PICO Search Assignment Worksheet **Name: Jay Kolasinac**

Brief description of patient problem/setting (summarize the case very briefly)

29F patient, along with her 7 y/o son, both who have a PMH significant for severe seasonal allergies, present to the urgent care for complaints of worsening allergies. Pts just can not seem to control their allergies at this time of year. They are using are using Flonase, Claritin, and Pataday with only minor relief. She has heard of *Dymista* and is wondering if that could possibly be the relief for their allergy symptoms.

Search Question: In patients with moderate/severe allergic rhinitis, is *Dymista* more effective at controlling symptoms compared to conventional medications?

Question Type: What kind of question is this? (boxes now checkable in Word)

☐Prevalence	☐Screening	☐Diagnosis
☒Prognosis	☒Treatment	☐Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Along with meta-analyses and systematic reviews, RCT are levels of evidence I will searching for. My question focuses on a treatment course, so RCT are the best way to try and create a controlled environment to witness if the treatment course can create any change in the patient's lives. Along with RCT, prospective cohort studies would also be in consideration since patients in prospective cohorts are followed over a long period of time which in this case, can demonstrate prolonged relief of symptoms following the use of this medication.

PICO search terms:

P	**I**	**C**	**O**
Allergic rhinitis	Dymista	Conventional medications	Improved symptoms
Seasonal allergies	MP-AzeFlu	Placebo	Symptom control
	Azelastine hydrochloride/fluticasone propionate		

Search tools and strategy used:

Database	Terms	Filter	# of Articles
PubMed	Dymista allergic rhinitis	Medline, last 5 years	15
	MP-AzeFlu allergic rhinitis	Medline, last 5 years	19
	Azelastine hydrochloride/fluticasone propionate allergic rhinitis	Medline, last 5 years	97
ScienceDirect	Dymista allergic rhinitis	Last 5 years, research articles	8
	MP-AzeFlu allergic rhinitis	Last 5 years, research articles	7
	Azelastine hydrochloride/fluticasone propionate allergic rhinitis	Last 5 years, research articles	21
MEDLINE Complete	Dymista allergic rhinitis	Last 10 years	3
	MP-AzeFlu allergic rhinitis	Last 10 years	17
	Azelastine hydrochloride/fluticasone propionate allergic rhinitis	Last 10 years	1

I narrowed down my results by using filters such as medline or within the last 5/10 years. It seems that my question and research topic does not have as many articles as I anticipated. Many of the articles were non-interventional studies. I tried to find systematic reviews/meta-analyses and RCTs.

Results found:

Article 1

Citation:

Debbaneh, P. M., Bareiss, A. K., Wise, S. K., & McCoul, E. D. (2019). *Intranasal Azelastine and Fluticasone as Combination Therapy for Allergic Rhinitis: Systematic Review and Meta-Analysis. Otolaryngology–Head and Neck Surgery, 019459981984188.* doi:10.1177/0194599819841883

https://pubmed.ncbi.nlm.nih.gov/30961435/

Article Type:

Systematic review/Meta-analysis

Abstract:

Objective: Combination therapy with intranasal azelastine and fluticasone propionate is an option for treatment of allergic rhinitis. This systematic review and meta-analysis examines existing literature to determine efficacy in treating allergic rhinitis compared to monotherapy.
Data sources: The PubMed, EMBASE, Cochrane, and MEDLINE databases were systematically searched for randomized controlled trials using AzeFlu nasal spray.
Review methods: Randomized, controlled trials that reported symptom relief of allergic rhinitis in males and females of all ages were included. Results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.
Results: Systematic review identified 8 articles suitable for review. The risk of bias was generally low. All studies exhibited a greater decrease in patient-reported symptom scores in patients treated with combination therapy compared to monotherapy or placebo. Meta-analysis revealed superiority of combination therapy in reducing Total Nasal Symptom Score compared to placebo (mean change from baseline: -2.41; 95% confidence interval [CI], -2.82 to -1.99; $P < .001$; $I^2 = 60\%$), azelastine (mean change from baseline: -1.40; 95% CI, -1.82 to -0.98; $P < .001$; $I^2 = 0\%$), and fluticasone (mean change from baseline: -0.74; 95% CI, -1.17 to -0.31; $P < .001$; $I^2 = 12\%$).
Conclusion: Current evidence supports both efficacy and superiority of combination intranasal azelastine and fluticasone in reducing patient-reported symptom scores in patients with allergic rhinitis. Combination nasal spray should be considered as second-line therapy in patients with allergic rhinitis that is not controlled with monotherapy.

Key points:

- Review included 8 articles.
- Meta-analysis revealed decreased TNSS (Total Nasal Symptoms Score) in patients who utilized azelastine/fluticasone proprionate compared to placebo/mono therapy alone.
- Azelastine/fluticasone propionate supports both efficacy and superiority of the combination medicine
- Shoulder be used as 2nd line treatment if monotherapy does not work

Why I chose this article:

- It was a meta-analysis/systematic review
- It specifically focused on my PICO question.
- Published in 2019
- Over 5,000 patients were seen across the U.S and India

Article 2

Citation:

Berger, W. E., & Meltzer, E. O. (2015). *Intranasal Spray Medications for Maintenance Therapy of Allergic Rhinitis. American Journal of Rhinology & Allergy, 29(4), 273–282.* doi:10.2500/ajra.2015.29.4215

https://pubmed.ncbi.nlm.nih.gov/26132312/

Article Type:
Systematic Review

Abstract:

Background: Intranasal sprays are recommended as targeted therapy for allergic rhinitis (AR) by providing direct delivery of medication to the nasal mucosa, reducing the potential for systemic adverse effects, decreasing burden of disease, and improving quality of life.

Objective: To review currently available intranasal sprays indicated for maintenance therapy of AR in the United States: intranasal antihistamines (INAH); intranasal corticosteroids (INCS); and MP-AzeFlu, a single formulation nasal spray of the INAH, azelastine hydrochloride, and the INCS, fluticasone propionate.

Methods: MEDLINE searches were conducted to identify placebo-controlled studies of commercially available prescription nasal sprays at U.S.-approved doses and indications, and published after an earlier systematic review of AR treatment. Inclusion criteria were ≥20 subjects; duration of ≥2 weeks for seasonal (or episodic) AR, ≥4 weeks for perennial (or persistent) AR, and reporting a total nasal symptom score as a primary or secondary outcome.

Results: Twenty studies met the inclusion criteria: 4 pediatric, 16 adult/adolescent. There were 4 perennial AR studies (381 children, 1607 adults) and 16 seasonal AR trials (3081 children, 6548 adults). In these studies, 2451 subjects (481 children, 1970 adults) received an INCS, 3001 (1116 children, 1885 adults) received an INAH, and 346 adult subjects received MP-AzeFlu. All active treatments were well tolerated and effective as measured by the reduction in nasal symptoms. Head-to-head comparisons were only available for MP-AzeFlu versus the individual active agent components. MP-AzeFlu provided significantly greater symptom relief than either azelastine or fluticasone propionate alone and with an onset starting at 30 minutes after the dose.

Conclusion: The most recent addition to intranasal sprays for the maintenance therapy of AR is MP-AzeFlu, a single formulation nasal spray of azelastine hydrochloride and fluticasone propionate in an advanced delivery system. Analysis of clinical data showed this to be the first new intranasal medication that provides greater clinical benefit than an INCS in treating AR.

Key points:
- 20 studies were included
- 4 studies focused on perennial AR while the other 16 focused on seasonal allergies

- 2451 subjects received INCS, 3001 subjects received INAH, and 346 subjects received MP-AzeFlu
- All treatments were well tolerated
- Onset of symptom reduction started after 30 mins
- In clinical trials, MP-AzeFlu provided more complete symptom relief than either the INAH or the INCS alone, with an onset of action at 30 minutes.
- This is the first time that a new drug has shown greater clinical benefit than an INCS, which raises the possibility of a new treatment standard for patients with moderate-severe AR.

Why I chose this article:

- It was a systematic review
- It specifically focused on my PICO question.
- Published in 2015, fairly recent
- Strong sample size

Article 3

Citation:

Kaulsay, R., Nguyen, D. T., & Kuhl, H. C. (2018). *Real-life effectiveness of MP-AzeFlu in Irish patients with persistent allergic rhinitis, assessed by visual analogue scale and endoscopy. Immunity, Inflammation and Disease, 6(4), 456–464.* doi:10.1002/iid3.237

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6247236/

Article Type:

Prospective cohort study

Abstract:

Introduction: Most allergic rhinitis (AR) patients have moderate-to-severe, persistent disease. Meda Pharma's AzeFlu (MP-AzeFlu) combines intranasal azelastine hydrochloride (AZE) and fluticasone propionate (FP) in a novel formulation in a single device to treat AR. This prospective, noninterventional study sought to assess the effectiveness of MP-AzeFlu (one spray/nostril twice daily; 548 µg AZE/200 µg FP daily dose) in relieving AR symptom severity.

Methods: A visual analogue scale (VAS) was used prior to MP-AzeFlu treatment on days 0, 1, 3, 7, 14, 21, 28, 35, and 42 by 53 persistent AR (PER) patients seen in routine clinical practice in Ireland. An endoscopy was performed on days 0 and 28, and symptoms of edema, discharge, and redness were scored on a three-point scale (for both nostrils).

Results: Patients using MP-AzeFlu experienced rapid VAS score reduction from 73.4 mm (standard deviation [SD], 20.3) at Day 0 to 31.5 mm (SD, 25.0) at day 28 ($P < 0.0001$) to 28.1 mm (SD, 24.1) at day 42 ($P < 0.0001$), a 45.3-mm reduction. On average, patients achieved a clinically relevant VAS score cutoff of 50 mm before Day 7. Total endoscopy score decreased from 7.5 mm (SD, 3.1) at baseline to 3.5 mm (SD, 2.5) at Day 28. The incidence of severe edema on endoscopy decreased from 53.1% at baseline to 3.8% at Day 28. A similar reduction in the incidence of thick/mucousy discharge (from 28.3% to 4.8%) and severe redness (from 34.9% to 0%) was also observed.

Conclusions: MP-AzeFlu provided effective, rapid control of PER as assessed by VAS in a real-world clinical setting in Ireland. Symptom improvement was observed at Day 1, sustained for 42 days, and associated with improved mucosal appearance after 28 days. These results confirm the safety of MP-AzeFlu and exceed the efficacy demonstrated in phase 3 clinical studies for controlling AR in PER patients.

Key points:

- Prospective cohort study
- Included adults/adolescents 12 years of age + who suffered from persistent AR
- Patients were followed for 42 days
- Patients assessed symptom severity using a 100-mm VAS ranging from 0 mm ("not at all bothersome") to 100 mm ("very bothersome") on Days 0, 1, 3, 7, 14, 21, 28, 35, and 42.
- An endoscopy was performed on Days 0 and 28 to evaluate the patients' nasal mucosa. Edema, discharge, and redness were scored on a three-point scale for both nostrils.
- VAS reductions were seen regardless of age group
- Sleep quality also improved over the course of treatment
- Nasal mucosa saw improvements as well
- MP-AzeFlu provides effective and rapid control of PER as assessed by VAS in a real-world clinical setting in Ireland

Why I chose this article:

- Published in within last 5 years (2018)
- Located in Ireland to see other world wide experiences with the drug other than the US
- Focused directly on PICO question
- The study also focused on other aspects along with symptom severity such as: sleep quality, nasal mucosa changes, and nasal discharge.

Article 4

Citation:

Berger, W., Bousquet, J., Fox, A. T., Just, J., Muraro, A., Nieto, A., … Wahn, U. (2016). *MP-AzeFlu is more effective than fluticasone propionate for the treatment of allergic rhinitis in children. Allergy, 71(8), 1219–1222.* doi:10.1111/all.12903

https://pubmed.ncbi.nlm.nih.gov/27043452/

Article type:

Randomized control trial

Abstract:

The objective was to evaluate the efficacy of MP-AzeFlu (Dymista) vs fluticasone propionate (FP), (both 1 spray/nostril bid), in children with allergic rhinitis (AR). MP-AzeFlu combines azelastine hydrochloride, FP and a novel formulation in a single spray. Children were randomized in a 3 : 1 ratio to MP-AzeFlu or FP in this open-label, 3-month study. Efficacy was assessed in children aged ≥ 6 to < 12 years (MP-AzeFlu: n = 264; FP: n = 89), using a 4-point symptom severity rating scale from 0 to 3 (0 = no symptoms; 3 = severe symptoms). Over the 3-month period, MP-AzeFlu-treated children experienced significantly greater symptom relief than FP-treated children (Diff: 0.14; 95% CI: 0.28, 0.01; P = 0.04), noted from the first day (particularly the first 7 days) and sustained for 90 days. More MP-AzeFlu children achieved symptom-free or mild symptom severity status, and did so up to 16 days faster than FP. MP-AzeFlu provides significantly greater, more rapid and clinically relevant symptom relief than FP in children with AR. Intranasal corticosteroids (INS) are recommended for the treatment of children with allergic rhinitis (AR) (1). However, they provide insufficient symptom control for many. Considering that AR is associated with poor asthma control (2), is a predictor of wheezing onset in school-aged children (3) and poorer examination performance at school (4), it is important to get it under control. Unfortunately, AR is undiagnosed and undertreated in children (5). MP-AzeFlu (Dymista, Meda, Solna, Sweden) comprises an intranasal antihistamine [azelastine hydrochloride (AZE)], an INS [fluticasone propionate (FP)] and a novel formulation in a single spray. Its efficacy and safety in adults and adolescent AR patients are well established (6–10), providing twice the overall nasal and ocular symptom relief as an INS or intranasal H1-antihistamine, and more complete and rapid symptom control (6). A lower treatment effect has been observed in paediatric allergy trials (11–13), possibly confounded by caregiver assessment (14, 15). The present study was primarily designed to assess the long-term safety of MP-AzeFlu (the results of which will be published in full elsewhere). Efficacy was assessed secondarily using a simple scoring system in an effort to minimize this confounder. The objective was to evaluate the efficacy of MP-AzeFlu compared to FP in children aged ≥ 6 to <12 years, with AR.

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Key points:

- This was a prospective, randomized, active-controlled, parallel-group, 3-month, open-label safety trial in children with AR carried out at 42 investigational sites in the USA (March–October 2013).
- The study comprised a 2- to 30-day lead-in period, and a 3- month treatment period, with study visits on Days, 1, 15, 30, 60 and 90.
- 405 children randomized who either received MP-AzeFlu or Fluticasone Proprionate

- In conclusion, MP-AzeFlu provides significantly greater, more complete and more rapid AR symptom control than FP in children (aged ≥ 6–12 years) and has been granted approval for use in this age group by the FDA

Why I chose this article:

- It was a randomized control trial
- Published in within the last 5 years
- Focused directly on my PICO question and compared the efficacy vs a fluticasone propionate group in children
- Utilized over 40 investigational sites across the US

What is the clinical "bottom line" derived from these articles in answer to your question?

MP-AzeFlu/Dymista/Azelastine-Fluticasone Proprionate seems to be an effective drug in treating moderate-severe persistent allergic rhinitis. I included articles that studied the effects of MP-AzeFlu in both the adult and children population and the results speak for themselves. Debbaneh et al., conluded that the use of MP-AzeFlu was superior at producing relief of nasal symptoms to that of monotherapy alone. Bereger et al., concluded that MP-AzeFlu was able to provide more complete symptom relief than either intranasal antihistamine/corticosteroid could alone with an onset of action at 30 minutes. Kaulsay et al., conducted a study in Ireland that followed children over a course of 42 days and concluded that MP-AzeFlu provided effective and rapid control in patients suffering from persistent allergic rhinitis. Berger et al., focused on the usage of MP-AzeFlu in comparison to conventional means (fluticasone propionate as monotherapy) in the children population and concluded that MP-AzeFlu provided significantly better AR symptom relief than FP in children aged ≥ 6 to < 12 years. Based on the evidence in these articles, MP-AzeFlu should certainly be considered as a treatment option for patients experiencing moderate-severe allergic rhinitis that are not controlled by conventional means.