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Reslizumab versus placebo for poorly controlled, severe eosinophilic asthma: meta-analysis

Reslizumab u odnosu na placebo za neadekvatno kontrolisanu, tešku eozinofilnu astmu: meta-analiza

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Abstract

Background/Aim. Reslizumab is humanized monoclonal antibody produced by recombinant DNA technology which binds to circulating interleukin-5 (IL-5) and down-regulates the IL-5 signaling pathway. Reslizumab is indicated for the add-on maintenance treatment of patients 18 years and older with severe eosinophilic asthma phenotype whose symptoms were inadequately controlled with inhaled corticosteroids. The aim of this meta-analysis was to assess the efficacy and safety of reslizumab compared to placebo in patients suffering from inadequately controlled, moderate-to-severe asthma with elevated blood eosinophil counts. **Methods.** Our meta-analysis was based on systematic search of literature and selection of high-quality evidence according to pre-set inclusion and exclusion criteria. The effects of reslizumab and placebo were summarized using Review Manager (RevMan) 5.3.5 and heterogeneity was assessed by the Cochrane Q test and I^2 values. Several types of bias were assessed and publication bias shown by Funnel plot and Egger's regression. **Results.** The meta-analysis included 5 randomized, placebo-controlled clinical trials. Reslizumab 3.0 mg/kg produced substantial improvements in forced expiratory volume in 1. second (FEV 1) (mean difference 0.15 [0.10, 0.21]) and in forced vital capacity (FVC) (mean difference 0.21 [0.09, 0.32]) over the 15 or 16-week treatment period, substantial decrease versus placebo in Asthma Control Questionnaire (ACQ) score (mean difference -0.28 [-0.41, -0.16]), and substantial increase vs. placebo from baseline in Asthma Quality of Life Questionnaire (AQLQ) total score (mean difference 0.24 [0.06, 0.43]). Also, reslizumab 3.0 mg/kg caused less adverse events versus placebo (OR 0.67 [0.51, 0.88]), especially asthma worsening (OR 0.53 [0.36, 0.77]) or bronchitis (OR 0.42 [0.24, 0.74]). **Conclusion.** On the basis of published clinical trials reslizumab could be considered as an effective and safe therapeutic option for severe, poorly controlled eosinophilic asthma for the time being.

Key words:
asthma; eosinophilia; anti-asthmatic agents; reslizumab; treatment outcome; meta-analysis as topic.

Apstrakt

Uvod/Cilj. Reslizumab je humanizovano monoklonsko antitelo, stvoreno rekombinantnom DNK tehnologijom, koje se vezuje za cirkulišući interleukin 5 (IL-5) i dovodi do nishodne regulacije signalnog puta koji pokreće ovaj interleukin. Reslizumab je indikovan kao dodatna terapija održavanja kod bolesnika starijih od 18 godina sa teškim oblikom eozinofilne astme, čiji simptomi nisu dovoljno kontrolisani inhalacionim kortikosteroidima. Cilj ove meta-analize je bio da proceni efikasnost i bezbednost reslizumaba u poređenju sa placebom kod bolesnika sa neadekvatno kontrolisanom, umerenom do teškom astmom, i sa povišenim brojem eozinofila u krvi. **Metode.** Naša meta-analiza je zasnovana na sistematskom pretraživanju literature i selekciji dokaza visokog kvaliteta prema prethodno postavljenim kriterijumima za uključivanje i isključivanje. Efekti reslizumaba i placebo su sumirani pomoću programa *Review Menager* (RevMan) 5.3.5, a hetereogenost studija je procenjena Kohranovim Q testom i vrednošću I^2. Ispitano je nekoliko tipova sklonosti (*bias*), pri čemu je i sklonost za izostavljanje publikacija analizirana pomoću Funnel grafika i Egerove regresije. **Rezultati.** Meta-analiza je uključila pet randomiziranih, placebo-kontrolisanih kliničkih studija. Reslizumab 3.0 mg/kg je doveo do značajnog poboljšanja forsiranog ekspiratornog volumena u 1. sekundi (FEV 1) (srednja razlika 0,15 [0,10, 0,21]) i forsiranog vitalnog kapaciteta (FVC-a) (srednja razlika 0,21 [0,09, 0,32]) posle perioda lečenja od 15 do 16 nedelja, značajnog smanjenja u odnosu na placebo *Ashtma Control Questionnaire* (ACQ) zbira (srednja razlika -0,28 [-0,41, -0,16]) i značajnog povećanja u odnosu na placebo od osnovne vrednosti *Asthma Quality of Life Questionnaire* (AQLQ) ukupnog zbira (srednja razlika 0,24 [0,06, 0,43]). Takođe, reslizumab 3,0 mg/kg je izazvao manje neželjenih dejstava u

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odnosu na placebo (OR 0,67 [0,51, 0,88]), posebno kada je u pitanju pogoršanje astme(OR 0,53 [0,36, 0,77]) ili bronhitis (OR 0,42 [0,24, 0,74]). **Zaključak.** Na osnovu publikovanih kliničkih studija reslizumab se može smatrati efikasnom i bezbednom terapijskom opcijom kod bolesnika sa teškom, neadekvatno kontrolisanom eozinofilnom astmom.

Ključne reči:
astma; eozinofilija; antiastmatici; reslizumab; lečenje, ishod; meta-analiza.

Introduction

There are several phenotypes of bronchial asthma according to specific cellular mechanism and characteristics of patients [1, 2]. Eosinophilic asthma involves subgroup of adult patients with late onset of disease, with hypereosinophilia in blood (> 1,000/mm^3) and in sputum (> 10%), with severe exacerbations which can be prevented by systematic and not by inhaled corticosteroids. Patients with this "endotype" of asthma have decreased level of athopy and their response on bronhodilatators is lower compared to subgroup of patients with allergic asthma [3–5]. This kind of inflammation pathway in asthma where eosinophiles dominate positively correlates with much more severe asthma exacerbations, higher rate of hospitalizations which contribute to increase burden of asthma [6]. Real prevalence of the eosinophilic asthma is not known, but it is estimated that 20% of patients with severe asthma would have this "endotype" of asthma [5]. Since eosinophiles mainly generate interleukin-5 (IL-5), blockade of pathways involving IL-5 can be effective therapeutic approach in patients with eosinophilic asthma [7].

Eosinophils exhibit a substantial role in airway remodeling by promoting and sustaining airway inflammation, airway wall thickening, fibrosis and angiogenesis [8, 9]. Therefore, suppressing the activity and number of eosinophils could be an important biological approach in the management of severe eosinophilic asthma [10]. IL-5 is a key cytokine for production, survival and maturation of eosinophils [11]. Due to a very specific effect on biology of eosinophils, IL-5 is considered to be an ideal molecular target for the treatment of severe eosinophilic asthma [10, 12]. Inhibition of signaling mediated by IL-5 interrupts maturation and survival of eosinophils thus reducing eosinophilic inflammation [12]. Mepolizumab was the first anti-IL-5 antibody that was tested in randomized clinical trials on eosinophilic asthma [13]. Use of mepolizumab decreased exacerbation risk, improved quality of life, lowered eosinophil counts, improved asthma control and lung function in patients with severe eosinophilic asthma in several clinical studies [14].

Reslizumab is humanized monoclonal antibody produced by recombinant DNA technology which binds to circulating IL-5 and down-regulates the IL-5 signaling pathway [12]. Reslizumab is indicated for the add-on maintenance treatment of patients 18 years and older with severe eosinophilic asthma phenotype whose symptoms were inadequately controlled with inhaled corticosteroids, with or without additional asthma controllers [15]. The recommended dosage regimen is 3 mg/kg once every 4 weeks administered by intravenous infusion over 20–50 min [16]. Although common adverse events of reslizumab are mild or moderate, like headache, nasopharyngitis and upper respiratory tract infection, reslizumab can also induce very serious adverse events as anaphylaxis [10]. Reslizumab is contraindicated in patients with known hypersensitivity to reslizumab or accompanying excipients [17].

Although a few clinical trials and one meta-analysis with reslizumab for inadequately controlled asthma with elevated blood eosinophil counts were published, there are still some unresolved issues concerning all possible outcomes of treatment. Summarizing available evidence about all measures of efficacy and safety of reslizumab in this indication tested in clinical trials would be helpful for planning future studies with reslizumab in asthma. The aim of this meta-analysis was to assess the efficacy and safety of reslizumab compared to placebo in patients suffering from inadequately controlled, moderate-to-severe asthma with elevated blood eosinophil counts.

Methods

Our study was registered in the international prospective register of systematic reviews and meta-analyses (PROSPERO) under the number CRD42016041459 prior to commencement of the research.

The following criteria for considering studies for this review were used: 1) types of studies – randomized, double-blind, placebo-controlled clinical trials; 2) types of participants – patients of both sex aged 12–75 years, with at least one blood eosinophil count of 400 cells per μL or higher during a 2–4 week period, or sputum eosinophils of 3% or more, with inadequately controlled asthma (Asthma Control Questionnaire-7 score ≥ 1.5), taking at least a medium dose of inhaled corticosteroids with or without another controller drug (including oral corticosteroids) and with airway reversibility [≥ 12% to short-acting beta-agonist (SABA)]; 3) types of interventions - intravenous infusion of reslizumab 3 mg/kg or of placebo (looking exactly the same as reslizumab) every 4 weeks, for 3 or more doses. Types of outcome measures used in our analysis were: change in forced expiratory volume in 1 second (FEV1) from baseline over 15 or 16 weeks of treatment, change in forced vital capacity (FVC) from baseline, change from baseline in asthma control questionnaire 7-point scale (ACQ-7) score, change from baseline in asthma symptom utility index (ASUI) score, rescue use of blood eosinophil count, asthma quality of life questionnaire (AQLQ) total score, immunogenicity and adverse events types and frequency.

Search methods for identification of studies primarily included electronic databases, and collection of journal articles and books of University Library, University of Kraguje-

vac, Kragujevac, Serbia. Electronic searches of the literature were conducted in Medical Literature Analysis and Retrieval System Online (MEDLINE) (Pub med, coverage from 1966 to present), Scopus/Elsevier (coverage from 1966 to present), Elton B. Stephens Company (EBSCO) (Discovery Service, coverage from 1944 to present), The Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library, coverage from 1966 to present) and a registry and results database of clinical studies of human participants ClinicalTrials.gov up to July 20, 2016. Additional searches were conducted up to November the 4th, 2016. The search was limited to articles reporting results from patients older than 12 years. Electronic databases were searched independently for relevant studies by three authors: MM, AP and VO. The searching strategies were presented in detail for each of the investigators in the Supplementary file. The most comprehensive strategy was used by the VO for the MEDLINE database, as following: (("reslizumab"[Supplementary Concept] OR "reslizumab"[All Fields]) OR Cinqair[All Fields] OR (SCH[All Fields] AND 55700[All Fields]) OR (DCP[All Fields] AND 835[All Fields])) AND (("asthma"[Medical Subject Heading – MeSH Terms] OR "asthma"[All Fields]) OR ("asthma"[MeSH Terms] OR "asthma"[All Fields] OR ("bronchial"[All Fields] AND "asthma"[All Fields]) OR "bronchial asthma"[All Fields]) OR ("pulmonary eosinophilia"[MeSH Terms] OR ("pulmonary"[All Fields] AND "eosinophilia"[All Fields]) OR "pulmonary eosinophilia"[All Fields] OR ("eosinophilic"[All Fields] AND "asthma"[All Fields]) OR "eosinophilic asthma"[All Fields]) OR (("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND ("eosinophilia"[MeSH Terms] OR "eosinophilia"[All Fields])) OR (("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND elevated[All Fields] AND ("eosinophils"[MeSH Terms] OR "eosinophils"[All Fields])) OR (severe[All Fields] AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])) OR (poorly[All Fields] AND controlled[All Fields] AND ("asthma"[MeSH Terms] OR "asthma"[All Fields])) OR (inadequately[All Fields] AND controlled[All Fields] AND ("asthma"[MeSH Terms] OR "asthma"[All Fields]))). There were no restrictions on publication date, format or language in the search strategy. The references of the retrieved articles were searched for further similar studies ("snowball search"). The collection of journal articles and books of University Library, University of Kragujevac was hand searched for relevant studies by two authors independently (AP and MM).

Data collection and analysis

The data collection sheet was created and the articles included in review were assessed for: 1) study ID; 2) report ID; 3) review author initials; 4) citation and contact details; 5) eligibility for review; 6) study design; 7) total study duration; 8) risk of bias (randomization if any, sequence generation, allocation sequence concealment, blinding, other concerns about bias); 9) total number of patients; 10) age of patients; 11) sex of patients; 12) setting; 13) country; 14) frequency of asthma exacerbations during the last year prior to inclusion in the study; 15) frequency of clinical asthma exacerbations per patient during the study treatment period; 16) mean change in FEV1 from baseline over 16 weeks of treatment; 17) mean change in FVC from baseline; 18) mean change in forced expiratory flow (FEF) at 25% to 75% of FVC (FEF25-75%) from baseline; 19) mean change from baseline in ACQ-7 score; 20) mean change from baseline in ASUI score; 21) frequency of rescue use of short-acting β-agonist per patient; 22) mean blood eosinophil count after 16 weeks of treatment; 23) mean change from baseline in AQLQ total score; 24) percentage of patients developing anti-reslizumab antibodies during the treatment course; 25) number of different intervention groups (reslizumab, placebo); 26) route of administration; 27) dose regimen; 28) duration of administration; 29) incidence of adverse events; 30) treatment discontinuation due to side effects. Values provided as percentages were converted into actual patient numbers for analysis as well as standard errors into standard deviations using number of patients, when reported as such.

Selection of studies

Based on the searching strategy, all titles and abstracts retrieved were independently scanned by five authors (AP, MM, MK, VO and JM). Eligibility of the retrieved articles was assessed at first from the title and the abstract, and if it was not possible, the full text of the articles was retrieved and searched. An article was included for review if all authors (AP, MK, JM, VO and MM) agreed that eligibility criteria had been met. In case that the reviewers had different opinions about eligibility of a study for inclusion, the matter was resolved by the corresponding author (SJ).

Data extraction and management

The data were extracted from eligible studies using the data collection sheet described previously (under the "data collection and analysis" subheading). The data collection sheet was made in electronic form, using an Excel 2007 worksheet. The data were extracted by four investigators independently (AP, MK, VO and MM) and then collating of the four tables was done by another investigator (JM), who produced the final extraction table.

Assessment of risk of bias in included studies

Risk of bias was assessed by two investigators independently (MK and JM), and collating the assessments was done by the corresponding investigator (SJ). The following sources of bias were assessed: 1) randomization if any; 2) sequence generation; 3) allocation sequence concealment; 4) blinding; 5) performance bias; 6) detection bias; 7) attrition bias; and 8) reporting bias. None of the studies had high risk of bias, so none was excluded from further analysis.

Measure of treatment effect

The following outcomes used in the studies were continuous: frequency of clinical asthma exacerbations per patient

during the study treatment period, change in FEV1 from baseline over 16 weeks of treatment, change in FVC from baseline, change in FEF at 25% to 75% of FVC [FEF25-75%]) from baseline, change from baseline in ACQ-7 score, change from baseline in ASUI score, rescue use of short-acting β-agonist, blood eosinophil count and AQLQ total score. For these outcomes the treatment effect was measured by mean difference, since the outcomes were measured on the same scale in all studies. However, two of the continuous outcomes could not be summarized because they were reported in only one of the included studies: frequency of clinical asthma exacerbations per patient during the study treatment period and change in FEF at 25% to 75% of FVC [FEF25-75%]) from baseline. The following outcomes were dichotomous: immunogenicity (whether antibodies are present or not) and adverse events frequency. For these outcomes the treatment effect was measured by odds ratio (OR).

Unit of analysis issues

Unit of analysis in the clinical trials that were included in this meta-analysis were individual patients. Individual participants were randomized to one of two parallel intervention groups, and a single measurement for each outcome from each participant was collected and analyzed.

Dealing with missing data

Missing data were requested directly from the original investigators, however they did not respond to our requests except with courtesy. The missing data were then retrieved from the results presented on ClinicalTrials.gov, when available. Finally, the potential impact of missing data on the findings of the meta-analysis will be addressed in the Discussion section.

Assessment of heterogeneity

Between-study heterogeneity was assessed with the Cochrane Q test using a χ^2 function (p values < 0.10 were considered significant). I^2 values were calculated to quantify inconsistency across studies. I^2 values of 30% or less may represent low heterogeneity, values from 30% to 50% may represent moderate heterogeneity, values from 50% to 90% substantial heterogeneity and values of 90% or more may represent considerably heterogeneity. An I^2 value > 30% was considered significant in this meta-analysis.

Assessment of reporting biases

The possibility of within-study selective outcome reporting was examined for each study included in this meta-analysis. First, by constructing matrix of the outcomes for all studies, we identified studies and specific outcomes that were not reported. Then we searched for published protocols of such studies at ClinicalTrials.gov and other forms of publications of the same studies, in order to find the missing outcomes. Finally, the authors were contacted with a request to provide the missing data, but they did not send us the data. The possibility of between-study publication bias was examined by construction of funnel plots for continuous outcomes and by Egger's regression for discrete outcomes [18]. Klein's number was also calculated for all outcomes [19].

Data synthesis

The random effects model (which includes both within-study and between-study variations in calculation of the weighted average) was used to combine the results from the studies. The Mantel-Haenszel method (fixed effect model) was also used to estimate how our conclusions could be influenced by assumptions about the model and by the study heterogeneity. Since significant heterogeneity of the studies was not found, subgroup analysis was not performed. All calculations were done by Review Manager (RevMan) software version 5.3.5 [20].

Sensitivity analysis

Sensitivity analysis was performed by excluding individual trials one at a time and recalculating the pooled odds ratio and mean difference estimates for the remaining studies. In this way we got insight how each of the included studies influenced our conclusions.

Results

Results of the literature search are shown in Figure 1. Only five clinical trials [21–24] fulfilled all inclusion and missed all exclusion criteria which were set prior the study commencement (two of the trials were published in the same publication. Characteristics of the included studies with risk of bias are shown in detail in Table 1.

Summaries of differences in effects of reslizumab vs. placebo for the main outcomes (using random effects model) were as following: reslizumab 3.0 mg/kg produced substantial improvements in FEV1 (mean difference 0.15) and in FVC (mean difference 0.21) over the 15 or 16-week treatment period; substantial decrease versus placebo in ACQ score (mean difference -0.28), substantial increase vs. placebo from baseline in AQLQ total score (mean difference 0.24) rescue inhaler use (mean difference -0.33) and blood eosinophil count after 15 or 16 weeks of treatment (mean difference -478.17) was observed with reslizumab 3.0 mg/kg; reslizumab 3.0 mg/kg caused less adverse events versus placebo (odds ratio 0.67), especially asthma worsening (odds ratio 0.53) or bronchitis (odds ratio 0.42) while there was no significant difference for nasopharyngitis (odds ratio 0.97) or upper respiratory tract infection (odds ratio 0.86). Details of the summaries of differences in effects are shown in Tables 2 and 3. Sensitivity analysis did not show significant changes with exclusion of single trials.

Table 1

Characteristics of the studies included in meta-analysis

Study	Bjermer 2016 [24]	Castro 2011 [22]	Castro 2015 [21]	Castro 2015 [21]	Corren 2016 [23]
Methods	Parallel group randomized trial	Parallel group randomized trial	Parallel group randomized trial	Parallel group randomized trial	Parallel group randomized trial
Participants	Patients aged 12-75 years with inadequately controlled asthma, ACQ-7 score ⩾1.5, airway reversibility (⩾12% to SABA), who were receiving treatment with at least a medium-dose inhaled corticosteroids (fluticasone propionate ⩾440 µg/day or equivalent) and had at least one blood eosinophil count of ⩾400 cells/µL during the screening period.	Patients aged 18 to 75 years with asthma (1) confirmed by airway hyperreactivity, (2) treated by high dose inhaled corticosteroids in combination with at least one other agent, (3) poorly controlled and (4) induced sputum eosinophils of 3% or more.	Patients aged 12 to 75 (Child, Adult, Senior) with at least one blood eosinophil count of 400 cells per µL or higher during a 2-4 week screening period and inadequately controlled asthma (ACQ-7 Score ⩾1.5) who were receiving at least a medium dose of inhaled corticosteroids (fluticasone propionate ⩾ 440 mg per day, or equivalent) with or without another controller drug (including oral corticosteroids).	Patients aged 12 to 75 (Child, Adult, Senior) with at least one blood eosinophil count of 400 cells per µL or higher during a 2-4 week screening period and inadequately controlled asthma (ACQ-7 Score ⩾1.5) who were receiving at least a medium dose of inhaled corticosteroids (fluticasone propionate ⩾ 440 mg per day, or equivalent) with or without another controller drug (including oral corticosteroids).	Patients aged 18 to 65 years, with asthma (1), ACQ score of at least 1.5 (2), minimum 12 % airway reversibility to beta-agonist administration (3), treated by fluticasone and stable asthma therapy regimens for 30 days before screening (4), surgically sterile female patients, 2 years postmenopausal, or a negative ßHCG result (5), reproductively potent female patients who agree to use contraception during and 30 days after participation in the study (6).
Interventions	Reslizumab 0.3 or 3.0 mg/kg or placebo	Reslizumab 3 mg/kg vs. placebo	Reslizumab 3 mg/kg vs. placebo	Reslizumab 3 mg/kg vs. placebo	Reslizumab 3 mg/kg vs. placebo
Outcomes	- change in FEV1 from baseline over 16 weeks of treatment - change in FVC from baseline - change in FEF 25-75% from baseline - change from baseline in ACQ-5, ACQ-6 and ACQ-7 scores - change from baseline in AQLQ score - change from baseline in ASUI score - rescue use of short-acting β-agonist - change from baseline in blood eosinophil count - immunogenicity - adverse events types and frequency	- change in FEV1 from baseline over 15 or 16 weeks of treatment - change in FVC from baseline - change from baseline in ACQ-7 score - blood eosinophil count - immunogenicity - adverse events types and frequency	- frequency of asthma exacerbations during the last year prior to inclusion in the study - frequency of clinical asthma exacerbations per patient during the study treatment period - change in FEV1 from baseline over 15 or 16 weeks of treatment - change from baseline in ACQ-7 score - change from baseline in ASUI score - change in frequency of rescue use of short-acting β-agonist per patient (puffs per day) - change from baseline in blood eosinophil count - change from baseline in AQLQ score - immunogenicity - adverse events types and frequency	- frequency of asthma exacerbations during the last year prior to inclusion in the study - frequency of clinical asthma exacerbations per patient during the study treatment period - change in FEV1 from baseline over 15 or 16 weeks of treatment - change from baseline in ACQ-7 score - change from baseline in ASUI score - change in frequency of rescue use of short-acting β-agonist per patient (puffs per day) - change from baseline in blood eosinophil count - change from baseline in AQLQ score - immunogenicity - adverse events types and frequency	- change in FEV1 from baseline at week 16 - change from baseline in ACQ over 16 weeks - change from baseline in FVC at weeks 4, 8, 12, and 16 - change from baseline in average daily use of SABA - change from baseline in blood eosinophil counts

Risk of random sequence generation bias	Low: Randomized study	Low: Randomized study	Low: Randomized study. Randomization was done with use of interactive response technology with computerized central randomization.	Low: Randomized study. Randomization was done with use of interactive response technology with computerized central randomization.	Low: Randomized study. Patients were randomized (4:1) to reslizumab 3.0 mg/kg or placebo given intravenously once every 4 weeks during the treatment period (total of 4 doses), stratified by the occurrence of exacerbations in the 12 months prior to screening (yes/no).
Risk of allocation concealment bias	Low: Randomized study	Low: Randomized study	Low: Randomized study	Low: Randomized study.	Low: Randomized study.
Risk of blinding of patients and personnel bias	Low: Double-blind, placebo-controlled study	High: Patients, investigators, and study personnel were blinded to study treatment group assignment, unlike each site's study pharmacist who were not blinded.	Low: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), placebo-controlled study	Low: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), placebo-controlled study	Low: Double blind (Subject, Caregiver, Investigator, Outcomes Assessor) study
Risk of blinding of outcome assessment bias	Unclear risk: Not described in the report.	Unclear: Not described in the report.	Low: The results of measuring were redacted after initiation of treatment to ensure integrity of masking.	Low: The results of measuring were redacted after initiation of treatment to ensure integrity of masking.	Low: A blind data review meeting was conducted before the database lock to determine the exclusion of affected, individual pulmonary function tests, ACQ, and SABA assessments.
Risk of incomplete outcome data bias	High: Of 315 enrolled patients 265 completed the study. The efficacy analysis set and safety analysis set included 311 of 315 patients.	Low: Only one patient in the reslizumab group and 3 patients in the placebo group were lost to follow-up before the end of the study.	High: Of 244 enrolled patients in placebo group, 215 completed study. Of 245 enrolled patients in reslizumab group, 218 completed study.	High: Of 232 enrolled patients in placebo group, 199 completed study. Of 232 enrolled patients in reslizumab group, 202 completed study.	High: A total of 869 patients were screened. Out of 98 patients who were randomized to placebo, 82 (84%) completed the study and out of 398 who were randomized to reslizumab, 340 (85%) completed the study.
Risk of selective reporting bias	Low: All of the study's pre-specified outcomes were reported in the pre-specified way.	High: Only 3 efficacy outcomes (out of 9 possible) were reported, apart from adverse events.	Low: All of the study's pre-specified outcomes were reported in the pre-specified way.	Low: All of the study's pre-specified outcomes were reported in the pre-specified way.	Low: All of the study's efficacy outcomes were reported.
Risk of other bias	High: Efficacy outcomes were not reported for entire intention-to-treat population.	High: Efficacy outcomes were not reported for entire intention-to-treat population.	Low: Efficacy outcomes were reported for entire intention-to-treat population.	Low: Efficacy outcomes were reported for entire intention-to-treat population.	Low: Efficacy outcomes were reported for entire intention-to-treat population.

ACQ – Asthma Control Questionnaire; SABA – Short acting beta-agonist; β-human chorionic gonadotropin; FEV1 – forced expiratory volume in 1st second; FVC – forced vital capacity;
AQLQ – Asthma Quality of Life Questionnaire; ASVI – Asthma Symptom Utility Index.

Table 2

Summary of continuous outcomes of the studies included in the meta-analysis

Reslizumab compared with placebo for poorly controlled, severe eosinophilic asthma					
Patient or population: patients 12 to 75 years old with poorly controlled, severe eosinophilic asthma Settings: outpatients; Intervention: reslizumab; comparison: placebo					
Outcomes	Comparative effect (95% CI)		Difference between means [95% CI]	Number of participants (Study)	Quality of the evidence (GRADE)
	Mean or mean change Placebo	Mean or mean change Reslizumab 3mg/kg			
Mean change in FEV1 from baseline over 15 or 16 weeks of treatment change expressed in liters 15-16 week of follow up	-0.08 ± 0.11 0.11 ± 0.06 0.09 ± 0.08 0.002 ± 0.238 0.126 ± 0.108	0.18 ± 0.10 0.25 ± 0.06 0.19 ± 0.08 0.272 ± 0.109 0.286 ± 0.107	0.26 ± 0.15 0.14 ± 0.08 0.10 ± 0.11 0.270 ± 0.206 0.160 ± 0.152 Summary difference: 0.15 [0.10, 0.21]	106 (Castro 2011)[22] 489 (Castro 2015)[21] 464 (Castro 2015)[21] 96 (Corren 2016)[23] 211 (Bjermer 2016)[24]	moderate high high low moderate
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 3.89, df = 4 (p = 0.42); I² = 0%, Test for overall effect: Z = 5.35 (p < 0.00001)				
Mean change in forced vital capacity [FVC] from baseline change expressed in liters 15–16 week of follow up	-0.130 ± 0.142 0.055 ± 0.284 0.172 ± 0.120	0.180 ± 0.125 0.230 ± 0.133 0.301 ± 0.120	0.310 ± 0.132 0.175 ± 0.248 0.129 ± 0.170 Summary difference: 0.21 [0.09, 0.32]	104 (Castro 2011)[22] 96 (Corren 2016)[23] 205 (Bjermer 2016)[24]	high low moderate
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 1.99, df = 2 (p = 0.37); I² = 0%, Test for overall effect: Z = 3.43 (p = 0.0006)				
Mean change from baseline in ASUI score Asthma Symptom Utility Index (from 0- worst possible symptoms to 1- no symptoms) 16 weeks of follow up	0.11 ± 0.023 0.08 ± 0.031 0.082 ± 0.042	0.17 ± 0.368 0.12 ± 0.031 0.129 ± 0.042	0.06 ± 0.375 0.04 ± 0.054 0.047 ± 0.059 Summary difference: 0.04 [0.01, 0.08]	476 (Castro 2015)[21] 451 (Castro 2015)[21] 204 (Bjermer 2016)[24]	high high moderate
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 0.04, df = 2 (p = 0.98); I² = 0%, Test for overall effect: Z = 2.34 (p = 0.02)				
Mean change in blood eosinophil count after 15 or 16 weeks of treatment change expressed in cells per µl 16 weeks of follow up	-118 ± 45.47 -76 ± 52.53 -35 ± 53.12	-584 ± 45.08 -555 ± 52.14 -529 ± 52.92	-466 ± 64.03 -479 ± 74.01 -494 ± 75.16 Summary difference: -478.17 [-518.84, -437.49]	484 (Castro 2015)[21] 456 (Castro 2015)[21] 205 (Bjermer 2016)[24]	high high moderate
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 0.31, df = 2 (p = 0.86); I² = 0%, Test for overall effect: Z = 23.04 (p < 0.00001)				
Mean change from baseline in AQLQ total score Asthma Quality of Life Questionnaire - scale range from 1 to 7 16 weeks of follow up	0.695 ± 0.172 0.777 ± 0.226 0.779 ± 0.356	0.933 ± 0.172 0.987 ± 0.227 1.138 ± 0.358	0.238 ± 0.244 0.210 ± 0.320 0.359 ± 0.505 Summary difference: 0.24 [0.06, 0.43]	457 (Castro 2015)[21] 429 (Castro 2015)[21] 200 (Bjermer 2016)[24]	high high moderate

Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 0.24, df = 2 (p = 0.88); I² = 0%, Test for overall effect: Z = 2.65 (p = 0.008)				
Change in frequency of rescue use of short-acting β-agonist per patient puffs per day	-0.360 ± 0.310 -0.440 ± 0.457 -0.100 ± 0.843 -0.300 ± 0.549	-0.640 ± 0.306 -0.500 ± 0.451 -0.800 ± 0.372 -0.900 ± 0.529	-0.280 ± 0.432 -0.060 ± 0.572 -0.700 ± 0.717 -0.600 ± 0.762 Summary difference: -0.33 [-0.64, -0.02]	478 (Castro 2015)[21] 368 (Castro 2015)[21] 96 (Corren 2016)[23] 204 (Bjermer 2016)[24]	moderate high low moderate
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 1.83, df = 3 (p = 0.61); I² = 0%, Test for overall effect: Z = 2.09 (p = 0.04)				
Mean change from baseline in ACQ-7 Asthma Control Questionnaire 7 score (0-totally controlled, 6-severely uncontrolled) 16 weeks of follow-up	-0.300 ± 0.271 -0.68 ± 0.129 -0.66 ± 0.170 -0.368 ± 0.471 -0.494 ± 0.241	-0.7 ± 0.274 -0.94 ± 0.125 -0.86 ± 0.170 -0.858 ± 0.216 -0.853 ± 0.241	0.4 ± 0.386 0.26 ± 0.181 0.20 ± 0.241 0.49 ± 0.408 0.359 ± 0.341 Summary difference: -0.28 [-0.41, -0.16]	106 (Castro 2011)[22] 483 (Castro 2015)[21] 458 (Castro 2015)[21] 96 (Corren 2016)[23] 204 (Bjermer 2016)[24]	moderate high high low moderate
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 1.67, df = 4 (p = 0.80); I² = 0%, Test for overall effect: Z = 4.54 (p < 0.00001)				
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.					

Table 3

Summary of adverse effects observed in the studies included in the meta-analysis

Reslizumab compared with placebo for poorly controlled, severe eosinophilic asthma			
Patient or population: patients 12 to 75 years old with poorly controlled, severe eosinophilic asthma Settings: outpatients Intervention: reslizumab Comparison: placebo			
Outcomes	Relative effect: OR [95% CI]	Number of participants (Study)	Quality of the evidence (GRADE)
Incidence of adverse events	0.86 [0.49, 1.50] 0.66 [0.27, 1.62] 0.74 [0.46, 1.18] 0.50 [0.31, 0.81] Summary OR: 0.67 [0.51, 0.88]	208 (Bjermer 2016)[24] 106(Castro 2011)[22] 488 (Castro 2015)[21] 464 (Castro 2015)[21]	moderate moderate high high

Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 2.39, df = 3 (p = 0.50); I² = 0%, Test for overall effect: Z = 2.89 (p = 0.004)		
Number of patients developing anti-reslizumab antibodies during the treatment course	27.91 [1.63, 477.84] 17.50 [1.00, 304.91] 15.47 [0.88, 272.38] Summary OR: 19.66 [3.78, 102.23]	211 (Bjermer 2016)[24] 489 (Castro 2015)[21] 464 (Castro 2015)[21]	moderate high high
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 0.09, df = 2 (p = 0.95); I² = 0%, Test for overall effect: Z = 3.54 (p = 0.0004)		
Asthma worsening	0.78 [0.38, 1.61] 0.60 [0.42, 0.86] 0.39 [0.26, 0.57] Summary OR: 0.53 [0.36, 0.77]	208 (Bjermer 2016)[24] 489 (Castro 2015)[21] 464 (Castro 2015)[21]	moderate high high
Heterogeneity estimate	Heterogeneity: Tau² = 0.06; χ^2 = 4.15, df = 2 (p = 0.13); I² = 52%, Test for overall effect: Z = 3.28 (p = 0.001)		
Nasopharyngitis	1.56 [0.43, 5.71] 2.51 [0.81, 7.83] 0.82 [0.48, 1.41] 0.76 [0.49, 1.18] Summary OR: 0.97 [0.63, 1.51]	208 (Bjermer 2016)[24] 106(Castro 2011)[22] 489 (Castro 2015)[21] 464 (Castro 2015)[21]	moderate moderate high high
Heterogeneity estimate	Heterogeneity: Tau² = 0.07; χ^2 = 4.55, df = 3 (p = 0.21); I² = 34%, Test for overall effect: Z = 0.13 (p = 0.90)		
Upper respiratory tract infection	1.73 [0.40, 7.45] 0.38 [0.07, 2.03] 1.25 [0.75, 2.07] 0.48 [0.20, 1.15] Summary OR: 0.86 [0.45, 1.66]	208 (Bjermer 2016)[24] 106 (Castro 2011)[22] 489 (Castro 2015)[21] 464 (Castro 2015)[21]	moderate moderate high high
Heterogeneity estimate	Heterogeneity: Tau² = 0.19; χ^2 = 5.27, df = 3 (p = 0.15); I² = 43%, Test for overall effect: Z = 0.45 (p = 0.66)		
Bronchitis	0.40 [0.08, 2.09] 0.65 [0.10, 4.08] 0.51 [0.26, 1.03] 0.14 [0.03, 0.60] Summary OR: 0.42 [0.24, 0.74]	208 (Bjermer 2016)[24] 106 Castro 2011[22] 489 (Castro 2015)[21] 464 (Castro 2015)[21]	moderate moderate high high
Heterogeneity estimate	Heterogeneity: Tau² = 0.00; χ^2 = 2.82, df = 3 (p = 0.42); I² = 0%, Test for overall effect: Z = 3.00 (p = 0.003)		
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.			

FEV1 – forced expiratory volume in 1st second; CI – confidence interval; FVC – forced vital capacity; ASUI – Asthma Symptom Utility Index.

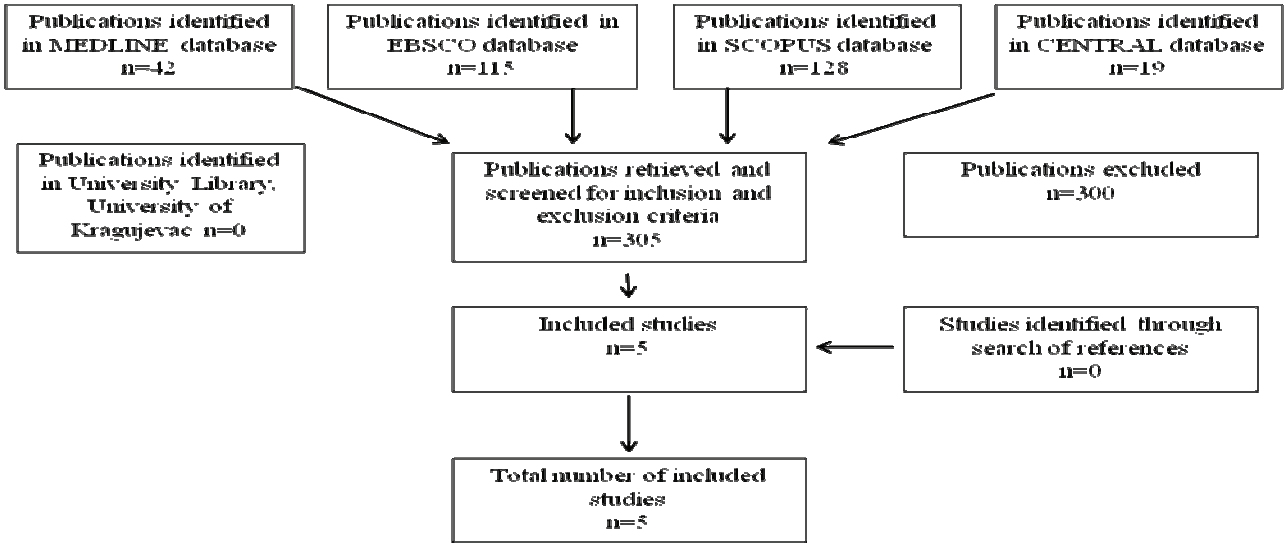

Fig. 1 – Study selection.

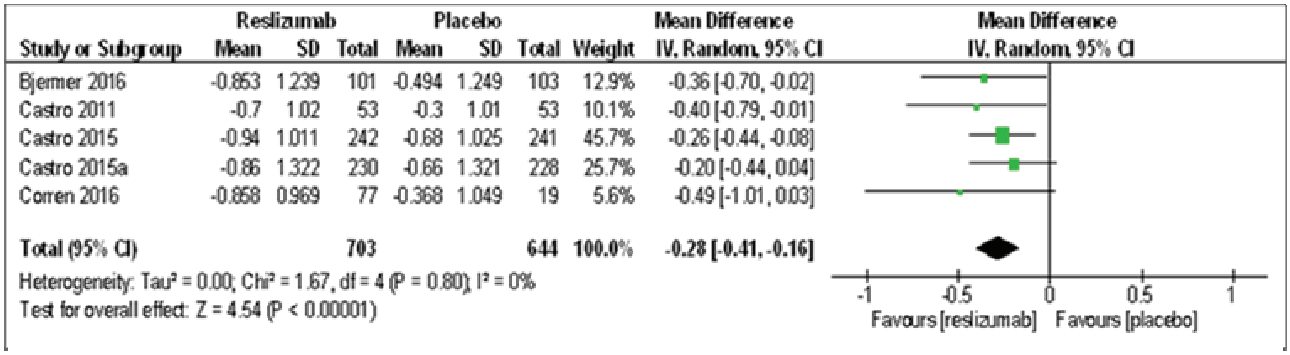

Fig. 2 – Summary of differences in Asthma Control Questionnaire (ACQ) score with reslizumab vs. placebo from baseline over 15-16 weeks of treatment.
SD – standard deviation; CI – confidence interval.

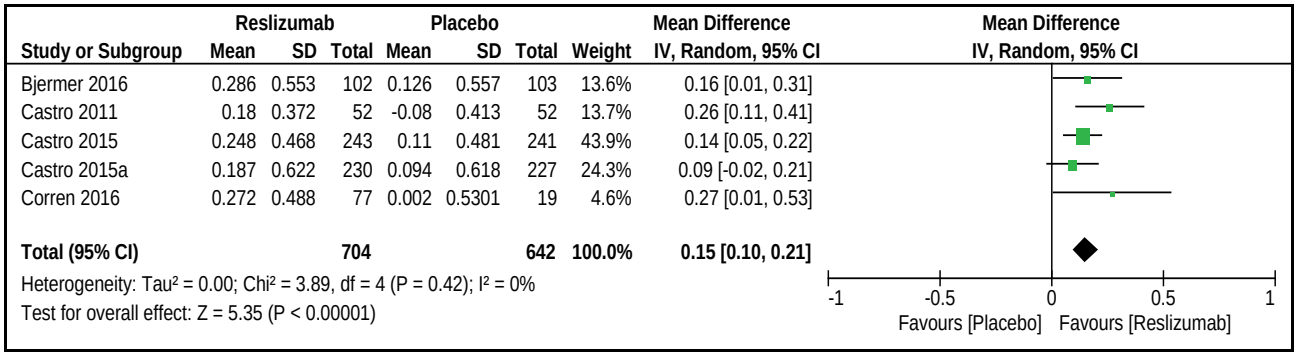

Fig. 3 – Summary of differences in forced expiratory volume in 1 second (FEV1) with reslizumab vs. placebo from baseline over 16 weeks of treatment.
SD – standard deviation; CI – confidence interval.

Summaries of differences in effects of reslizumab and placebo for the most important outcomes (improvements in FEV 1 and decrease in ACQ score) with heterogeneity estimates are shown by Forest plots (Figures 2 and 3).

The reporting bias was assessed by Funnel Plot, using "trim and fill" method for continuous outcomes. The central symmetry axis of Funnel Plots for all tested continuous outcomes did not change place significantly after "trim and fill" exercise. In Figures 4 and 5 Funnel Plots are shown before and after "trim and fill" exercise for two continuous outcomes: improvements in FEV 1 and decrease in ACQ score from baseline over the 15–16 weeks period.

For discrete outcomes (frequencies of adverse effects) the reporting bias was assessed by Klein's number and Egger's regression. Klein's number for total incidence of adverse effects was 4.52 and the Egger's regression showed minimal correction of the summary effect estimate: from OR = 0.67 to OR = 0.42 (Figure 6). For percent of patients developing anti-reslizumab antibodies the Klein's number was 6.79, and OR was corrected by the Egger's regression from 19.66 to 42.23. Klein's number for incidence of asthma worsening was 16.92 and the Egger's regression corrected the summary effect estimate: from OR = 0.53 to OR = 2.25. For incidence of nasopharyngitis, incidence of upper respiratory tract infection and incidence of bronchitis the Klein's numbers were -3.96, -3.45 and 5.48, respectively, and OR was corrected by the Egger's regression from 0.97 to 2.47, from 0.86 to -1.16, and from 0.42 to -0.83, respectively.

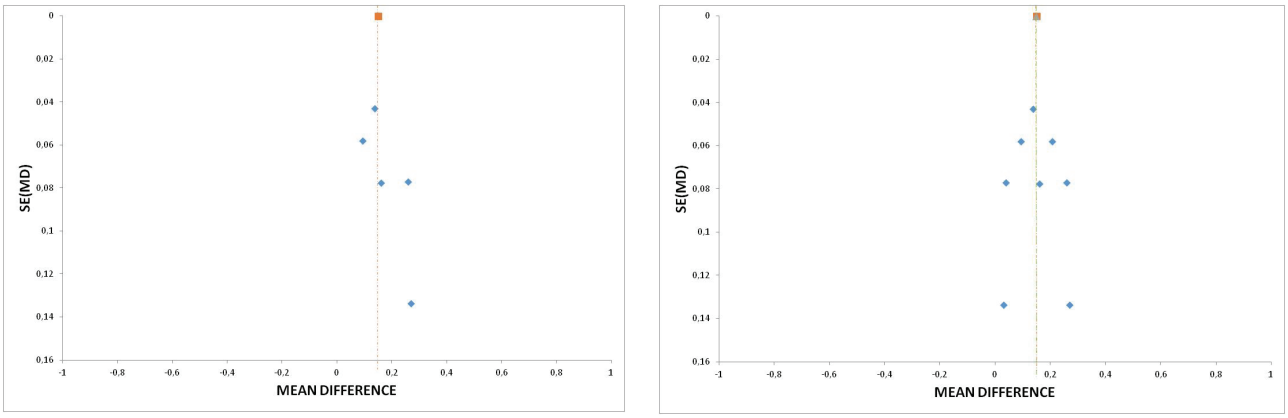

Fig. 4 – Funnel Plots before and after "trim and fill" exercise for improvement in forced expiratory volume in 1 sec (FEV1) from baseline over the 15-16 weeks period.

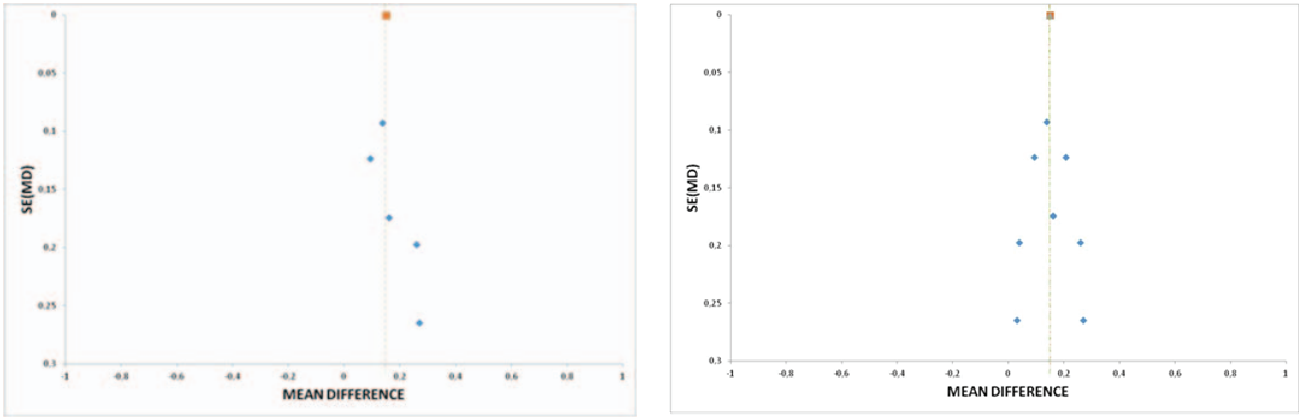

Fig. 5 – Funnel Plots before and after "trim and fill" exercise for decrease in Asthma Control Questionnaire (ACQ) score from baseline over the 15-16 weeks period.

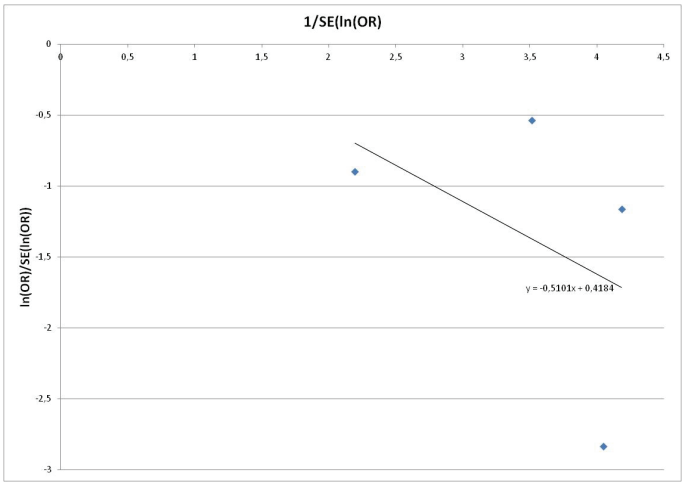

Fig. 6 – Egger's regression for incidence of all adverse effects in the included studie.

Discussion

Results of our study showed that reslizumab is significantly more efficient than placebo in the treatment of severe, poorly controlled eosinophilic asthma. Our results indicated that reslizumab led to significantly greater increase in FEV1 and FVC compared to placebo. On the other hand, reslizumab led to greater reduction of ACQ score and blood eosinophil counts compared to placebo, which also suggested that administration of reslizumab in patients with eosinophilic asthma had significant benefits. These results were in agreement with results of the recently published meta-analysis of reslizumab efficacy and safety [25]. However, in this meta-analysis authors did not analyze impact of reslizumab to AQLQ score, as it was done in another meta-analysis which compared effects of mepolizumab (also monoclonal antibody against IL-5) with placebo in the same clinical entity [26]. After we summarized results of clinical trials with reslizumab in our meta-analysis, it turned out that it improved the AQLQ score much more than placebo. Therefore, reslizumab not only had beneficial effects on clinical outcomes of severe, poorly controlled eosinophilic asthma, but it also markedly improved quality of life of these severely ill patients. Heterogeneity of the included studies was low and publication bias small, so effects were consistent from study to study.

Our meta-analysis indicated that reslizumab use was associated with significantly lower overall incidence of adverse events, asthma worsening and bronchitis compared to placebo. In addition, there was no significant difference in incidence of nasopharyngitis and upper respiratory tract infections in general between reslizumab and placebo. Our results are in agreement with results of the recently published meta-analysis of reslizumab efficacy and safety which has reported that there was no difference in proportion of individuals who withdrew due to adverse events as well as in incidence of upper respiratory adverse events [25]. Although reslizumab use can be associated with development of anti-reslizumab antibodies, they did not appear to have impact on its efficacy and safety and their appearance is transient [21, 27]. All these imply that reslizumab is generally well tolerated, although longer-term safety still needs to be assessed. The risk of anaphylaxis, which was reported in 0.3% of the patients, remains the main reason why reslizumab should be administered in a health care setting where patient can be observed and managed properly in the case of allergy [28].

Our results should be taken with certain reserve, since some of the important clinical outcomes were reported in only one of the included studies [frequency of clinical asthma exacerbations per patient during the study treatment period and change in forced expiratory flow from 25% to 75% of FVC (FEF25-75%) from baseline], and overall number of the included studies was low. Since several clinical trials with reslizumab are ongoing, new meta-analysis should be made in close future to challenge our results.

Conclusion

On the basis of published clinical trials reslizumab could be considered as effective and safe therapeutic option for severe, poorly controlled eosinophilic asthma for the time being. Future studies which would include ongoing clinical trials are necessary to confirm this conclusion.

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