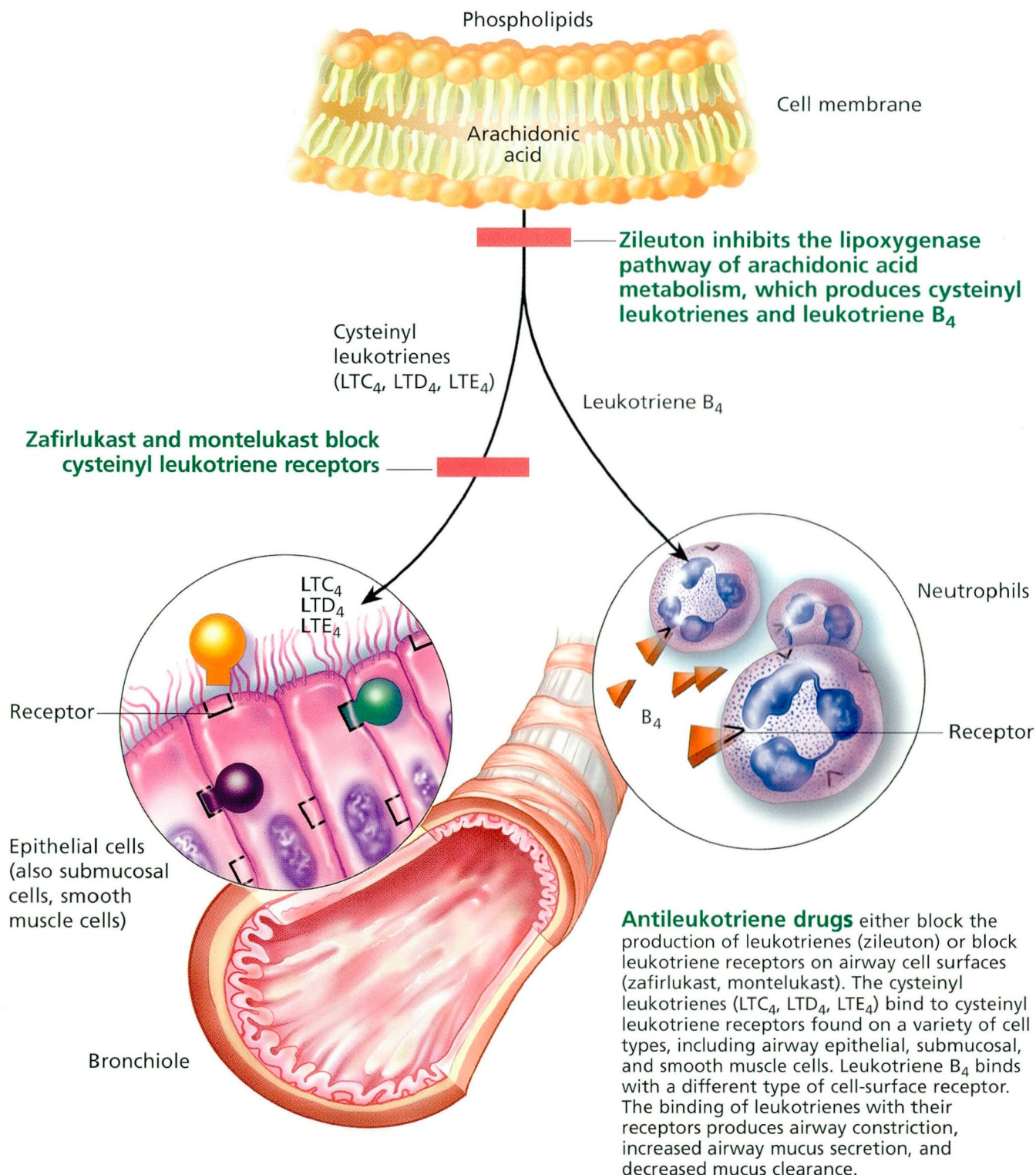


FIGURE 1

Clinical trials

A 4-week trial of zileuton⁷ was conducted in 139 patients with mild to moderate asthma, defined as a forced expiratory volume in 1 second (FEV₁) of 40% to 70%. The patients were not taking inhaled or oral corticosteroids. They were randomized to take zileuton 600 mg four times a day, 800 mg twice a day, or placebo. Zileuton produced a 14.6% increase in FEV₁ within 1 hour of administration ($P < .001$) compared to placebo and a 13.4% increase after 4 weeks ($P = .02$). Airway function and symptom improvement was greater in the group taking the higher (2.4-g) daily dose.

In another study,⁸ 401 patients with mild to moderate asthma were randomized to receive zileuton 600 mg, 400 mg, or placebo four times a day for 13 weeks. Those in the 600-mg group experienced significantly fewer exacerbations requiring oral steroids (6.1% vs 15.6%, $P = .02$). The average FEV₁ improved 15.7% in the 600-mg group vs 7.7% in the placebo group ($P = .006$).

Liver function abnormalities (alanine aminotransferase levels more than three times normal) occurred in 5 patients in the 600-mg group, 3 in the 400-mg group, and none in the placebo group. Alanine aminotransferase abnormalities reversed after drug withdrawal.

Comments

Taken together, these two studies suggest that zileuton has modest objective benefit compared to placebo for patients with mild to moderate asthma. They also show a 5% incidence of reversible hepatic aminotransferase abnormalities, with levels up to more than three times the upper limit of the reference range. Baseline alanine aminotransferase measurement and follow-up monitoring approximately seven times during the first year of therapy are recommended. Many patients with elevated alanine aminotransferase levels may continue to take zileuton, provided they have no symptoms of hepatitis, and provided liver function tests do not increase progressively.

Drug interactions. Zileuton interacts with several commonly used medications. In patients taking warfarin, it can significantly increase the prothrombin time. In addition, it

can cause a doubling of theophylline serum levels and increase the beta-blocking action of propranolol.

■ ZAFIRLUKAST

Zafirlukast, a selective, competitive antagonist of cysteinyl leukotriene receptors, is given orally, 20 mg twice a day, and is well absorbed (TABLE 1). It should be given on an empty stomach; otherwise, drug levels may be reduced by 40%.

Clinical trials

Three US double-blind, randomized, placebo-controlled studies⁹ of zafirlukast were performed in 1,380 patients with mild to moderate asthma over 6 to 13 weeks. A 13-week, controlled trial of mild to moderate asthma compared the effectiveness of zafirlukast 20 mg twice daily ($n = 103$) vs placebo ($n = 43$) in patients who took inhaled beta-agonists as needed.¹⁰ Zafirlukast therapy was more effective by a variety of clinical and economic parameters, even though FEV₁ did not improve significantly. The zafirlukast group had 89% more days without symptoms (7.0 vs 3.7 days per month, $P = .03$), 89% more days without the use of inhaled beta-agonist rescue (11.3 vs 6.0 days per month, $P = .001$), 55% fewer health care visits (18.5 vs 40.7 per 100 per month, $P = .007$), and 55% fewer days of absence from work or school (15.6 vs 35 per 100 per month, $P = .04$).

Comments

At the currently recommended dose, the risk of liver function abnormalities appears to be quite low, and routine monitoring is unnecessary. However, isolated cases of liver function abnormalities have been reported. These abnormalities become more prominent at higher-than-recommended doses (eg, 80 mg per day).

Churg-Strauss syndrome. A recent study¹¹ described 8 patients with steroid-dependent asthma who developed Churg-Strauss vasculitis syndrome (allergic granulomatosis angiitis) while taking zafirlukast. All but one of these patients were receiving systemic corticosteroids, and this syndrome occurred with tapering or discontinuation of steroid therapy. As of January 1998, there were 14 confirmed cases of Churg-Strauss syndrome associated with zafirlukast therapy. In addi-

**TABLE 1****Comparison of approved antileukotrienes**

	ZILEUTON (ZYFLO)	ZAFIRLUKAST (ACCOLATE)	MONTELUKAST (SINGULAIR)
Age	12 years and over	12 years and over	6 years and over
Usual dose	600 mg four times daily	20 mg twice daily	Adults: 10 mg at bedtime Children: 5-mg chewable tablet once daily
Mechanism	Inhibits leukotriene production by inhibiting 5-lipoxygenase	Blocks leukotriene D ₄ receptors	Blocks cysteinyl leukotriene subtype 1 and leukotriene D ₄ receptors
Metabolism	Liver, P-450 system	Liver, P-450 system	Liver, P-450 system
Warnings	Increases liver enzymes; monitor liver enzymes seven times during first year of therapy	May be associated with Churg-Strauss syndrome ^{11,12}	None
Dosing considerations	None	Take on an empty stomach; food decreases absorption by 40%	None
Drug interactions	Increases action of: Warfarin Theophylline Propranolol	Increases action of: Warfarin Phenytoin Carbamazepine	None
Average wholesale price*	\$74.99 per month	\$55.86 per month	\$66.96 per month

*According to Redbook 1998, Medical Economics Co

The exact role of antileukotrienes in long-term treatment of asthma is unknown

tion, 26 other asthma patients taking zafirlukast developed systemic eosinophilia (personal communication, American Thoracic Society Annual Meeting, April 1998). Whether this complication is related to zafirlukast (either as an idiosyncratic drug reaction or by cysteinyl leukotriene receptor blockade) or to tapering of systemic steroids and unmasking a forme fruste of Churg-Strauss syndrome remains unknown.¹²

Drug interactions. Zafirlukast may significantly increase the prothrombin time in patients taking warfarin. In addition, care should be taken with concomitant therapy with phenytoin, carbamazepine, and erythromycin, among others.

■ MONTELUKAST

Montelukast, a potent antagonist of cysteinyl leukotriene subtype 1 receptors and leukotriene D₄ receptors, has advantages over zafirlukast or zileuton (TABLE 1), in terms of ease of dosing and absence of significant drug interactions. Dosing is once a day, and food does not significantly affect absorption.

Clinical trials

Several studies indicate that montelukast 10 mg given once daily at bedtime significantly improves symptoms in chronic mild to moderate asthma when compared to placebo. A 3-month double-blind parallel group study¹³

(N = 681 with FEV₁ 50% to 80%) showed significant improvement in the montelukast group: FEV₁ increased by 13.1%, asthma exacerbation decreased by 31%, and symptom-free days increased by 37%.

Another randomized trial¹⁴ in 226 adults with moderate to severe asthma showed that montelukast 10 mg allowed significant tapering of inhaled steroids in patients requiring moderate to high doses.

A 4-week, controlled trial¹⁵ involving 80 adults with aspirin-induced asthma showed that montelukast 10 mg given at bedtime significantly improved asthma control.

An 8-week randomized, double-blind study was completed in children (ages 6 to 14 years) with mild to moderate asthma (FEV₁ 50% to 80%).¹⁶ The mean morning FEV₁ increased from 1.85 L to 2.01 L (8.23%) in the montelukast group and from 1.85 L to 1.93 L (3.58%) in the placebo group ($P < .001$). Secondary parameters—eg, the use of beta-agonists for exacerbation of asthma symptoms, the percentage of days with an exacerbation, and the percentage of patients with an exacerbation—also improved significantly in the montelukast group.

Antileukotrienes may be particularly beneficial in aspirin-induced asthma

Comments

Early experience shows montelukast has an excellent safety profile with no significant effect on liver function tests.^{13,14,16} Alanine aminotransferase levels were elevated in 2.5% of patients taking montelukast and in 1.5% of those in the placebo group, but this difference was not statistically significant. Elevation of other liver enzymes occurred rarely in both the placebo and montelukast groups. The 5-mg chewable tablets have been shown to be safe and effective in young patients with asthma (ages 6 to 14).¹⁶

No significant drug interactions have been noted in patients using montelukast.

■ WHAT ROLE FOR ANTILEUKOTRIENES?

The exact role of antileukotrienes in long-term maintenance therapy for asthma is yet to be established. The National Asthma Education Prevention Program Expert Panel Report-2 indicates a possible role for these agents in the initial therapy of mild persistent

asthma as an alternative to inhaled corticosteroids (or cromolyn or nedocromil).¹

The report also indicates a possible role for antileukotrienes as an adjunct to inhaled corticosteroid therapy for control of symptoms at any level of severity in patients with persistent asthma. They affect the early and delayed asthma response and therefore act as a bronchodilator within 1 to 3 hours after administration and as a chronic “controller agent” starting at 2 to 4 weeks. These agents should not be used for relief of acute symptoms, since beta-agonists are effective and have a much more rapid onset of action.

Comparison of antileukotrienes and inhaled corticosteroids

No published studies have directly compared inhaled steroids and antileukotrienes. However, TABLE 2 offers a cursory comparison of the clinical properties of inhaled steroids and antileukotrienes based on data from various studies.^{17–22} Inhaled steroids likely are more potent than antileukotrienes, especially in patients with moderate to severe disease.

Noncompliance. A major cause for poor outcome of asthma treatment is patient non-compliance with prescribed inhaled steroid therapy.^{2,3,18} Once-daily or twice-daily oral therapy with an antileukotriene offers a significant advantage in terms of compliance. In addition, montelukast in a 5-mg chewable tablet form represents a significant advance for asthmatic children ages 6 to 14.

Other considerations. The antileukotrienes help reduce the need for inhaled beta-agonists and inhaled corticosteroids, thereby minimizing well-known side effects. In addition, some patients appear to respond much more dramatically to antileukotrienes than other patients do, usually within the first 30 days. If there is no response within 1 to 3 months, it is reasonable to stop these agents. However, whether there are “responders” and “non-responders” to antileukotriene therapy is not known.

Antileukotrienes may be particularly beneficial in the small subset of adults with aspirin-induced asthma.¹⁵ They may also have benefit in patients with exercise-induced asthma, a condition in which leukotrienes are thought to be important mediators.^{23,24}



TABLE 2

Comparison of clinical properties of inhaled steroids and antileukotrienes

	INHALED STEROIDS	ANTILEUKOTRIENES
Availability	Since 1970s	1997–1998
Dosing considerations	Patient must learn complex techniques (metered dose inhalers, spacers)	Oral therapy, once or twice a day
Acute or subacute response	None	Moderate, onset 1 to 2 hours, 5% to 10% increase in FEV ₁
Chronic response	15% to 25% increase in FEV ₁	10% to 14% increase in FEV ₁
Effect on airway hyperresponsiveness	Moderate ^{19*}	Moderate ²⁰
Anti-inflammatory effect	Nonspecific; well established ²¹	Very specific; data are limited
Safety	Topical and systemic side effects, dependent on dose, duration, use of spacer, mouth rinsing, susceptibility ³	Generally safe, liver enzyme elevations (zileuton), association with Churg-Strauss syndrome (?) (zafirlukast)
Reduction in need for oral steroids in severe asthma	Definite ^{22,23}	Probable ¹⁵

*Nonspecific airway hyperresponsiveness as assessed by methacholine or histamine bronchoprovocation

Current recommendations

For patients in whom inhaled steroids produce toxicity (eg, those requiring high doses of inhaled corticosteroids, children, postmenopausal women), antileukotrienes seem a reasonable alternative.

For patients whose symptoms continue despite high doses of inhaled corticosteroids, addition of an antileukotriene, salmeterol, cromolyn sodium, a methylxanthine,²⁵ or

nedocromil sodium also seems reasonable.

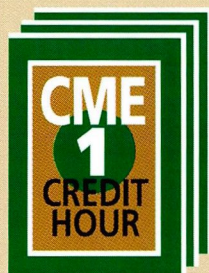
The future

Further data are required for both inhaled steroids and antileukotrienes as to their long-term effects on airway remodeling and systemic toxicity. Additional studies directly comparing inhaled corticosteroids and antileukotrienes for newly diagnosed bronchial asthma are underway.



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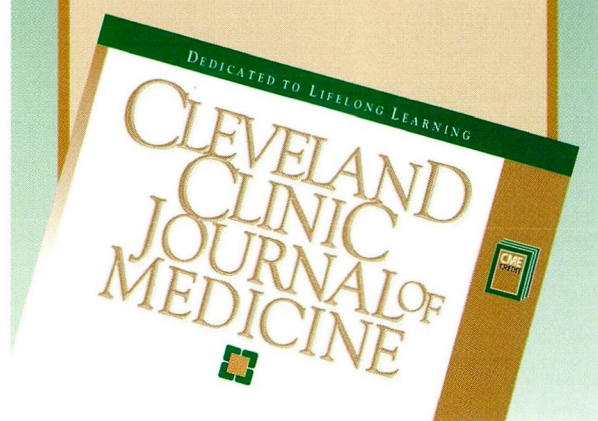
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