MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2016;16(Suppl5):e6799 doi: 10.5867/medwave.2016.6799

Are leukotriene inhibitors useful for bronchiolitis?

Authors: Fernanda Pérez-Gutiérrez**[1,2]**, Isidora Otárola-Escobar**[1,2]**, Deidyland Arenas**[2,3]**

Affiliation:
[1] Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile
[2] Proyecto Epistemonikos, Santiago, Chile
[3] Departamento de Pediatría, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

E-mail: darenas@med.puc.cl

Citation: Pérez-Gutiérrez F, Otárola-Escobar I, Arenas D. Are leukotriene inhibitors useful for bronchiolitis?. *Medwave* 2016;16(Suppl5):e6799 doi: 10.5867/medwave.2016.6799
Publication date: 16/12/2016

Abstract

Bronchiolitis is a prevalent disease in children under two years of age, which carries significant morbidity and mortality. However, there is controversy regarding the optimal therapeutic management. Leukotriene inhibitors have been proposed as an alternative, although its efficacy is not clear yet. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified two systematic reviews comprising six randomized trials addressing the question of this article. We extracted data, combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded leukotriene inhibitors might not decrease mortality levels on bronchiolitis patients and it is not clear whether they decrease length of hospital stay. They might reduce recurrent wheezing, but the certainty of the evidence is low, and they increase adverse effects.

Problem

Bronchiolitis is characterized by low respiratory tract inflammation due to a viral infection. It mainly affects children under two years of age, especially in winter, and demands health services, leads to high hospitalization rates, ventilation requirements and even mortality. In addition, a higher incidence of recurrent wheezing has been observed in these patients. In general, there is controversy regarding the management of bronchiolitis. Among the therapeutic alternatives, the efficacy of leukotriene inhibitors has been proposed, since the pathogenesis of bronchiolitis involves the stimulation of the enzyme lipoxygenase-5, which participates on leukotriene synthesis. These molecules have been identified as contributors to airway inflammation, airway and alveolar obstruction, mucosal edema and increased bronchial reactivity.

The present summary seeks to evaluate whether leukotriene inhibitor therapy is a useful and safe alternative for the management of pediatric patients with bronchiolitis.

Methods

We used Epistemonikos database, which is maintained by screening multiple databases, to identify systematic reviews and their included primary studies. With this information, we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Leukotriene inhibitors might not decrease mortality in patients with bronchiolitis, and it is unclear whether hospitalization length decreases because the certainty of the evidence is very low.
- Leukotriene inhibitors may decrease incidence of recurrent wheezing in patients with bronchiolitis, but the certainty of the evidence is low.
- Leukotriene inhibitors increase adverse effects in patients with bronchiolitis, although the magnitude of this increase is uncertain.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found two systematic reviews [1],[2], including six randomized controlled trials, reported in 12 references [3],[4],[5],[6],[7],[8], [9],[10],[11],[12],[13],[14].
What types of patients were included	The six trials only included patients diagnosed with bronchiolitis [3],[4],[6],[7],[8],[9]. Regarding to age, the six trials included patients younger than 24 months [3],[4],[6],[7],[8],[9]. If this age group is subdivided, one trial included patients between 1 and 24 months [6], two trials included patients between 3 and 24 months [4],[9], one trial included patients between 4 and 24 months [8], one trial included patients between 6 and 24 months [3] and one trial included patients younger than 24 months [7]. Two trials included patients with a first episode of bronchiolitis of any etiology [6],[8], two trials included a first episode of bronchiolitis caused by respiratory syncytial virus [3],[7] and one trial included first or second episode of bronchiolitis caused by respiratory syncytial virus [9]. The six trials only included inpatient population [3],[4],[6],[7], [8],[9]. Of these, two trials required a minimum stay of 24 hours [7],[9]. No trial considered outpatient population.
What types of interventions were included	The six trials compared oral montelukast versus placebo [3],[4],[6],[7],[8],[9]. Regarding dosing, four trials used 4 mg/day [3],[4],[6],[7], one trial used 8 mg/day [8] and one trial used doses of 4 and 8 mg/day [9]. Regarding intervention duration, two trials administered montelukast since admission day until discharge [6],[8], two trials used it for three months [3],[7], one trial between 1 and 4 weeks [4] and one trial between 4 and 20 weeks [9].
What types of outcomes were measured	The systematic reviews reported the following outcomes: All cause-mortality, incidence of recurrent wheezing, length of hospital stay, clinical adverse effects, percentage of children requiring ventilation, percentage of symptom-free days, frequency of recurrent wheezing, serum eosinophil-derived neurotoxin levels, corticosteroids usage, clinical severity score, oxygen saturation and respiratory rate. Follow-up was one year in two trials [3],[7], six months in one [9] and 18 months in one [4]. In two trials the follow-up was not reported [6],[8].

Summary of findings

The information regarding the effects of leukotriene inhibitors for bronchiolitis is based on six randomized trials [3],[4],[6],[7],[8],[9]. Only one trial [9] reported mortality (952 patients), two trials [6],[8], reported length of hospital stay (136 patients), two trials [4],[7], reported adverse effects (328 patients) and three trials reported the incidence of recurrent wheezing (1160 patients). No trial assessed ventilation requirements.

The summary of findings is the following:

- Leukotriene inhibitors might not decrease mortality in bronchiolitis, but the certainty of the evidence is low.
- It is not clear whether leukotriene inhibitors decrease hospitalization length in bronchiolitis, because the certainty of the evidence is very low.
- Leukotriene inhibitors might decrease recurrence of wheezing in bronchiolitis, but the certainty of the evidence is low.
- Leukotriene inhibitors increase clinical adverse effects in patients with bronchiolitis, although the magnitude of this increase is uncertain. The certainty of the evidence is moderate.
- None of the studies found evaluated the effect of leukotriene inhibitors on ventilation requirements.

Leukotriene inhibitors for bronchiolitis				
Patients	Children with bronchiolitis			
Intervention	Leukotriene inhibitors			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT leukotriene inhibitors	**WITH leukotriene inhibitors**		
	Difference: patients per 1000			
Mortality	0** per 1000	1 per 1000	RR 2.51 (0.12 a 52.16)	⨁⨁◯◯[1] Low
	Difference: 1 patient more per 1000 (Margin of error: 0 to 16 more)			
Hospitalization days	4 days***	3.05 days	--	⨁◯◯◯[1,2] Very low
	Difference (MD): 0.95 days less (3.08 less to 1.19 more)			
Incidence of recurrent wheezing	349 per 1000	272 per 1000	RR 0.78 (0.55 a 1.11)	⨁⨁◯◯[1] Low
	Difference: 77 patients less per 1000 (Margin of error: 157 less to 38 more)			
Adverse Effects	6.7% of patients who received the intervention developed clinical adverse effects, compared with none in the control group.		RR 9.3 (1.24 a 69.81)	⨁⨁⨁◯[1,3,4] Moderate
Ventilation Requirements	No study reported this outcome		---	--

RR= Risk ratio.
MD= mean difference.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT leukotriene inhibitors** is based on the risk in the control group of the trials. The risk **WITH leukotriene inhibitors** (and its margin of error) is calculated from relative effect (and its margin of error).

** No deaths were reported in the control group of the trials. The risk estimator was calculated using a value of 0.1 events in the control group (cannot be done with a value of 0).
*** Approximate mean in the control group of the trials

[1] The certainty of the evidence was downgraded in two levels for imprecision because the confidence interval was very wide including the possibility of no effect or even harm.
[2] The certainty of the evidence was downgraded in one level for inconsistency because one trial showed increased hospitalization days and the other decreased hospitalization days.
[3] The certainty of the evidence was downgraded in one level for moderate risk of bias in the trials
[4] The certainty of the evidence was upgraded in one level for large effect size.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to patients with bronchiolitis, diagnosed in the context of upper respiratory symptoms (cough and/or rhinorrhea) followed by signs of respiratory distress (costal retraction and/or tachypnea) and added respiratory sounds (wheezing, audible rales, crackles and/or roncus). Regarding the etiology, it includes any type of virus, predominantly respiratory syncytial virus.
- It does not apply to children older than 24 months.
- None of the trials were conducted in the outpatient setting. However, it is reasonable to extrapolate the information presented in this summary to this context.

About the outcomes included in this summary

- For the summary of findings we selected the outcomes: mortality, lenght of hospital stay, incidence of recurrent wheezing, clinical adverse effects and ventilation requirements as they are critical for decision making on use of leukotriene inhibitors in bronchiolitis. This selection is based on the opinion of the authors of the summary, but generally agrees with the outcomes mentioned by the systematic reviews.
- The outcome ventilation requirements was considered important despite it was not reported by the primary studies.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make an adequate balance because the certainty of the evidence about the benefits is low or very low.
- If there is indeed an effect, it would be a decrease in recurrence of wheezing, which should be weighed against mild adverse effects.
- Regarding adverse effects, the trials reported leukotriene inhibitors were in general well tolerated and reported adverse effects were considered mild. The most common adverse effect were abdominal pain, vomiting, diarrhea, insomnia and rash. None of them led to treatment discontinuation [7],[8],[9].
- Only one trial reported deaths. Neither of the two deaths was attributed by the investigators to the use of leukotriene inhibitors [9].

What would patients and their doctors think about this intervention

- Considering there is uncertainty and it is an intervention in which the balance between benefits and risks is not clear, most patients and caregivers should lean against their use.

- However, it is expected there would be variability in the decision, especially in scenarios without resource limitations. Those patients or caregivers who put more value on an uncertain benefit may tend to favor their use, and those who give a greater value to the certainty of the evidence, adverse effects or costs, will abstain from their use.
- It is important to note, as it is a tablet, it has advantages in terms of adherence compared to inhalers and aerocamera, which could influence the decision in some cases.

Resource considerations

- It is not possible to make an appropriate balance between benefits and costs due to the existing uncertainty.
- The cost per dose of leukotriene inhibitors is greater than that of the most commonly used inhalation therapies. In spite of this, its use for a limited period of time as in the trials identified, could reduce expenses related to the treatment of recurrences.
- In scenarios with limited resources, it is unlikely to be a cost effective intervention.
- It is reasonable to do a formal economic assessment in scenarios where its use is being considered.

Differences between this summary and other sources

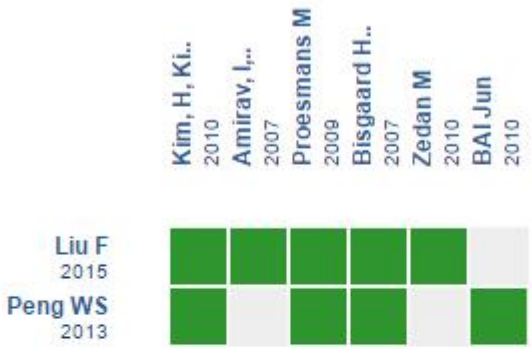
- The conclusions of this summary are consistent with those presented in the two identified systematic reviews in relation to the outcomes of mortality, hospitalization days and adverse effects [1],[2].
- Our summary suggests there may be a decrease in the incidence of recurrent wheezing, since the confidence interval is interpreted as one of the elements that decreases the certainty of the evidence (according to the GRADE methodology) and not in a dichotomous way only on the basis of statistical significance. This differs in part from the reviews identified, which indicated that it might not reduce the incidence of recurrent wheezing [2] or that montelukast did not reduce the incidence of recurrent wheezing compared to placebo [1].
- The guideline of the American Academy of Pediatrics on Diagnosis, management and prevention of bronchiolitis does not mention antileukotrienes amid possible treatments for bronchiolitis [15].

Could this evidence change in the future?

- The probability that future research changes the conclusions of this summary is high because of the existing uncertainty.
- We did not identify ongoing studies in the International Clinical Trials Registry Platform of the World Health Organization or published studies not included in any of the identified systematic reviews.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

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Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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Author address:
[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile