Anti-inflammatory treatment after discharge home from the emergency department in adults with acute asthma

Jerry A. Krishnan, MD, PhD,[a] Richard Nowak, MD, MBA,[b] Steven Q. Davis, MD,[c] and Michael Schatz, MD, MS[d]

Chicago, Ill, Detroit, Mich, Fort Worth, Tex, and San Diego, Calif

Key words: *Asthma exacerbation, acute asthma, emergency department, discharge medications, corticosteroids, leukotriene modifiers*

Airway inflammation from respiratory infections or exposure to allergens, irritants, or both leads to increased airflow obstruction and respiratory symptoms in patients with acute asthma. Anti-inflammatory therapy with systemic corticosteroids (CSs) is therefore a cornerstone of the management of patients with acute asthma, particularly those presenting to the emergency department (ED).[1,2] After initial management in the ED, most patients improve sufficiently to be discharged home with instructions to complete a short course of daily oral corticosteroids (OCSs) and short-acting inhaled bronchodilators as needed for symptom relief. Unfortunately, up to one third of patients who initially respond to therapy relapse within the first 3 to 4 weeks after ED discharge (eg, require treatment escalation, urgent care or ED visits, or hospitalizations for asthma).[3,4] The propensity of many patients to relapse after ED discharge has led to a number of randomized clinical trials evaluating alternative outpatient anti-inflammatory treatment strategies in this population, including the use of inhaled corticosteroids (ICSs), intramuscular corticosteroids (IMCSs), and non-corticosteroid anti-inflammatory regimens.

The objective of this systematic review is to synthesize the results of randomized clinical trials in adults with acute asthma, comparing alternative outpatient anti-inflammatory treatment strategies to reduce the risk of relapse after discharge home from the ED. More specifically, this systematic review examined the following anti-inflammatory treatment options in adults after ED discharge: (1) IMCSs versus OCSs, (2) ICSs versus OCSs, (3) combination of ICSs plus OCSs versus OCSs alone, and (4) noncorticosteroid anti-inflammatory agents (macrolide antibiotics and leukotriene modifiers) in addition to systemic corticosteroids. This report updates previously published systematic reviews in acute asthma[5-7] with subsequently published studies and provides a single document summarizing this body of literature for easy use by clinicians.

Abbreviations used
ED: Emergency department
ICS: Inhaled corticosteroid
IMCS: Intramuscular corticosteroid
OCS: Oral corticosteroid
RCT: Randomized clinical trial

METHODS

The following key words and combinations were used for the search: asthma exacerbation + discharge + medication; acute asthma + discharge medication; asthma + emergency department + discharge medication; asthma + emergency + department + adherence; and severe + asthma + adherence + emergency + department.

Additional details of the methodology for all literature reviews in this supplement are provided in the introduction to this supplement.[8] The task force specified the level of evidence used to justify the recommendations being made, and the system used to describe the level of evidence is also defined in the introduction to this supplement.

RESULTS

The literature search identified 37 clinical randomized controlled trials (RCTs) and 5 meta-analyses potentially relevant to the study questions. After excluding noneligible studies, 5 RCTs were identified comparing IMCSs with OCSs; 1 meta-analysis of 7 trials comparing ICSs with OCSs, 2 of which were specifically in adults; 1 meta-analysis of 3 trials comparing ICSs plus OCSs versus OCSs alone; and 2 RCTs of noncorticosteroid anti-inflammatory agents.

IMCSs versus OCS

There are 5 randomized, placebo-controlled clinical trials comparing IMCSs with OCSs in a total of 599 adults with acute asthma (Table I).[4,9-12] All 5 trials used a double-dummy design (IMCS plus oral placebo vs intramuscular placebo plus OCS) to keep patients and investigators masked to treatment assignment. These studies compared a single dose of various formulations of IMCSs with a 5- to 8-day course of OCSs and assessed outcomes

From [a]the Asthma and COPD Center, Department of Medicine, and Department of Health Studies, University of Chicago; [b]the Department of Emergency Medicine, Henry Ford Health System, Detroit; [c]Texas Pulmonary & Critical Care Consultants, PA, Fort Worth; and [d]the Department of Allergy, Kaiser Permanente Medical Center, San Diego.

Disclosure of potential conflict of interest: J. A. Krishnan has declared that he has no conflict of interest. R. Nowak has declared that he has no conflict of interest. S. Q. Davis has declared that he has no conflict of interest. M. Schatz has been a consultant for GlaxoSmithKline and has received research support from Aerocrine, Genentech, GlaxoSmithKline and Merck.

This article is part of the Joint Task Force Report: Supplemental Recommendations for the Management and Follow-up of Asthma Exacerbations, an official statement of the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American Academy of Emergency Medicine (AAEM), and the American Thoracic Society (ATS). It was approved by the AAAAI Board of Directors, January 16, 2008, the AAEM Board of Directors, January 14, 2008, and the ATS Board of Directors, March 13, 2009.

The Joint Task Force Report is copublished in the *Journal of Allergy and Clinical Immunology*, the *Journal of Emergency Medicine*, and the *Proceedings of the American Thoracic Society*.

Reprint requests: Jerry A. Krishnan, MD, PhD, Associate Professor of Medicine and Epidemiology, Director, Asthma and COPD Center, Section of Pulmonary & Critical Care Medicine, University of Chicago, 5841 S. Maryland Ave, MC 6076, Room M644, Chicago, IL 60637. E-mail: jkrishna@medicine.bsd.uchicago.edu.

J Allergy Clin Immunol 2009;124:S29-34.
0091-6749/$36.00

doi:10.1016/j.jaci.2009.05.007

TABLE I. Randomized clinical trials comparing IMCSs with OCSs after ED discharge (total n = 599 participants)

Reference	Study design*	Treatment groups†	Country	Age (y)	No. (%)‡	Follow-up (d)§	Relapse (%)‖
Hoffman and Fiel, 1988[9]	RCT, double-dummy	Methylprednisolone sodium acetate, 80 mg IM, vs methylprednisolone, 32 mg BID PO with an 8-day taper	United States	15–55	16/18 (89)	5-7	20.0% vs 0%, P = NS
Lee et al, 1992[10]	RCT, double-dummy	Dexamethasone, 10 mg IM, vs dexamethasone, 1.5 mg BID PO with an 8-day taper, vs double placebo (IM and PO)	Taiwan	16–60	52/52 (100)	7	5.9% vs 6.2%, P = NS
Shuckman et al, 1998[11]	RCT, double-dummy	Triamcinolone diacetate, 40 mg IM, vs prednisone, 40 mg/d PO × 5 days	United States	18–50	154/168 (92)	7	9.0% vs 14.5%, P = NS
Chan et al, 2001[4]	RCT, double-dummy	Betamethasone sodium phosphate, 6 mg, + betamethasone acetate, 6 mg IM, vs prednisone, 50 mg/d PO × 7 days	Canada	>18	159/171 (93)	21	36.8% vs 31.0%, P = NS
Lahn et al, 2004[12]	RCT, double-dummy	Methylprednisolone acetate, 160 mg IM, vs methylprednisolone, 32 mg PO with an 8-day taper	United States	18–45	180/190 (95)	21	18.5% vs 22.7%, P = NS

IM, Intramuscularly; *BID*, twice daily; *PO*, by mouth; *NS*, not significant.
*Double-dummy refers to use of a placebo in both treatment groups.
†Corticosteroid treatment groups.
‡Study completion rate: numbers (percentages) of participants who completed versus enrolled in the study are shown.
§Follow-up period during which outcomes were compared between treatment groups.
‖Relapse during the follow-up period in the IMCS versus OCS groups, as defined in individual studies (eg, need for treatment intensification, ED visit, or hospitalization).

over a 5- to 21-day period. Rates of study completion were high, ranging from 89% to 100%. Overall, there were no significant differences in symptoms, lung function parameters, or rates of relapse between the 2 treatment groups. Some studies, however, reported a higher rate of complications at the injection sites (eg, pain or bruising) in patients who received IMCSs. For example, in the study by Lahn et al,[12] mean pain scores (3.3/10 vs 1.9/10, $P < .05$) and rates of bruising (8% vs 0%, $P < .05$) were significantly higher in the IMCS group compared with those in the OCS group at the follow-up visit. Taken together, these studies suggest that IMCSs represent a similarly effective regimen in preventing relapse after ED discharge compared with several days' therapy with OCSs.

ICSs versus OCSs

For more information, see Table II.[13,14] A meta-analysis by Edmonds et al[7] evaluated the results of 7 trials comparing ICSs with OCSs in patients with acute asthma. In this meta-analysis 4 trials focused on pediatric populations and 1 study focused on patients presenting to their primary care physicians' offices. The remaining 2 trials, in a total of 269 adults, compared high-dose ICSs with OCSs for 7 to 10 days, using a double-dummy design, in adults with acute asthma discharged from the ED after initial therapy.[13,14] Rates of study completion were high (96%[13] and 89%[14]), and there were no significant differences in relapse or other outcomes, including need for rescue medications, improvements in lung function, asthma symptoms, and quality of life. The low relapse rates in the control groups (7% at 7 days[13] and 12% at 10 days[14]), together with lung function measurements on ED discharge (FEV_1 of 64% of predicted value[13] and peak expiratory flow of 407 L/min[14]), suggest that participants in this study had mild or moderate forms of acute asthma. There were also no significant differences in outcomes when analysis included all patients (adults and children) across the 7 trials.[7]

Combination of ICSs plus OCSs versus OCSs alone

For more information, see Table III.[15-17] Edmonds et al[5] performed a meta-analysis of 3 trials (total n = 912 adults) that investigated the efficacy of combining ICSs and OCSs versus use of OCSs alone in patients discharged from the ED after initial treatment for acute asthma.[15-17] Only 2 of these studies have been published.[15,16] Moderate-to-high doses of ICSs combined with 5- to 7-day courses of oral prednisone at 40 to 50 mg/d were compared with oral prednisone alone, and outcomes were assessed up to 20 to 24 days after ED discharge. The study by Rowe et al,[15] which had the highest follow-up rate (97%) and the highest overall relapse rate (19%) of all 3 studies, reported a significant reduction in the risk of relapse in patients assigned combination therapy versus an OCS alone (12.8% vs 24.5%, $P = .049$). In contrast, no significant differences in relapse rates by treatment group were reported in the other 2 studies. When data were pooled across all 3 studies, there was a nonsignificant trend toward a reduction in relapse rates with combination therapy (odds ratio for relapse with combination