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Is reslizumab effective in improving quality of life and asthma control in adolescent and adult patients with poorly controlled eosinophilic asthma?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not reslizumab is effective in improving quality of life and asthma control in adolescent and adult patients with poorly controlled eosinophilic asthma.

STUDY DESIGN: This is a systematic review of three randomized controlled trials, published in peer-reviewed journals from 2015 and 2016.

DATA SOURCES: Three randomized, placebo-controlled, double-blind clinical trials comparing the effectiveness of reslizumab to a placebo in improving quality of life and asthma control. Articles were found using CINAL and PubMed databases.

OUTCOMES MEASURED: Outcomes measured include quality of life, assessed using the Asthma Quality of Life Questionnaire (AQLQ), and asthma control, assessed using the Asthma Control Questionnaire-7 (ACQ-7).

RESULTS: Bjermer et al. and Castro et al. showed significant improvement in quality of life in patients who received reslizumab compared to placebo. In Bjermer et al., 64% of patients receiving reslizumab achieved an improvement in their AQLQ score, compared to 48% for those receiving a placebo ($p=0.0189$). In Castro et al., 74% of patients receiving reslizumab had an improvement in their AQLQ score, compared to 65% of those receiving a placebo ($p=0.03$). Corren et al. showed a significant improvement in asthma control, with 71% of patients receiving reslizumab having improvement, compared to 57% of patients in the control group ($p=0.01$).

CONCLUSION: Reslizumab is an effective treatment to improve quality of life and asthma control in patients with inadequately controlled eosinophilic asthma.

KEY WORDS: Reslizumab, asthma

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways that is characterized by reversible obstruction, airway inflammation, bronchial hyperreactivity, and airway narrowing. Asthma is a common respiratory disease, affecting approximately 7.8% of the United States' population.[1] About 10% of these individuals have poorly controlled asthma.[2] An estimated $56 billion are spent annually for asthmatic patients.[3] It is important to note that the subgroup of patients with poorly controlled asthma disproportionately contributes to these costs, likely due to increased exacerbations and hospitalizations. According to the CDC, the percentage of physician office visits for patients with asthma is 6.3% annually.[4] The primary diagnosis of asthma accounts for an estimated two million emergency department visits annually.[4]

It is known that asthma is caused by inflammation of the airways due to the infiltration of eosinophils, neutrophils, and T lymphocytes. This inflammation leads to airway edema and bronchial hyperreactivity that activates the immune system. Together, this leads to bronchoconstriction and limitation of airflow. There is a subgroup of asthmatic patients with an eosinophil-predominant inflammatory infiltrate in the airways and increased blood and sputum eosinophil levels.[5] This subgroup is associated with poor treatment outcomes and increased risk of exacerbations.[6] Eosinophils are regulated by interleukin-5 (IL-5) and require its signaling for growth and survival.[5] This makes IL-5 inhibition a possible target for the treatment of eosinophilic asthma.

Patients with asthma typically present with wheezing, dyspnea, cough, and other respiratory symptoms. A patient's daily activity and quality of life may be limited depending on symptom severity. Standard treatments for asthma include short-acting agents that quickly treat airway narrowing, and long-term controller medications that aim to reduce airway inflammation.

Short-acting agents include inhaled short-acting beta-agonists (SABAs), such as albuterol, that work to cause bronchodilation and reverse airflow limitation. SABAs are required for all asthmatic patients for the immediate treatment of symptoms. Long-term controller medications include inhaled corticosteroids (ICS), long-acting beta-agonists, and leukotriene modifiers. Daily ICS therapy is currently the treatment of choice for persistent asthma. Systemic corticosteroids, supplemental oxygen, and other medications may be used in acute exacerbations.

All of the medications previously listed are effective for managing symptoms or controlling asthma. However, they are not enough in cases of asthma with poor control, such as in the eosinophilic subgroup. Reslizumab (Cinqair) is a monoclonal antibody against IL-5 that has been approved by the FDA as an add-on therapy for poorly controlled eosinophilic asthma. By targeting IL-5, it works to decrease the number of eosinophils that cause airway inflammation. Therefore, the medication aims to improve asthma control and quality of life by targeting inflammation.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not reslizumab is effective in improving quality of life and asthma control in adolescent and adult patients with poorly controlled eosinophilic asthma.

METHODS

Several criteria were used to search for and select studies for this EBM review. Each study included participants 12 years of age and older with inadequately controlled eosinophilic asthma. In each study, the intervention was a reslizumab 3.0 mg/kg infusion. Comparisons were

made between an experimental group receiving reslizumab infusions and a control group receiving a placebo infusion. Outcomes measured included quality of life and asthma control. Types of studies included in this selective EBM review include three randomized, placebo-controlled, double-blind clinical trials.

Articles were found using CINAL and PubMed databases, searching with key words "reslizumab and asthma." The selected articles were published in the English language in peer reviewed journals from 2015-2016. Articles were chosen based on their relevance to the clinical question and if they included patient oriented outcomes. Inclusion criteria were randomized, placebo-controlled, double-blind clinical trials. Exclusion criteria were patients under the age of 12 years old or who had well controlled asthma. Statistics reported in this review include relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), and p-values. Table 1 demonstrates the demographics and characteristics of each study.

Table 1: Demographics & Characteristics of included studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Bjermer[5] (2016)	Double-blind, placebo-controlled RCT	315	12-75	-ACQ-7 score ≥ 1.5. -Airway reversibility of 12% or more after SABA administration. -Blood eosinophil count of ≥400/μL. -Receiving at least a medium dose ICS daily with or without another controller drug.	-Confounding lung disorders/pulmonary conditions. -Hypereosinophilic syndrome. -Use of systemic corticosteroids 30 days prior to screening. -Current smoker. -Use of systemic immunosuppressive or immunomodulating agents in the past 6 months prior to screening. - Other clinically relevant	50	Reslizumab infusion 3.0 mg/kg q 4 weeks x 16 weeks

					comorbidities with potential to interfere with the study schedule, procedures, or safety.		
Castro[6] (2015)	Double-blind, placebo-controlled RCT	489	12-75	-Same inclusion criteria as Bjermer (2016) in addition to the following: -At least one asthma exacerbation ≥ 3 days within the past year before screening.	-Same exclusion criteria as Bjermer (2016) in addition to the following: -Females could not be pregnant. -Prior use of reslizumab. -Requirement for treatment for an asthma exacerbation within 4 weeks of screening period.	56	Reslizumab infusion 3.0 mg/kg q 4 weeks x 1 year
Corren[8] (2016)	Double-blind, placebo-controlled RCT	496	18-65	-Same inclusion criteria as Bjermer (2016)	-Same exclusion criteria as Bjermer (2016)	74	Reslizumab infusion 3.0 mg/kg q 4 weeks x 16 weeks

OUTCOMES MEASURED

Outcomes measured included quality of life and asthma control following the intervention. Bjermer et al. and Castro et al. used the Asthma Quality of Life Questionnaire (AQLQ) to assess quality of life in the participants at baseline and the end of the treatment period, which was at weeks 16 and 52, respectively.[5-6] The AQLQ consists of 32 questions that assess asthma symptoms, activity limitation, emotions, and environmental stimuli.[7] The participants are asked to evaluate how each area has impacted them in the previous two weeks, and rate each question on a 7-point scale; 1 meaning severely impaired, 7 meaning not impaired at all.[7] The score for the AQLQ is an average of all of the responses. The creators of the AQLQ state that an improvement in the baseline score of ≥ 0.5 is the minimally important difference

(MID) that has clinical significance, because this improvement can warrant a change in a patient's treatment plan.[7] Both Bjermer et al. and Castro et al. used this MID, which allows for dichotomous data. Both studies used a stratified Cochran-Mantel-Haenszel test to identify the proportion of patients with a MID of ≥ 0.5-point improvement in their AQLQ score from baseline.[5-6]

Corren et al. used the Asthma Control Questionnaire-7 (ACQ-7) to assess asthma control at baseline and 16 weeks, the end of the treatment period.[8] The participant uses a 7-point scale to answer questions related to night time awakenings, symptoms and severity, activity limitation, and rescue inhaler use that have occurred within the previous week.[9] The scale ranges from 0 (totally controlled asthma) to 6 (severely uncontrolled). The ACQ-7 also includes a FEV component measured by the researchers. The final ACQ-7 score is an average of all the responses. Asthma is considered to be well controlled with a score <1.5.[5] Similar to the AQLQ, a change in baseline of ≥ 0.5-point decrease is the accepted MID for clinical significance.[9] Corren et al. used this MID, allowing for dichotomous data.

RESULTS

All three of the studies included in this review compared adolescent and adult patients in an experimental group receiving a 3.0 mg/kg reslizumab infusion to a control group receiving a placebo infusion. The intervention was studied as an adjuvant therapy for patients already taking at least a medium-dose ICS with or without another controller medication. All patients had a blood eosinophil count of ≥ 400/μL. A full set of inclusion and exclusion criteria can be found in Table 1 above. The first two studies assessed the efficacy of reslizumab in improving quality of life, while the third study assessed the efficacy of the medication to improve asthma control.

In the Bjermer et al. study, 315 patients were randomly allocated into experimental (n=106) and control (n=105) groups. 265 patients completed the trial, with 88 in the experimental group, and 85 in the placebo group. Another treatment group of 92 patients was included in the study, but this group received a different dose of reslizumab and was therefore excluded from this review. Patients were given an AQLQ at baseline and every 4 weeks until the end of the treatment period at 16 weeks. This review will focus on the AQLQ changes from baseline to week 16. Refer to Table 2 below for a summary of results from this study. Overall, 64% of patients receiving reslizumab achieved a MID of ≥ 0.5-point improvement in their AQLQ score, compared to 48% for those receiving a placebo.[5] This difference is statistically significant, with a p-value of 0.0189. Determining the number needed to treat (NNT) value is important to establish the clinical significance of the intervention. The NNT value in this study was 7, meaning that for every 7 patients with inadequately controlled eosinophilic asthma treated with reslizumab 3.0 mg/kg infusions every 4 weeks, 1 more patient will have an improvement in their quality of life compared to those receiving placebo.

In the Castro et al. study, 489 patients were randomly assorted into experimental (n=245) and control (n=244) groups. 433 patients completed the trial, with 218 in the reslizumab group and 215 in the control group. It is important to note that this review focuses on the group of patients who completed Study 1 in the Castro et al. article, as two different studies are reported. Patients were given an AQLQ at baseline and weeks 16, 32, and 52. This review will focus on changes in AQLQ scores from baseline to week 52 at the end of the trial. Refer to Table 2 below for a summary of results from this study. A total of 74% of patients receiving reslizumab had a MID of ≥ 0.5-point improvement in their AQLQ score, compared to 65% of those receiving a placebo.[6] This difference is statistically significant, with a p-value of 0.03. The NNT value in

this study was 12, meaning that for every 12 patients with inadequately controlled eosinophilic asthma treated with reslizumab 3.0 mg/kg infusions every 4 weeks, 1 more patient will have an improvement in their quality of life compared to those receiving placebo.

Table 2: Comparison of improved AQLQ scores between reslizumab and placebo

Study	Control event rate (CER)	Experiment event rate (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)	P value
Bjermer et al.[5]	0.48	0.64	0.33	0.16	7	0.0189
Castro et al.[6]	0.65	0.74	0.14	0.09	12	0.03

In the Corren et al. study, 496 patients were randomized into experimental and control groups, with 398 receiving reslizumab and 98 receiving placebo. At the end of the 16-week treatment period, 422 patients completed the trial, with 340 enrolled in the experimental group and 82 in the control group. ACQ-7 scores were compared from baseline and 16 weeks. Refer to Table 3 below for a summary of results. 71% of patients receiving reslizumab had an improvement in their asthma control with a ≥ 0.5-point decrease from baseline, compared to 57% of patients in the control group.[8] This difference is statistically significant, with a p-value of 0.01. The NNT value in this study was 8, meaning that for every 8 patients with poorly controlled asthma treated with reslizumab 3.0 mg/kg infusions q 4 weeks, 1 more patient will have an improvement in their asthma control compared to those receiving placebo.

Table 3: Comparison of improved ACQ-7 scores between reslizumab and placebo (Corren et al.[8])

Control event rate (CER)	Experiment event rate (EER)	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)	P value
0.57	0.71	0.25	0.14	8	0.01

DISCUSSION

Reslizumab was recently approved by the FDA as an adjunctive controller medication for the management of inadequately controlled eosinophilic asthma. As mentioned previously, it was studied in patients taking at least a medium-dose ICS with or without another controller medication. It does not have any other treatment indications and should not be used for the treatment of acute symptoms or asthma exacerbations. It is approved for a monthly intravenous dosing of 3.0 mg/kg.[10] Although this medication cannot be taken by the patient at home, it is still feasible because they only have to get it once per month, and it only takes 20-50 minutes to infuse.[10] Adverse effects reported for reslizumab include headache, URI, nausea and vomiting, allergic rhinitis, back pain, sinusitis, UTI, dyspnea, dizziness, and oropharyngeal pain.[10] It is important to note that reslizumab has a Black Box warning for anaphylaxis.[10] The only contraindication is an allergy to the medication.

The first two studies showed that those treated with reslizumab had significant improvement in AQLQ scores, and the third study showed significant improvement in the ACQ-7 score for those treated with reslizumab compared to placebo. The treatment effects of reslizumab in improving quality of life and asthma control were large based on the small NNT values listed above, considering this medication is an adjunctive therapy and the drug is relatively tolerable. Since the treatment effects are large, reslizumab holds a justified clinical importance as an adjuvant treatment for inadequately controlled eosinophilic asthma.

While data show that there was a statistically significant number of patients who had a MID of ≥ 0.5-point decrease in their ACQ-7 score (i.e. improvement in asthma control), it is possible that their asthma was still not controlled. Adequately controlled asthma correlates with an ACQ-7 score of <1.5.[5] It is possible that some patients, while achieving a MID in

improvement, still had an ACQ-7 score ≥1.5 indicating they still had inadequately controlled asthma after receiving reslizumab. While an improvement in their score is certainly a step in the right direction, it may not be enough to justify the use of this medication to convert a patient's status to well controlled asthma. Since the clinical question posed in this review only investigates an improvement in asthma control, this would be an area of interest for further study.

One limitation to the studies is the route of administration, but unfortunately this cannot be avoided. Researchers discuss that receiving an IV infusion may cause patients to perceive stronger treatment effects due to the route of administration, so this could have affected the outcomes measured.[6] However, the intervention was compared to a placebo infusion and had a statistically significant difference in outcomes. Patient self-report and honesty on the AQLQ and ACQ-7 could have affected outcomes as well. The questions covered a span of the previous 1 or 2 weeks, and patients may have an error in their memory that affected their responses and therefore the outcomes measured. Another limitation explained by the original researchers is that using a MID of ≥ 0.5-point improvement in AQLQ scores is not a valid measure to assess outcomes for groups of patients when an adjuvant therapy is added to their current ICS regimen.[5] While not explicitly mentioned by Corren et al., the validity of the MID for the ACQ-7 score may be questionable as well. Further studies are warranted to determine the validity of using a MID for both the AQLQ and ACQ-7 when adding a therapy to an ICS regimen.

CONCLUSION

Reslizumab is an effective treatment to improve both quality of life and asthma control in a subgroup of patients with poorly controlled eosinophilic asthma. Future study is warranted to evaluate if a significant number of patients achieve a MID in improvement in their ACQ-7 score

in addition to an ACQ-7 score of <1.5, indicating well controlled asthma. Reslizumab should not be indicated as monotherapy in these patients, but considered as an add-on treatment in those who are not well controlled with the use of a medium-dose ICS, as this was the population in each study.

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