The Effect of Anti-Leukotrienes vs Inhaled Corticosteroids as Monotherapy in Children and Adolescents with Mild-Moderate Persistent Asthma: A Systematic Review and Meta-Analysis

Katherine M. Kovacs, SPH-UMDNJ
Outcomes Research – May 2013

ABSTRACT

PURPOSE: Inhaled corticosteroids (ICDs) are currently the preferred monotherapy for the treatment of mild-moderate persistent asthma in children and adolescents. However, a 2003 systematic review concluded that ICDS are more effective than anti-leukotrienes in adults, but found insufficient evidence to conclude on the efficacy of anti-leukotrienes in children.[1] In addition, because ICDs pose potential safety and compliance issues, it is important to understand the efficacy benefits relative to oral anti-leukotriene agents. This meta-analysis examined relevant randomized clinical trials (RCTs) assessing the efficacy of anti-leukotrienes vs ICDs to provide better insight into the direction and magnitude of treatment effects in a pediatric population.

OBJECTIVE: To determine the efficacy of oral anti-leukotriene agents vs inhaled corticosteroids (ICDs) as monotherapy in the management of mild/moderate persistent asthma in children and adolescents. The outcome of interest was the number of pediatric patients with at least one exacerbation requiring treatment with a systemic steroid, a proxy of severity and emergency care resource utilization.

METHODS: Randomized controlled trials (RCTs) were identified from an extensive literature search. Studies were selected that included patients between the ages of 2 and 14 with mild or moderate persistent asthma who were treated with either an anti-leukotriene or an ICD as monotherapy for a minimum of four weeks. A total of six (6) RCTs met inclusion criteria were identified that randomized a total of 2,848 pediatric patients to either an anti-leukotriene or ICD. Meta-analysis using a fixed effects model was undertaken to estimate the odds ratio. A subgroup analysis examining difference in outcome by length of trial (i.e. less than or greater than 6 months) was also performed.

RESULTS: The odds of a child/adolescent requiring at least one course of systemic steroids due to an acute asthma exacerbation is 1.55 times higher in those treated with an anti-leukotriene vs an ICD [OR 1.55 (95% CI 1.32-1.82)]. This is both a statistically and clinically important finding. A subgroup analysis suggests the odds with anti-leukotriene reach significance after 6 months of treatment.

CONCLUSION: This study adds to the body of evidence supporting ICDs as the cornerstone of pediatric asthma management. The subgroup analysis suggests that theoretically higher compliance rates with oral agents do not necessarily confer a meaningful efficacy advantage to the anti-leukotriene class. Additional research on the impact of ICDs on growth rates and long-term effectiveness should be assessed via observational studies to better understand the risk and benefits of the ICDs relative to oral agents.

INTRODUCTION AND BACKGROUND

Asthma is a chronic, inflammatory lung condition that impairs an individual's ability to breathe properly and derives from the Greek word, *aazein*, meaning to pant or exhale with an open mouth.[2] The classic symptoms of asthma are wheezing, coughing, and dyspnea (i.e. shortness of breath). It is a complex, heterogeneous disease process characterized by inflammation of the bronchial airways.[3]

A serious condition in adults, asthma is even more problematic for children. Children with asthma present challenges not seen in adults because of maturing respiratory and immune systems, difficulty in diagnosis, scarcity of good evidence, and a diverse and frequently unpredictable treatment response.[4]

Asthma is an increasingly common pediatric condition. It the third major cause of hospitalizations in children under 15 years of age.[2] According to the most recent estimates from the 2011 National Health Institute Survey, over 10 million children in the US have ever been diagnosed with asthma (14%). Asthma is disproportionately higher in black and multiracial children, with prevalence rates of about 20%.

There are a number of pharmaceutical classes recommended for the treatment of mild-moderate persistent asthma in children and adolescents. The 2007 NHLBI Expert Panel Guidelines for the treatment of Asthma recommend a step approach for pediatric asthma management, starting with short-acting beta2-agonist for intermittent, moving to a low-dose inhaled corticosteroid (ICD) for persistent asthma. ICDs belong to a class of steroid hormones that are part of the feedback mechanism in the immune system that regulates inflammation. If control with an ICD is insufficient, then an anti-leukotriene, long-acting beta2-agonist or theophylline may be considered.

While inhaled glucocorticoid steroids are effective in improving lung function and symptoms with fewer side effects than steroids administered systemically, they pose a number of potential side effects in children. The main concern with ICDs in children are with regard to the hypothalamic-pituitary-adrenal axis, growth and bone metabolism and density, including a potentially increased risk of osteoporosis.[5] In children with very mild asthma, there may even be an effect on growth with doses of ICDs as low as 400 ug/day of beclamethosone diproprionate or equivalent.[5,6]

Compliance with ICDS can be problematic and potentially interfere with compliance. Young children, in particular, often experience delivery and technique problems with both pressurized metered-dose inhalers and dry powder inhalers, even when supervised by an adult. [5] As a result, children can fail to respond to inhaled corticosteroid therapy due to lack of compliance with inhalations. Therefore, it is possible that ICDs, may be associated with reduced effectiveness over time due to issues related to inhaler compliance. There are studies to suggest that oral treatments, such as montelukast, may be associated with better adherence. [7]

Anti-leukotrienes, including montelukast (Singulair), are administered orally and offer a potential significant advantage over inhaled medications in the pediatric population.[8] First introduced in 1996, anti-leukotrienes were the first new class of asthma medication in two decades. Leukotrienes are inflammatory mediators whose effects on asthma include bronchoconstriction, increased vascular permeability, and increased mucus production. In chronic asthma, regular use of anti-leukotrienes has shown significant improvement in pulmonary function and clinical symptoms. [9]

If oral anti-leukotrienes improve compliance, they also offer the potential for greater effectiveness. While the theoretical benefits of improved compliance and corticosteroid-sparing effects of leukotriene inhibitors are appealing, they have not been consistently demonstrated. [8]

A Cochrane systematic review of asthma in adults and children conducted in 2000 tentatively concluded that control of asthma was better in patients treated with inhaled glucocorticoids as single agents than with anti-leukotrines.[1] A systemic review of randomized controlled trials comparing anti-leukotrienes with inhaled glucocorticoids published in 2003 concluded that inhaled glucocorticoids are more effective than leukotriene receptor antagonists in the treatment of adults with mild or moderate asthma. [1] However, there was insufficient evidence to conclude on the efficacy of anti-leukotrienes in children.

SPECIFIC HYPOTHESES: While there is a strong body of evidence on the efficacy of inhaled corticosteroids in adults with mild and moderate asthma, there is less data to confirm this finding in children.

This meta-analysis was undertaken to answer two primary questions: 1) based on RCT evidence, is there a difference in efficacy between anti-leukotrienes and ICDs and 2) Does the efficacy differential between anti-leukotrienes and ICDSs change over time?

The outcome of interest is the number of pediatric subjects requiring at least one course of systemic steroids during the study period. Systemic steroids are given for severe acute exacerbations or in mild-moderate acute exacerbations if inhaled short-acting $beta_2$ agonists are insufficient. Asthma exacerbations are of critical importance as they are associated with high morbidity, including emergency visits, hospitalizations, and occasional mortality.[4] The administration of systemic steroid within one hour of emergency department presentation decreases the need for hospitalization.[10] Therefore, acute exacerbations requiring systemic steroids provide a surrogate for emergency treatment. Although there was interest in exploring hospitalizations as an outcome, only three (3) pediatric RCTS with this endpoint including anti-leukotrienes and ICDs were identified; therefore, the number of subject requiring systemic steroids was selected as an alternative to enhance the power of the analysis and precision of the meta-analysis by expanding the number of studies to six (6).

METHODS:

SEARCH STRATEGY

Studies were identified using electronic searches of Ovid/Medline, Pubmed, and the Cochrane Library.

Search terms included the following:

(((((asthma) AND children) AND (leukotriene* OR lukast*)) AND ("inhaled corticoid*" OR "inhaled glucocorticoid*" OR corticosteroid OR flucatisone OR budoneside OR triamcinolone)) AND (randomized OR RCT)) AND (mild OR moderate))))

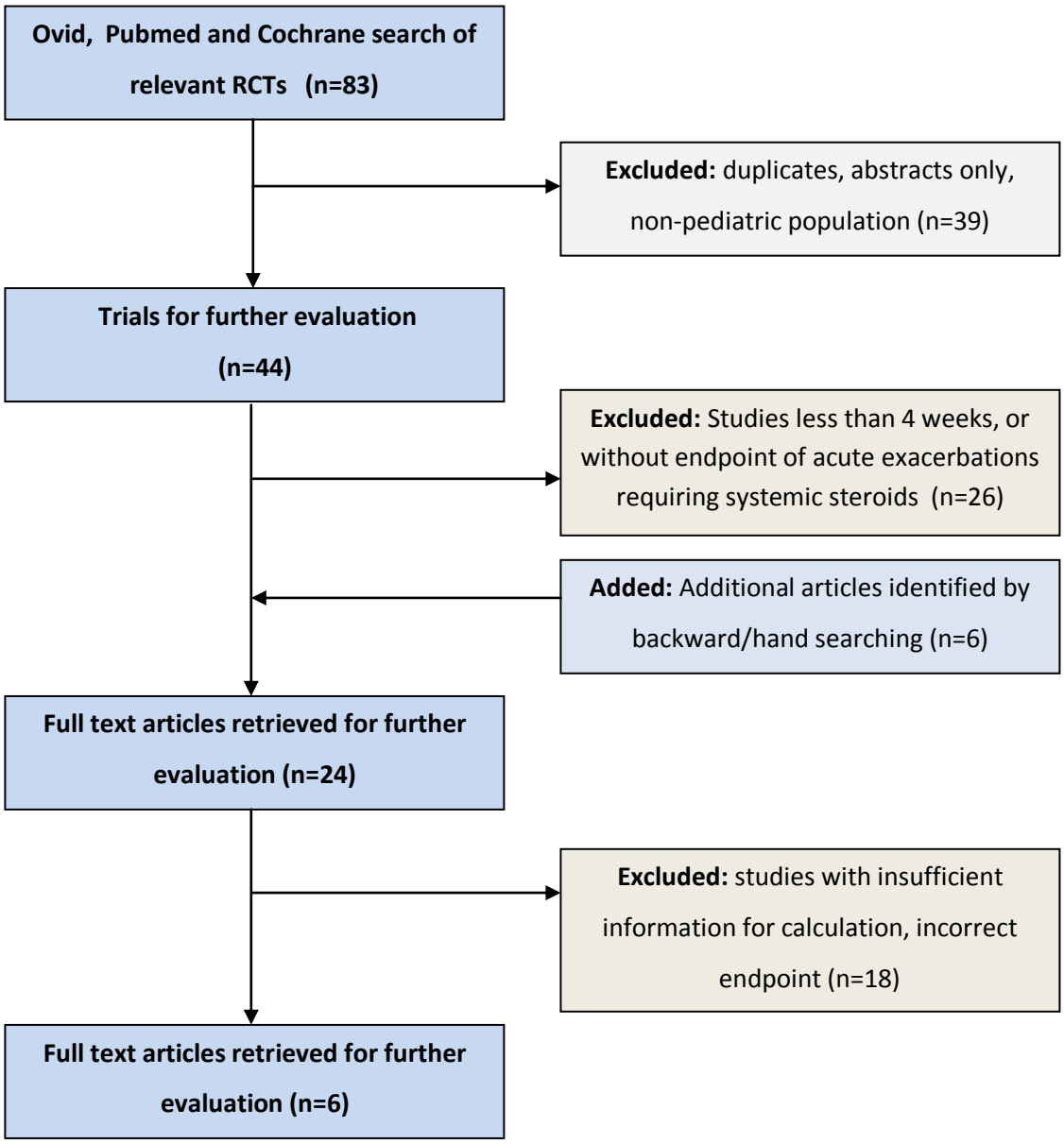

Figure 1. Literature search strategy – Flow Diagram for Study Selection Process

ELIGIBILITY AND DATA ABSTRACTION

Randomized controlled trials (RCTs) in which pediatric patients were randomized to an anti-leukotriene and an ICD were the basis of the analysis. Inclusion criteria included:

- English language
- Full text availability
- Study published between January 2000 and April 2013
- Pediatric subjects between the ages of 2 and 14
- A minimum intervention period of four weeks
- A minimum of two treatment arms that included an anti-leukotriene agent and an inhaled corticosteroid

CALCULATIONS AND STATISTICAL ANALYSIS: The unit of analysis was the number of patients requiring at least one course of systemic steroids for an acute asthma exacerbation. Thus, the statistical analysis was used methods appropriate for a dichotomous outcome. The trial version of Comprehensive Meta-Analysis V2 software was used for the meta-analysis calculations (Biostat, Englewood NJ). The effects of anti-leukotrienes and ICDs were assessed using both fixed effects and random effects modeling. Subgroup analyses were planned a priori, specifically study length (≤ 24 weeks, >24 weeks). Heterogeneity between studies was tested using Cochrane's Q value. To assess publication bias, a funnel plot was constructed and visually examined. A fail-safe N test was also used for bias assessment. Sensitivity analysis was performed by assessing the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the combined OR for the remained studies.[11]

RESULTS:

SEARCH RESULTS:

The six (6) RCTs brought forwarded for the meta-analysis are described in Table 1. .

				LTRAs (montelukast)			ICDs		
Study Name	Length of Follow-up	Sub-group	Subject Age	Dosing	# of patients	N	Dosing*	# of patients	N
Maspero 2001	24 weeks	24 weeks or less	6-11	5 mg Qd	11	83	150 µg	7	41
Garcia 2005	52 weeks	> 24 weeks	5-15	5 mg QD	86	482	200 µg	51	484
Ostrom 2005	12 weeks	24 weeks or less	6-12	5 mg QD	33	172	100 µg	25	170
Caffey 2005	4 weeks	24 weeks or less	6-12	5 mg QD	0.5	24	100 µg	0.5	24
Szefler 2007	12 weeks	24 weeks or less	2-8	4-5 mg QD	29	197	200 µg	21	196
	26 weeks	> 24 weeks			44	197		34	196
	52 weeks	> 24 weeks			63	197		50	196
Sorkness 2007	48 weeks	> 24 weeks	6-14	10 mg QD	15	95	100 µg	6	94
					282	1447		195	1401

* Dosing of ICD in beclomethasone equivalents as a method of standardization

Table 1: Study description

Note: As per the Cochrane Collaboration, where no events are observed in both groups of a study, there is no information about the relative probability of the event and the study should be omitted from the analysis. However, in Caffey 2005, although no events were observed in either the anti-leukotriene or the ICDs arms, one event was recorded in the placebo arm. For this reason, 0.5 was added the anti-leukotriene and ICD cells.

Study name	Subgroup within study	Time point	Statistics for each study				
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Maspero 2001	24 weeks or less	24 weeks	0.742	0.362	1.522	-0.814	0.416
Garcia 2005	More than 24 weeks	52 weeks	1.844	1.413	2.406	4.503	0.000
Ostrom 2005	24 weeks or less	12 weeks	1.377	0.919	2.062	1.552	0.121
Caffey 2005	24 weeks or less	4 weeks	1.000	0.061	16.463	0.000	1.000
Szefler 2007	24 weeks or less	12 weeks	1.438	0.939	2.203	1.671	0.095
Szefler 2007	More than 24 weeks	26 weeks	1.370	0.962	1.952	1.745	0.081
Sorkness 2007	More than 24 weeks	48 weeks	2.750	1.326	5.703	2.718	0.007
			1.547	1.314	1.820	5.247	0.000

Table 2: Study Summary

Maspero 2001[12] was a randomized, multicenter, open-label extension study including 124 children between 6-11 years of age with moderate asthma. The study was funded by Merck Frosst. Eligibility criteria included baseline FEV_1 predicted values (a measure of respiratory function) between 60-85%. A total of 83 children were randomized to montelukast, 5 mg QD and 41 children to an ICD (beclomethasone, 100 µg tid). Asthmatic children reported higher compliance on montelukast oral therapy vs inhaled beclomethasone, a statistically significant difference. At conclusion of the 6-month extension study, the investigators found that 11 patients on montelukast required at least one dose of an oral corticosteroid vs 7 patients on an ICD (Odd ratio [OR] .742 [95% CI, .362-1.522]).

Garcia 2005[13] enrolled 994 patients between the age 5-15 with a clinical history of mild asthma. Eligibility criteria included baseline FEV_1 of 80% of the predicted value. Four of six study authors were employees of Merck, manufacturers of Singulair (montelukast). A total of 495 children were randomized to an LTRA (montelukast 5 mg or 10 mg if the child turned 15 during the study) and 499 randomized to an ICD (fluticasone, 100 µg BID). Four (4) of (6) of the authors were employees of Merck, the manufacturer of montelukast. Outcomes were reported at 52 weeks. The study found that montelukast was associated with a significantly higher risk of a child experiencing an acute exacerbation requiring a systemic steroid ([OR] 1.844 [95% CI, 1.413-2.406]).

Ostrom 2005[14] included 342 patients between the age 6-12 with at least a 6-month history as chronic asthma. Study eligibility required a baseline FEV_1 between 60% to 80% of the predicted value. Five of the eight authors were employees of GlaxoSmithKline, manufacturers of Flonase (fluticasone). A total of 170 children were randomized to an LTRA (montelukast 5 mg QD) and 172 to an ICD (fluticasone, 50 μg BID). Outcomes were reported at 12 weeks. The study found that no statistically significant difference between montelukast and fluticasone in the outcome of interest ([OR] 1.377 [95% CI, .919-2.062]).

Caffey 2005[15] was a three-way crossover comparison of four (4) weeks each of therapy with an ICD (fluticasone), anti-leukotriene (montelukast) and placebo. Children 5-12 years old with a physician diagnosis of mild to moderate persistent asthma, clinically stable on only one long-term controller drug, and who were capable of performing spirometry were eligible. A total of 24 children were randomized to either an LTRA (montelukast 10 mg QD), an ICD (fluticasone, 50 μg BID), or placebo. The study found only one patient in the placebo arm requiring treatment with an oral systemic steroid, but none in the LTRA or ICD arm. Therefore, because events were equal to zero in the treatment arms, the odds ratio was not estimable but was entered into the model as a fraction to enhance power.

Szeffler 2007[16] was a parallel-group, randomized clinical trial including 395 patients between the 2 and 8 years of age with symptoms of mild, persistent asthma. Baseline predicted FEV_1% was not reported. A total of 198 children were randomized to an LTRA (montelukast 4 or 5 mg QD) and 197 to an ICD (budosenide, 0.5/mg equivalent to 50 μg BID of fluticasone). Outcomes were reported at 12, 26 and 52 weeks. The study found that no statistically significant difference between montelukast and budosenide at 12 weeks ([OR] 1.438 [95% CI, .939-2.203]) or at greater than 26 weeks ([combined OR] 1.37 [95% CI, .962-1.952]). All three time points were used in the meta-analysis to enhance power.

Sorkness 2007[17] enrolled 285 patients between the ages of 6 and 14 with mild and moderate persistent asthma in a parallel-group, randomized clinical trial to assess the effectiveness of three (3) regimens in achieving asthma control. Baseline predicted FEV_1% of 97-98% was reported. A total of 95 children were randomized to an LTRA (montelukast 10 QD) and 96 to an ICD (fluticasone, 100 μg BID). At 48 weeks, the study found that the montelukast arm resulted in a significantly higher number of exacerbations requiring systemic steroids ([OR] 2.75 [95% CI, 1.326-5.703]).

PUBLICATION BIAS: A funnel plot was used to assess publication bias due to the possibility that studies were selectively published and not representative. In the absence of publication bias, studies are expected to be symmetrically distributed across the combined effect size[11]. As shown below in Figure 2, in this analysis large studies cluster around the top of the graph near the log of the mean effect size, with smaller studies toward the bottom of the chart. Thus, a visual examination of the plot suggests little evidence of publication bias.

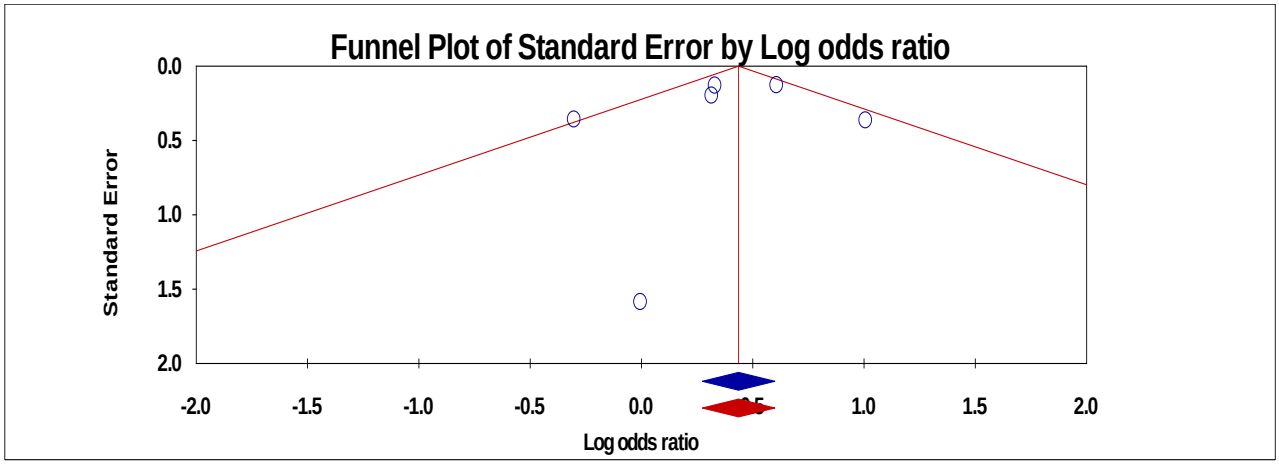

Figure 2: Funnel plot of precision and treatment effect

Fail-Safe N

Fail-Safe N is another method for helping assess the effect of non-published studies with non-significant effects due to the "file-drawer" problem. This method addresses this potential issue by estimating the number of non-significant studies required to nullify the combined treatment effect. In statistical terms, the fail-safe N addresses how many additional results would it take to reduce the overall result to non-significance given a significant result for an overall combined effect.[18]

Classic fail-safe N

Z-value for observed studies	4.23372
P-value for observed studies	0.00002
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	6.00000
Number of missing studies that would bring p-value to > alpha	22.00000

Table 3: Results of Fail=Safe N

The meta analysis incorporates data from 6 studies, yielding a z-value of 4.23372 and corresponding 2-tailed p-value of 0.00002 with a fail-safe N of 22. This means that we would need to locate and include 22 'null' studies in order for the combined 2-tailed p-value to exceed 0.050.[11] Or, said another way, there would be need to be 3.7 missing studies for every observed study for the effect to be nullified. [11] However, Fail-safe N assumes that the effect in the hidden studies is nil, rather than considering the possibility that some of the studies could have shown an effect in the reverse direction. Therefore, the number of studies required to nullify the effect may be smaller than 22.[11] In addition, as per the Cochrane Collaboration, " the estimate of fail-safe N is highly dependent on the mean intervention effect that is assumed for the unpublished studies (Lyengar 1988), and available methods lead to widely varying estimates of the number of additional studies (Becker 2005)".[19] As a result, the Fail-safe N should be used as a guideline only, rather than as a definitive test of bias.

FIXED VS RANDOM EFFECTS

Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared
Fixed	7	1.547	1.314	1.820	5.247	0.000	9.055	6	0.171	33.737
Random	7	1.506	1.207	1.879	3.626	0.000				

Table 4: Fixed vs Random Effects

Although the Q-statistic suggested a fixed effects model was appropriate, the studies were analyzed under a fixed and a random effects model to see how effect size varied. As per the Cochrane Collaboration, methods of fixed effect meta-analysis are based on the mathematical assumption that a single common (or 'fixed') effect underlies every study in the meta-analysis, while a random effects analysis assumes studies estimate different treatment effects. Table 4 shows treatment effects are similar under both fixed and random effect models, providing further evidence of study similarity. Thus , there is little evidence of heterogeneity and a fixed effects model was employed. In the fixed-effects model, individual study results are pooled using weights that are sample size dependent.

RESULTS

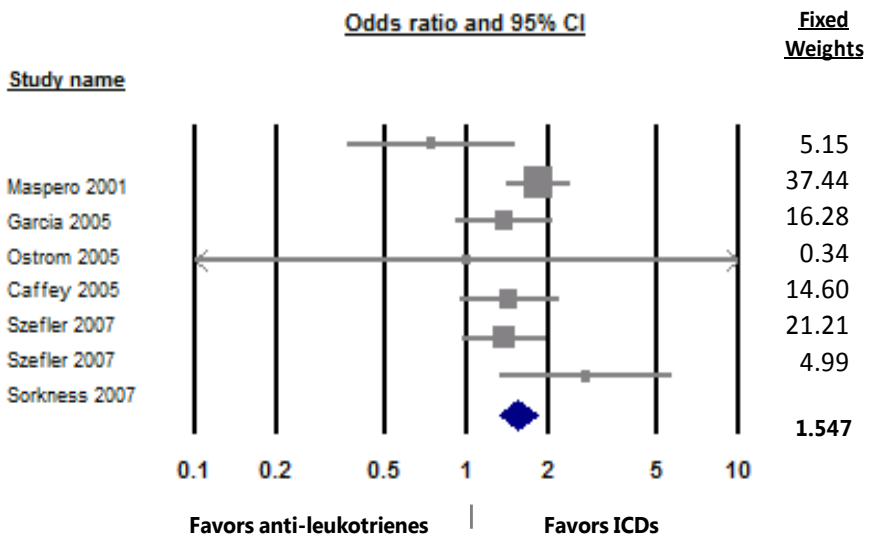

Figure 3: Efficacy of anti-leukotrienes compared with ICDs in the risk of acute exacerbations requiring the need for systemic steroids

A total of 477 acute asthma exacerbations requiring systemic steroids occurred among the 2,878 patients included in the analysis. The odds ratio using a fixed effects model was 1.55; (95% CI 1.31 – 1.82, p=0.00002); in other words, use of an anti-leukotriene agent vs an ICD increased the odds of a pediatric patient requiring at least one course of systemic steroids due to an acute exacerbation by 1.55.

Test for Heterogeneity

		Heterogeneity				Tau-squared			
	Number Studies	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	6	9.025	5	0.108	44.60	0.040	0.061	0.004	0.199
Random	6								

Table 5: Test for Heterogeneity

To justify the development of integrated results across studies, it is important to assess the degree to which studies are dissimilar or heterogeneous . The Q-value is a chi-squared statistic that describes the percentage of variability in effect estimates that is due to heterogeneity rather than to sampling error (i.e. chance) with k-1 degrees of freedom, where k=# of studies.[20] With a Q-value of 9.025 and a p-value of .108, we do not reject the null hypothesis of homogeneity and conclude the studies effect sizes differ only by sampling error. This suggests a fixed-effects model is appropriate.

The I^2 statistic depends on the magnitude and direction of effect, as well as the degree of heterogeneity. As per the Cochrane Collaboration, an I^2 of 0-40% indicates that heterogeneity "may not be important" and a value between 30% to 60% "may represent moderate heterogeneity". On the basis of both these guidelines, it does not appear that heterogeneity is a significant factor in the analysis. This provides further evidence of study similarity and the validity of combining results in a meta-analysis.

SENSITIVITY ANALYSIS

A sensitivity analysis was conducted to assess the impact of each study on the combined effect, a way of assessing the robustness of the analysis. Results are shown in Figure 4. The output displays the combined endpoint if each of the studies were removed from the analysis. If Maspero 2005 were removed from the analysis, the magnitude of effect decreases from an OR 1.61 from 1.55 because the effect of this study is in the opposite direction of the others (i.e. favorable to anti-leukotrienes). Conversely, the Garcia 2005 study was most favorable to ICDs and removing it from the meta-analysis weakened the magnitude of effect, although the combined endpoint remained statistically significant. The remaining studies had a negligible impact on combined effect. Overall, the impact on effect size is small and the direction of effect remains unchanged. On this basis, we can conclude the study results are robust.

Study	Point	Upper	Lower	Z-value	P-value
Maspero 2001	1.610	1.362	1.903	5.577	0.000
Garcia 2005	1.392	1.133	1.711	3.150	0.002
Ostrom 2005	1.582	1.324	1.890	5.050	0.000
Caffey 2005	1.549	1.316	1.824	5.256	0.000
Szefler 2007	1.566	1.313	1.868	4.987	0.000
Szefler 2007	1.598	1.330	1.920	5.005	0.000
Sorkness 2007	1.501	1.270	1.774	4.760	0.000
Fixed effects	1.547	1.314	1.820	5.247	0.000

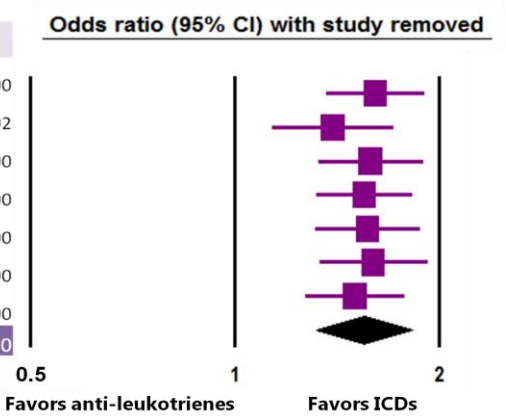

Figure 4: Sensitivity Analysis

SUBGROUP ANALYSIS

To further explore the hypothesis that ICD efficacy may erode over time vs anti-leukotrienes (due, perhaps, to lower compliance with the inhaled delivery formulation), the analysis divided studies into those 24 weeks or less (i.e. Maspero 2001, Ostrom 2005, and Caffey 2005) vs more than 24 weeks in duration (i.e. Garcia 2005 and Sorkness 2007). One study, Szefler 2007, reported outcomes at 12, 26 and 52 weeks. All three (3) time points were included in the analysis.

Model	Group by Subgroup within	Study name	Subgroup within study	Time point	Statistics for each study					Odds ratio and 95% CI
					Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0.01 0.10 1.00 10.00 100.00
	24 weeks or less	Maspero	24 weeks or	24 weeks	0.742	0.362	1.522	-0.814	0.416	
	24 weeks or less	Ostrom	24 weeks or	12 weeks	1.377	0.919	2.062	1.552	0.121	
	24 weeks or less	Caffey 2005	24 weeks or	4 weeks	1.000	0.044	22.763	0.000	1.000	
	24 weeks or less	Szefler	24 weeks or	12 weeks	1.438	0.939	2.203	1.671	0.095	
Fixed	24 weeks or less				1.281	0.977	1.678	1.793	0.073	
Random	24 weeks or less				1.281	0.977	1.678	1.793	0.073	
	More than 24	Garcia 2005	More than	52 weeks	1.844	1.413	2.406	4.503	0.000	
	More than 24	Szefler	More than	26 weeks	1.370	0.962	1.952	1.745	0.081	
	More than 24	Sorkness	More than	48 weeks	2.750	1.326	5.703	2.718	0.007	
Fixed	More than 24				1.723	1.405	2.114	5.223	0.000	
Random	More than 24				1.743	1.294	2.349	3.653	0.000	
Fixed	Overall				1.547	1.315	1.821	5.248	0.000	
Random	Overall				1.472	1.205	1.798	3.782	0.000	

The results of the subgroup analysis show that the difference between anti-leukotrienes and ICDs with respect the outcome of interest does not achieve statistical significance in studies less than 24 weeks of duration (OR 1.281 95% CI .98-1.68). When the results are isolated to those more than 24 weeks in duration, the magnitude of effect increases vs the pooled effect and achieves statistical significance (OR 1.74, 95% CI 1.41-2.11). It should be noted that inclusion of studies of varying duration did introduce some degree of heterogenity as per the identical odds ratios under fixed and random models in both of the subgroups, i.e. the subgroups show greater similiarity to each other than the pooled results.

DISCUSSION:

This meta-analysis of six (6) randomized clinical trials demonstrated that anti-leukotrienes as compared with ICDs are associated with higher odds (1.55) of an acute exacerbation requiring treatment with a systemic steroid. This result has both statistical and clinical significance with regard to the management of pediatric asthma. The magnitude of effect favoring ICDs was greatest in studies of greater than 24 weeks duration.

A strength of this meta-analysis is the relative consistency of the study population and treatment interventions in the individual studies. Patient characteristics were similar in terms of age and baseline respiratory function. Interventions were also similar. All six (6) trials included montelukast (i.e. Singulair) as the anti-leukotriene agent, which was dosed within a fairly narrow range. Four of the six studies included fluticasone as the ICD.

Only one study, Maspero 2005, suggested an outcome favoring anti-leukotrienes. This study was the only one to use beclomethasone as the ICD, a possible factor in the direction of the effect. In addition, Maspero 2005 was an open label extension study where patients elected to opt-in after completing a base study and then re-randomized to either montelukast or an ICD. Patients were allowed to use short-acting B-agonists on an "as needed" basis throughout the study, which may have mitigated the need for oral systemic steroids. It is not known if the rate of SABA use was greater in the anti-leukotriene or the ICD arm of the study.

As with any meta-analysis, the study is subject to potential biases. Although the analysis did not show any significant publication bias, the techniques are of limited sensitivity. The fail-safe N suggests that the findings are only moderately robust. The number of studies required to nullify the effect may be less than 22 if studies show an effect in the reverse direction. However, it is reassuring that the study that was least favorable to anti-leukotrienes, Garcia 2005, had four out of its six authors from Merck, the manufacturer of montelukast. So, while only published studies were included, this is mitigated by the fact that a number of

pharmaceutical sponsored studies, which might have been expected to favor anti-leukotrienes, also showed results that favoring ICDs with respect to the outcome of interest.

Another limitation is that only six (6) studies were included in the meta-analysis, including one study that showed no events in either treatment arm (but one event in the placebo arm). In addition, studies of varying length were included in the pooled analysis, although the direction of the effects was consistent in both subgroups.

All the studies included children between the ages of 6-14, with the exception of study Szefler 2007, which examined effects in children 2 to 8 years of age. While it is arguable this study should have been excluded due to the differential in age, the study showed a trend favoring an ICD, consistent with the overall meta-analysis. Additional research should be done on a younger pediatric population to determine the extent to which the inhaled delivery system may negatively impact compliance and, by extension, efficacy.

In addition, observational studies to determine the relationship between compliance and efficacy of various delivery mechanisms would be informative. An RCT, although valuable etc representing the gold standard, might overestimate compliance by virtue of care and follow-up provided.

CONCLUSION

Overall, the meta-analysis adds to the body of evidence that ICDs are the cornerstone of pediatric asthma management. The data also suggests that use of ICDs may reduce the need for hospitalizations and other emergency care vs other therapeutic classes. In addition, the analysis does not lend support to the hypothesis that ICDs become less effective over time relative to oral anti-leukotrienes. Additional research is needed to better understand the relationship between acute exacerbations and long-term compliance.

BIBLIOGRAPHY

1- Ducharme, Francine. Inhaled glucocorticoids versus leukotriene receptor antagonists as single agent asthma treatment: systemic review of current evidence. BMJ 2003; 326:621

2- Asthma in Children In-Depth Report, The New York Times, http://health.nytimes.com/health/guides/disease/pediatric-asthma/print.html

3- Wahn U, Dass SB. Review of recent results of montelukast as a monotherapy in children with mild asthma. Clinical Therapeutics. 2008;30 Spec No:1026-35. doi: 10.1016/j.clinthera.2008.05.018.

4- Papadopoulos NG, Arkawa H, Carlsen KH, et al. International consensus on (ICON) pediatric asthma. European Journal of Allergy and Clinical Immunology 2012;67: 976-977

5- Warner JO. The role of leukotriene receptor antagonists in the treatment of chronic asthma in childhood. Allergy. 2001: 56 Suppl 66:22-9. Review.

6- Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child. 1989 Oct; 64(10):1452-6.

7- Williams B, Noonan G, Reiss TF, Knorr B, Guerra J, White R, Matz J. Long-term asthma control with oral montelukast and inhaled beclomethasone for adults and children 6 years and older. Clin Exp Allergy. 2001 Jun;31(6):845-54. PubMed PMID: 11422148.

8- Morden, Nancy E. How effective are leukotriene inhibitors for asthma in children?. The Journal of Family Practice Aug 2004 (53), No. 4)

9- Tan RA, Spector SL. Antileukotriene agents. Current Opinion in Pulmonary Medicine. 3(3): 215-220, May 1997.

10- Pollart SM, Compton RM, et al. American Family Physician, 2001 Jul 1; 84(1):40-47.

11- Piccini J, Berger J. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. European Heart Journal (2009) 30, 1245-1253)

12- Maspero J, Duenas-Mesa E, Volovitz B, et al. Oral montelukast versus inhaled beclomethasone in 6- to 11-year-old children with asthma: Results of an open-label extension study evaluating long-term safety, satisfaction, and adherence with therapy. Current Medical Research and Opinion 2001: 17 (2):96-104.

13- Garcia Garcia U, Wahn U, et al. Montelukast, compared with fluticasone, for control of asthma among 6-14 year-old patients with mild asthma: the MOSAIC study. Pediatrics 2005; 116(2):360-9.

14- Ostrom NK. Decotiis B, et al. Comparative efficacy and safety of low-dose fluticasone propionate and montelukast in children with persistent asthma. Journal of Pediatrics. 2005; 147 (2):213-20.

15- Caffey LF. et al. A crossover comparison of fluticasone propionate and montelukast on inflammatory indices in children with asthma. Pediatric Asthma Allergy & Immunology. 2005;18(3): 123-30.

16- Szefler SJ, Baker JW, Uryniak T, Goldman M, Silkoff PE. Comparative study of budesonide inhalation suspension and montelukast in young children with mild persistent asthma. J Allergy Clin Immunol. 2007 Nov;120(5):1043-50. PubMed PMID: 17983871.

17- Sorkness CA. Lemanske Jr RF. et al. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma. The Pediatric Asthma Controller Trial. Journal of Allergy and Clinical Immunology 2007; 119(1): 64-72.

18- Schrodle, B. Tests for funnel plot asymmetry and Fail-safe N. University of Zurich, 2009, http://www.biostat.uzh.ch/teaching/phd/doktorandenseminar/schroedle.pdf)

19- Cochrane Collaboration 2008, Chapter 10, http://handbook.cochrane.org/chapter_10/10_4_4_3_fail_safe_n.htm

20- Cochrane Collaboration 2008, Chapter 9, Higgens et al. http://handbook.cochrane.org/chapter_9

21- Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and Childern (Review). 2012 The Cochrane Collaboration.