

Original

**A Comparison of Adverse Effect Profiles of Two Anti-IL-5 Therapies
in Adults with Uncontrolled Asthma
—A Network Meta-analysis of Phase 3 Trials—**

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Abstract : The aim of this study was to compare the adverse effect profiles of mepolizumab (MPZ) and benralizumab (BRZ) in adults with uncontrolled asthma. A network meta-analysis of phase 3 trials was conducted to compare the adverse effects of MPZ and BRZ in patients with uncontrolled asthma. The MEDLINE-PubMed, Scopus and the Cochrane library databases were searched to identify any relevant articles. The outcome measures of fatal adverse events, headache, and injection site reaction are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The surface under the cumulative curve (SUCRA) for each outcome was also compared among MPZ, BRZ, and placebo treatments. Four randomized controlled trials of MPZ (100 mg s/c every four weeks) (100-MPZ) or BRZ (30 mg s/c every eight weeks) (30-BRZ) met the criteria for inclusion in the study. The ORs and 95% CIs of 100-MPZ compared with BRZ for fatal adverse events, headache, and injection site reaction were 0.26 (0.01–4.90), 0.79 (0.40–1.54), and 2.32 (0.79–6.80), respectively. SUCRAs for 100-MPZ, 30-BRZ, and placebo were 0.8, 0.3, and 0.4 for fatal adverse events, 0.5, 0.1, and 0.8 for headache, and 0.0, 0.6, and 0.8 for injection site reaction, respectively. There were no significant differences in the incidence of fatal adverse events, headache, and injection site reaction between MPZ and BRZ treatment. However, the SUCRA values indicate an association between administration of BRZ and the occurrence of fatal adverse event or headache, or between administration of MPZ and the occurrence of injection site reaction. Moreover, the incidence odds of injection site reaction were significantly higher in the MPZ group than in the placebo group. Further analysis will be needed to clarify the details of safety profiles of these anti-IL-5 therapies.

Key words : mepolizumab, benralizumab, adverse effect, asthma, network meta-analysis

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Introduction

The increased global use of inhaled corticosteroids (ICS) has contributed to a significant reduction in the frequency of hospitalization for acute exacerbation in patients with bronchial asthma^{1,2}. However, there are still many patients whose asthma is not optimally controlled by a combination of ICS and systemic glucocorticoids³. Thus, there remains an unmet medical need for additional treatment options metrological for these patients with uncontrolled asthma¹⁻³.

Several drugs are now available for patients with uncontrolled severe asthma even after treatment with high doses of ICS and two or more controller therapies¹. Recent phase 3 trials of anti-interleukin (IL)-5 therapy showed significant reductions in the number/severity of exacerbations in patients with asthma that is refractory to current conventional therapies^{4,5,10,11}. Mepolizumab (MPZ), a humanized monoclonal antibody against IL-5, selectively inhibits eosinophilic inflammation and reduces exacerbations and the treatment required with systemic glucocorticoids⁴⁻⁶.

Several randomized controlled trials (RCTs) have examined the effects of benralizumab (BRZ), an anti-IL-5 receptor α monoclonal antibody, on uncontrolled asthma⁷⁻⁹. The results showed that a relatively low dose of benralizumab (30 mg/body) significantly reduced exacerbation rates and improved both asthma symptoms and the quality of life in patients with uncontrolled asthma^{10,11}. However, a comparison of safety between MPZ and BRZ has not been performed. An understanding of the safety profiles of MPZ and BRZ would lead to increased safety of asthma treatment. Therefore, the aim of this study was to compare the adverse effect profiles of MPZ and BRZ in adults with uncontrolled asthma through a network meta-analysis (NMA) of phase 3 trials.

Methods

Publication search and inclusion criteria

We searched the entries in MEDLINE-Pubmed, Scopus, and Cochrane library databases until August 2016 by using the combination of terms including “mepolizumab”, “benralizumab”, and “asthma”.

PubMed was mainly used for the publication search because it is an open access database that is suitable for a comprehensive literature search. Scopus was used to ensure that all eligible articles had been detected in PubMed. We also used the Cochrane library database to search for any additional references. No restrictions were imposed on the search language. Studies were considered eligible if they met the following criteria: phase 3 studies that assessed the clinical efficacy and safety of MPZ or BRZ in uncontrolled asthma.

Data extraction and quality assessment

Studies of children aged 12 years or younger, case reports, and single arm studies were excluded. The methodological quality of included trials was evaluated using the Jadad score, which assesses studies on the basis of their description of randomization, blinding and dropout¹². A Jadad score of 3 or over indicates that the articles were of high quality.

Data analysis

A NMA of four studies was performed to evaluate the safety of MPZ and BRZ using the statistical methods described by White *et al* and Chaimani *et al*^{13,14}. The incidence of fatal adverse effect, headache, and injection site reaction were compared among MPZ, BRZ, and placebo. The summary effect sizes are represented as odds ratios (ORs) with 95% confidential intervals (CIs). Data analysis was performed using STATA ver. 14.0 (Stata Corp., College Station, TX, USA). One of the benefits of NMA is that the analyses were able to compare among multiple treatments and to rank each treatment.

Ranking investigation

The ability of an NMA to rank treatments allows us to propose the best probable treatment based on their rank^{13,14}. The surface under the cumulative ranking (SUCRA) curve is the ratio of the area under the cumulative ranking curve to the entire area in the plot. SUCRA was used to compare each treatment to an ideal treatment that is consistently the best without uncertainty. In this analysis, the treatments with larger SUCRA values are those with greater safety^{13,14}.

Inconsistency test

A NMA can be carried out based on the assumption of consistency, which should be confirmed by a global inconsistency test. The difference between direct and indirect evidence is expressed as a *P* value, and is calculated by analyzing the equality of the direct and indirect evidence. *P* values were calculated for each outcome, and $P < 0.05$ was considered to indicate that significant inconsistency was present^{13,14}.

Results

Search results and characteristics of included studies

The study selection process is shown in Fig. 1. A total of 51 citations were retrieved from all databases. Ten articles were reviews and 37 were non-phase 3 trials of anti-IL-5 therapy. Finally, a total of four randomized control trials (RCTs) for MPZ or BRZ were included in the NMA^{4,5,10,11}. All comparisons in the network are shown in Fig. 2. The characteristics of the four RCTs and the interventions in these trials are shown in Table 1. Two trials compared MPZ (100 mg s/c every four weeks) (100-MPZ) with placebo, and two trials compared BRZ (30 mg s/c every eight weeks) (30-BRZ) with placebo. The mean age of the patients ranged from 47.6 to 52.4 years and the study duration ranged from 20 to 56 weeks. All of the studies had Jadad scores of 5, indicating that the included studies were of high quality.

Comparison of adverse effect profiles of MPZ, BRZ, and placebo

The ORs and 95% CIs of 100-MPZ compared with 30-BRZ for fatal adverse events, headache, and injection site reaction were 0.26 (0.01–4.90), 0.79 (0.40–1.54), and 2.32 (0.79–6.80), respectively (Table 2). Although these results are not significant, the risks of fatal adverse

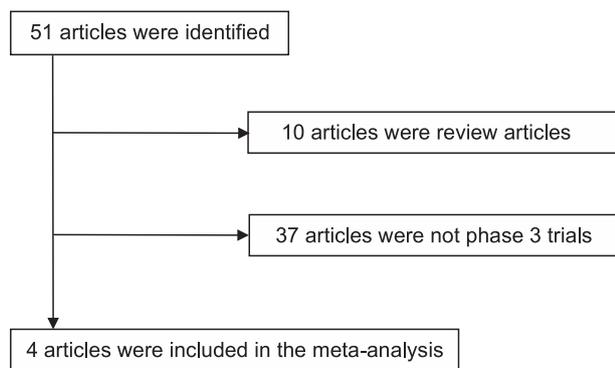


Fig. 1. Flow diagram of the study selection process

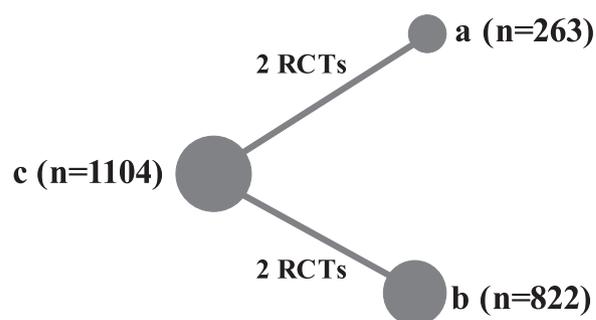


Fig. 2. Network of eligible comparisons of adverse effects in a network meta-analysis. The width of the lines represents the number of studies compared for each pair of treatments. The size of the balloons represents the total sample size of each treatment. a: 100 mg mepolizumab administered subcutaneously every four weeks; b: 30 mg benralizumab administered subcutaneously every eight weeks; c: placebo.

events and headache were lower with 100-MPZ compared to 30-BRZ, whereas the risk for injection site reaction was higher in 100-MPZ. The risk of injection site reaction was significantly higher with MPZ than placebo (OR 2.69; 95% CI 1.17–6.21), whereas there was no significant difference between 30-BRZ and placebo (OR 1.16; 95% CI 0.59–2.30). Furthermore, the risk for fatal adverse events and headache did not differ significantly between 100-MPZ and placebo or between 30-BRZ and placebo (Table 2).

Analysis of ranking probability

SUCRAs for 100-MPZ, 30-BRZ, and placebo calculated using the Monte Carlo simulation^{13,14} were 0.8, 0.3, and 0.4 for fatal adverse effects, 0.5, 0.1, and 0.8 for headache, and 0.0, 0.6, and 0.8 for injection site reaction, respectively (Fig. 3, Table 3).

Inconsistency test

P values calculated in a global inconsistency test^{13,14} were 0.81 for fatal adverse effects, 0.11 for headache, and 0.66 for injection site reaction. These results suggest that significant inconsistency was not present and that the NMA was valid.

Discussion

In this NMA, we compared the adverse effect profiles of 100-MPZ and 30-BRZ. Although not significant, the results suggest that the risks for fatal adverse events and headache were lower with 100-MPZ than 30-BRZ, whereas the risk for injection site reaction was higher with 100-MPZ. SUCRAs for fatal adverse events and headache were higher in 100-MPZ, indicating greater safety, whereas SUCRA for injection site reaction was lower in 100-MPZ. The risk for

Table 1. Characteristics of the studies included in the network meta-analysis

| Reference | Study name | Study design | Phase | Group | Enrolled, n (M/F) | Average age, y | Severity of asthma | Study duration | Jadad score |
|---|------------|--------------|-------|----------|-------------------|----------------|--------------------|----------------|-------------|
| Bel <i>et al</i> 2014 ⁵⁾ | SIRIUS | RCT | III | 100-MPZ | 66 (36 / 30) | 50 | severe | 24 weeks | 5 |
| | | | | placebo | 69 (25 / 44) | 50 | | | |
| Ortega <i>et al</i> 2014 ⁴⁾ | MENSA | RCT | III | 100-MPZ | 194 (116 / 78) | 49 | severe | 32 weeks | 5 |
| | | | | 75-MPZ | 191 (106 / 85) | 50 | | | |
| | | | | placebo | 191 (107 / 84) | 51 | | | |
| Bleecker <i>et al</i> 2016 ¹⁰⁾ | SIROCCO | RCT | III | *30-BRZ | 399 (124 / 275) | 50.1 | severe | 48 weeks | 5 |
| | | | | **30-BRZ | 398 (146 / 252) | 47.6 | | | |
| | | | | placebo | 407 (138 / 269) | 48.7 | | | |
| FitzGerald <i>et al</i> 2016 ¹¹⁾ | CALIMA | RCT | III | *30-BRZ | 425 (155 / 270) | 50.0 | severe | 56 weeks | 5 |
| | | | | **30-BRZ | 441 (168 / 273) | 49.0 | | | |
| | | | | placebo | 440 (176 / 264) | 48.8 | | | |

RCT: randomized controlled trial; 100-MPZ: 100 mg mepolizumab administered subcutaneously every four weeks; 75-MPZ: 75 mg benralizumab administered intravenously every four weeks; *30-BRZ: 30 mg benralizumab administered subcutaneously every four weeks; **30-BRZ: 30 mg benralizumab administered subcutaneously every eight weeks.

Table 2. Results from the network meta-analysis

| Treatment comparison | ORs (95% CI) | | |
|----------------------|-----------------------|---------------------|-------------------------|
| | Fatal adverse effects | Headache | Injection site reaction |
| 100-MPZ vs. 30-BRZ | 0.26 (0.01 to 4.90) | 0.79 (0.40 to 1.54) | 2.32 (0.79 to 6.80) |
| 100-MPZ vs. placebo | 0.32 (0.03 to 3.11) | 1.12 (0.68 to 1.85) | 2.69 (1.17 to 6.21)* |
| 30-BRZ vs. placebo | 1.25 (0.19 to 8.25) | 1.42 (0.92 to 2.19) | 1.16 (0.59 to 2.30) |

*Significant difference between comparisons.

Results are expressed as odds ratios (ORs) with 95% confidence interval (95% CI) for incidence of fatal adverse events, headache, and injection site reaction with the first treatment compared to the reference second treatment.

100-MPZ: 100 mg mepolizumab administered subcutaneously every four weeks.

30-BRZ: 30 mg benralizumab administered subcutaneously every eight weeks.

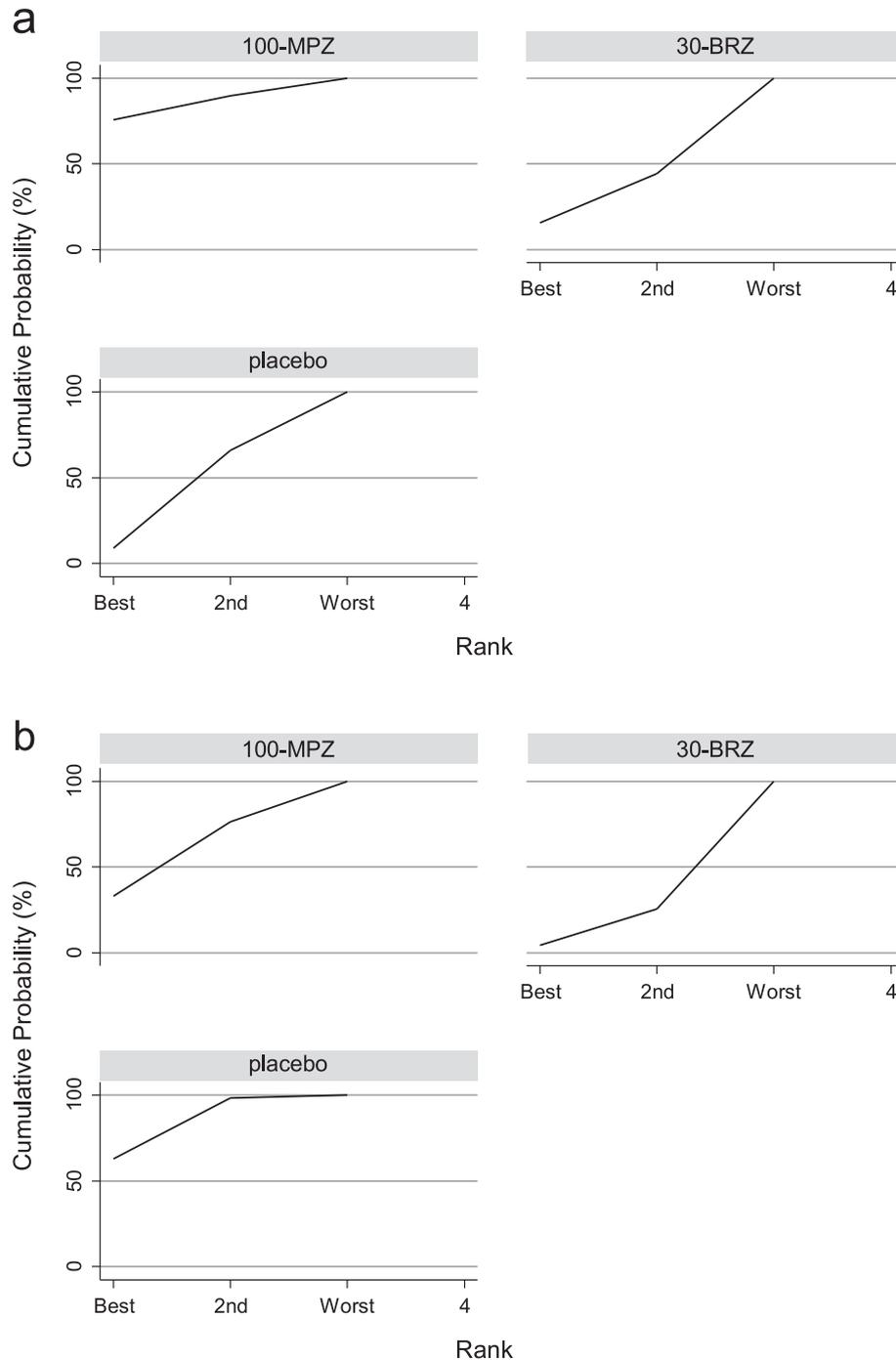
injection site reaction was significantly greater in 100-MPZ compared to placebo, whereas there was no significant difference in the risks for fatal adverse events and headache between 30-BRZ and placebo.

This analysis represents a novel comparative NMA of the adverse effect profiles of two anti-IL-5 therapies in adults with uncontrolled asthma. The results highlight the need to be aware of the possibility of fatal adverse events and headache in patients treated with BRZ, and of injection site reaction with MPZ treatment.

The mechanisms underlying the association of BRZ with fatal adverse events and headache are unclear. The causes of death in the BRZ treatment groups were: one unknown cause in the SIROCCO study¹⁰⁾, suicide, road traffic accident, unknown cause, and colon neoplasm (n = 1 each) in the CALIMA study¹¹⁾. All of the fatal adverse events in these trials included in this

meta-analysis were not necessarily treatment-related adverse events. Further analyses are needed to assess the association of BRZ with fatal adverse events and with headache.

The SUCRA values showed that an injection site reaction was induced more frequently by MPZ than by BRZ, although there were no significant differences in the incidence between the two groups. This result suggests that further analyses are needed to confirm the association between the administration of MPZ and occurrences of injection site reaction.



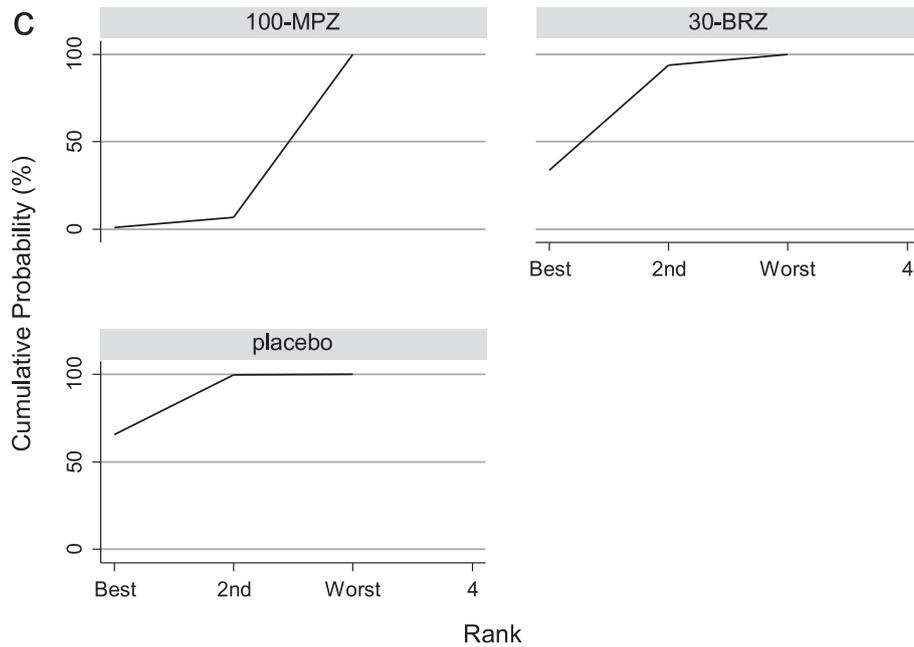


Fig. 3. Surface under the cumulative ranking curves (SUCRA) for fatal adverse events, headache, and injection site reaction. a: fatal adverse events ; b: headache ; c: injection site reaction.

Table 3. Probabilities of being the best, second best, and third best treatment calculated based on the network meta-analysis and surface under the cumulative ranking (SUCRA) curves for fatal adverse events (a), headache (b), and injection site reaction (c).

| (a) | Treatment | Ranking probabilities | | | Mean rank | SUCRA |
|-----|-----------|-----------------------|------|------|-----------|-------|
| | | Best | 2nd | 3rd | | |
| | 100-MPZ | 75.5 | 14.2 | 10.3 | 1.3 | 0.8 |
| | 30-BRZ | 15.5 | 28.7 | 55.8 | 2.4 | 0.3 |
| | Placebo | 9 | 57.1 | 33.9 | 2.2 | 0.4 |

| (b) | Treatment | Ranking probabilities | | | Mean rank | SUCRA |
|-----|-----------|-----------------------|------|------|-----------|-------|
| | | Best | 2nd | 3rd | | |
| | 100-MPZ | 32.9 | 43.3 | 23.8 | 1.9 | 0.5 |
| | 30-BRZ | 4.3 | 21.1 | 74.6 | 2.7 | 0.1 |
| | Placebo | 62.8 | 35.6 | 1.6 | 1.4 | 0.8 |

| (c) | Treatment | Ranking probabilities | | | Mean rank | SUCRA |
|-----|-----------|-----------------------|------|------|-----------|-------|
| | | Best | 2nd | 3rd | | |
| | 100-MPZ | 0.9 | 5.8 | 93.3 | 2.9 | 0 |
| | 30-BRZ | 33.5 | 60.2 | 6.3 | 1.7 | 0.6 |
| | Placebo | 65.6 | 34 | 0.4 | 1.3 | 0.8 |

Our study had some limitations that should be acknowledged. Firstly, only published studies were included and, therefore, some publication bias may have been present. Secondly, a meta-analysis is a retrospective study, which is subject to the certain metrological deficiencies of the studies included in the analysis. For example, all of the four studies included in the present meta-analysis were supported by a pharmaceutical company, and authors reported receiving grant support or uncompensated support. Therefore, the source of funding might have influenced the outcomes as a result of outcome selection bias. Finally, the sample of studies of four studies included in the analysis is small and may have affected the outcome. While meta-analyses involving a small sample of studies are not uncommon in orphan disease, they may be confounded by the presence of inconsistency, which was not observed in this meta-analysis.

In summary, we assessed the safety of anti-IL-5 therapies using a NMA for fatal adverse events, headache, and injection site reaction in patients with uncontrolled asthma. The results showed no statistically significant differences in the risks of fatal adverse events, headache, and injection site reaction between MRZ and BRZ. However, the results of SUCRAs indicate an association between administration of BRZ and the occurrence of fatal adverse event or headache, or between administration of MPZ and the occurrence of injection site reaction. Moreover, the incidence odds of injection site reaction were significantly higher in the MPZ group than in the placebo group. These results together with the limitations of this analysis indicate that further research on the safety profiles of anti-IL-5 therapies is necessary.

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Conflict of interest disclosure

None of the authors have a conflict of interest to disclose.

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