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Mepolizumab-Related Adverse Events in Severe Eosinophilic Asthma: A Real-Life Study

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ABSTRACT

Objective: Mepolizumab, an anti-interleukin 5 humanized monoclonal antibody, which is listed among the treatment options in the Global Initiative for Asthma 2020, is recommended as a step 5 therapy option for patients with uncontrolled severe eosinophilic asthma. Real-life data on adverse drug reactions of mepolizumab are limited. We aimed to analyze the safety profile of mepolizumab retrospectively among patients who were treated with mepolizumab with the diagnosis of eosinophilic severe asthma.

Materials and Methods: Severe eosinophilic asthma patients from two different centers who were treated with mepolizumab between June 2018 and July 2020 were analyzed retrospectively. The data of the mepolizumab-related adverse event forms, which were filled out at each visit, were retrospectively evaluated.

Results: Eighty three patients were included in the study. The most commonly reported adverse events which could be related to mepolizumab were myalgia/arthralgia, headache, and local injection site reactions. Nevertheless, none of these required the discontinuation of the drug. Mepolizumab-related adverse events that required discontinuation of mepolizumab treatment were observed in two (2.4%) cases but their association with the drug could not be clearly defined. Anaphylaxis or herpes infection was not detected in any of the cases.

Conclusion: These outcomes reveal that mepolizumab is a well-tolerated drug in real-life. However, further large-scale real-life studies with long-term follow-up are still needed.

Keywords: Mepolizumab, mepolizumab adverse events, severe asthma treatment, adverse events, mepolizumab treatment

INTRODUCTION

Severe asthma is a heterogeneous state in which patients manifest various clinical and physiological features and results with different treatment outcomes; this heterogenic spectrum requires individualized treatment protocols (1). Particularly in the last two decades, significant improvements have been made on the endotype-focused targeted treatments for controlling asthma. Treatment strategies with target-specific biological agents have been an especially important step for the control of asthma (2). Mepolizumab, an anti-Interleukin 5 (IL-5) humanized monoclonal antibody (mAb), which is among the treatment options in GINA (Global Initiative for Asthma) 2020, is recommended as a step 5 therapy option for patients with uncontrolled severe eosinophilic asthma (SEA) (3). Updated randomized controlled trials (RCT) reported that mepolizumab has a consistent safety profile (4).

The most common adverse events during treatment with mepolizumab are respiratory tract infections, headache, worsening of asthma, and local injection site reactions, while myalgia, arthralgia, allergic hypersensitivity, and opportunistic infections were less commonly reported (4-7).

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Randomized controlled trials before marketing have shown that mepolizumab is a safe and well-tolerated drug (5,6). However, the potential of the safety data, which is obtained from RCTs and extension studies, can be questioned as regards representing "real-life" patients due to the selected patient groups that were included in these clinical studies. Therefore, real-life data is needed to support and add new data to the results of pre-marketing clinical studies and extension studies.

In the current study, we aimed to analyze the safety profile of mepolizumab retrospectively among patients who were treated with mepolizumab with the diagnosis of eosinophilic severe asthma.

MATERIALS and METHODS

The data of patients aged over 18 years who were followed-up at two different centers in Turkey with a diagnosis of SEA and treated with mepolizumab between June 2018 and July 2020 were analyzed retrospectively. All patients were under treatment with high-dose inhaled glucocorticosteroids (ICS) and long-acting β2 agonists along with a second controller montelukast at least 6 months before mepolizumab treatment. Mepolizumab treatment was prescribed to the patients according to the Healthcare Implementation Communique. Accordingly, in patients with adult severe eosinophilic persistent asthma a) Blood eosinophil count ≥ 300 cells/ μL (≥ 150 cells/ μL in patients who were under treatment of regular OCS therapy for a long-time), b) controlled or uncontrolled asthma with systemic steroid treatment for at least 6 months and/ or uncontrolled asthma (approximately two attacks per year requiring systemic corticosteroids for at least 3 days) despite use of a high combination dosage of ICS (>800 μg/ day budesonide, or equivalent) and long-acting inhaled β2 agonist for at least one year. Mepolizumab treatment was prescribed to patients who met the aforementioned criteria with a subcutaneous dose of 100 mg every four weeks, and 83 patients who received at least one dose of mepolizumab were included in the study. The data of the adverse reaction forms, which were filled out at each visit, were retrospectively evaluated. At each injection visit the patients were questioned for all mepolizumab-related advers events. Following the injection;

Local reactions at the injection site: Pain, swelling and redness at the injection site were questioned.

Headache: Headache, which was not present before and started after the injection, was questioned on the day of injection.

Arthralgia/Myalgia: Arthralgia/myalgia, which was not present before and started after the injection, was questioned on the day of injection.

Anaphylaxis/Hypersensitivity reaction: Skin and mucosa reactions, respiratory symptoms, gastrointestinal involvement, end-organ damage and blood pressure changes that started especially within the 6 hours following the injection were questioned.

Cardiac adverse events: Palpitation, chest pain, dyspnea and any newly diagnosed cardiac, vascular or thromboembolic event between the two doses were questioned.

Opportunistic infections: New onset cough, sputum, dyspnea, hemoptysis, rhinitis, itching, rash, fever, weight loss, night sweats and diarrhea that occurred between the two doses of mepolizumab were questioned and additional diagnostic tests were performed.

Urticaria: The patients were questioned at each visit in terms of redness, wheals, itching and disappearing lesions within 24 hours after mepolizumab injection.

The patients were also asked if they had any other complaints that started after the injection.

The study was approved by the Erciyes University Ethics Committee (Decision number: 2021/344, Date: 05.05.2021).

Definitions

Terminology for drug safety needs to be clear and appropriately used. The terminology used in clinical studies (pre-marketing phase studies) and real-life studies should be easy to understand for the readers.

Adverse event: This is a negative outcome that happens during the process while receiving the drug or in the following period, independent from the drug. All "adverse drug reactions" are "adverse events" but all "adverse events" are not an "adverse drug reaction". Adverse outcomes are described as "adverse events" rather than "adverse effect" or "adverse reaction" as researchers assume it is not always possible to demonstrate the causality (8).

Adverse effect: This is described as a potential harm caused by the drug. This situation may be related or not to a clinically significant adverse reaction and/or an abnormal laboratory test result (9).

Adverse reaction: This is an unwanted or harmful situation that happens in normal doses of the drug used

for the prophylaxis, diagnosis, and treatment of a disease or to change a physiological function (10).

Side effect: This is any unwanted effect of a drug that is related to its pharmacological characteristics, which happens while the patient is using the drug in normal doses (10).

Causality Assessment of Suspected Adverse Drug Reactions (8,11)

Certain: A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, which cannot be explained by concurrent disease or other drugs or chemicals.

Probable/likely: A clinical event, including a laboratory test abnormality, with a reasonable time relation to the administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).

Table I: Demographic data of the patients treated with mepolizumab.

Variables (n= 83)	
Age, years, mean±SD	47.6±11.4
Female gender, n (%)	60 (71.4)
Current smoker, n (%)	1 (1.2)
Mepolizumab treatment duration, mean months±SD	12.6±5.9
Asthma duration, mean years±SD	11.1±5.8
Atopy, n (%)	34 (40.9)
Nasal polyps, n (%)	45 (54.2)
Allergic rhinitis, n (%)	20 (24)
Atopic dermatitis, n (%)	27 (32.5)
Baseline FEV_1; %, mean±SD	71.4±19
Baseline FEV_1; mL	1920±806
Baseline peripheral eosinophil count; %, mean±SD	13.3±8.9
Baseline peripheral eosinophil count, cells/mm^3	1371.9±1182.2
Baseline total IgE levels, IU/ml, mean±SD	211.2±118.5
Patients with a history of omalizumab treatment, n (%)*	8 (9.6)

*The shortest interval between the last dose of omalizumab and the first dose of mepolizumab was 4 months. Therefore, advers reactions were not attributed to omalizumab in these patients.

Possible: A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.

Unlikely: A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/unclassified: A clinical event, including a laboratory test abnormality, reported as an adverse reaction, where more data are essential for a proper assessment or the additional data are being examined.

Unassessable/unclassifiable: A report suggesting an adverse reaction that cannot be judged, because the information is insufficient or contradictory and cannot be supplemented or verified.

Statistical Analyses

Data recording and analyses were performed using SPSS v17.0 (SPSS Inc.; Chicago; IL; USA). Distribution of the data was established using the Kolmogorov-Smirnov test. Numerical data were expressed as mean ± standard deviation (SD).

RESULTS

A total of 83 patients, consisting of 60 (71.4%) women and 23 (28.6%) men, were included in the study. The patient characteristics and demographic data are presented in Table I.

In Table II, mepolizumab-related adverse events (adverse drug reaction) have been summarized. The most commonly reported adverse events that could be related

Table II: Summary of drug-related adverse events

Drug-related AE	n (%)
Local reactions at the injection site	14 (16.7)
Headache	15 (17.9)
Arthralgia/Myalgia	22 (26.2)
Cardiac	1 AR required to discontinue the drug (Possible)
Serum disease-like findings	1 AR required to discontinue the drug (Probable)

AE: Adverse event, **AR:** Adverse reaction.

to mepolizumab were myalgia/arthralgia, headache, and local injection site reactions. Nevertheless, none of these required discontinuation of the drug.

The use of antihistamines and/or antidepressants by the patients was screened retrospectively, and 35.7% (n=5) of those who developed local side effects and 8.6% (n=6) of those who did not develop local side effects had a history of using antihistamines and/or antidepressants.

Treatments of two patients were discontinued due to adverse reactions with mepolizumab. In the first patient, mepolizumab treatment was stopped when fever (38.3°C), chills, persistent diarrhea, and nausea symptoms following the third dose were added to symptoms of arthralgia, myalgia, and weakness that occurred on the next day after the first two doses. After the discontinuation of the treatment, the symptoms did not recur. Therefore, the serum disease-like findings were probably associated with mepolizumab treatment. In the other patient, the patient was referred to cardiology 10 days after the second dose of mepolizumab treatment due to the development of pitting edema in both legs, despite the normal echocardiographic findings in the previous year (ejection fraction: 64%, pulmonary artery pressure: normal). Control echocardiography revealed global hypokinesia in the left ventricle in the patient who had elevation of Troponin T and pro-Brain Natriuretic Peptide (ejection fraction: 40-45%, pulmonary artery pressure: 50-55 mmHg). One month after the discontinuation of mepolizumab treatment, a regression was detected in the signs of heart-failure in the cardiology follow-up.

DISCUSSION

In our study, the most commonly detected drug-related adverse events were myalgia/arthralgia, headache and local reactions at the injection site. These were all mild reactions that did not require the discontinuation of the mepolizumab treatment. Adverse drug reactions that required discontinuation of treatment were observed in 2 (2.4%) cases. Anaphylaxis or herpes infection was not detected in any of the cases.

Local injection site reactions were observed in 16.7% of the cases in our study and this rate was a little higher than the results reported in previous real-life studies. The local reactions related to mepolizumab were developed irrespective of the history of antihistamine use. In a real-life study that analyzed the efficiency and safety results of one-year treatment with mepolizumab, the most common adverse event was local reactions at the injection site (4.3%), which was relatively less common than in our study (7). In the study by Pelaia et al. (12), only one drug-related adverse event was reported, consisting of mild local irritation at the injection site, after the first dose of the drug. In other real-life studies, mepolizumab-related adverse events at the local injection site were reported but the rates were not given (13,14). The higher rates of local reactions at the injection site in our study may be caused by recording all the signs and symptoms such as pain, erythema, and edema even if they were mild local reactions that did not irritate the patients. Even though it was not a real-life study, in COLUMBA study, the drug-related adverse events made up > 3% of the long-term safety outcomes of mepolizumab. Also the most common adverse event reported was injection site reactions (12%) (6).

The rate of arthralgia/myalgia was 26.2% and the rate of headache was 17.9% in our study. These reactions were reported as drug-related adverse events. All of these adverse events were mild reactions that did not require discontinuation of the drug and they disappeared in continuation doses of mepolizumab treatment. Enríquez-Rodríguez et al. (15) have reported a total of 5 cases of adverse events in 69 patients, with 3 cases of arthromyalgia, one case of skin rash at the injection site, and one case of headache. Contrary to our study, mepolizumab treatment was discontinued in 2 patients with arthromyalgia that was refractory to analgesics. Bagnasco et al. (7) reported that the rate of headache, myalgia and arthralgia was < 1%. Another real-life study by Lombardi et al. (13) reported only mild side effects (headache, mild local reaction at the injection site) and all of resolved within one hour without need for extra medication. In a clinical prospective observational real-life study, mild adverse events such as myalgia, itching, rash, local injection site pain, fever, and headache were reported in 11 patients (18%) (14). Unlike real-life studies, the most commonly reported adverse event in the DREAM study was headache (in 21% of the mepolizumab arm and 17% of the placebo arm). In the COLUMBA study, headache was the second most common drug-related adverse event (4%) following local injection site reactions (6). The rate of headache reported in our study was higher than the previous real-life studies while our rates were close to those from pre-marketing clinical and extension studies. We speculate that the higher rates of headache in our study may be caused by differences in the pain thresholds of the patients.

The drug-related adverse events which required drug discontinuation were observed in two patients in our

study. In the first patient developing the serum sickness-like case, findings were evaluated in the category of probable drug related adverse reaction. In a study, among 335 patients who were analyzed for anti-mepolizumab antibodies, 6 (2%) of them had at least one anti-mepolizumab antibody but neutralizing antibodies were not detected in any of the patients. No relationship was reported between the frequency of adverse events or hypersensitivity reactions and the presence or absence of anti-mepolizumab antibodies (5). In the COLUMBA study, all the samples were detected as negative for neutralizing antibodies, and positive anti-drug antibodies (ADA) were rarely (8%) detected. In many cases, positive titers of ADA were not related to low, temporary, or increasing immunogenicity with increasing treatment duration. No relationship was reported between the frequency of adverse events or hypersensitivity reactions and the presence or absence of ADA (6). In our case, serum disease secondary to ADA may have occurred but this is a speculative comment as anti-mepolizumab antibodies were not tested. Nevertheless, as we have mentioned before, this was accepted as a probable drug-related adverse reaction since a strong association was not made between mepolizumab and this reaction. In the second patient, mepolizumab was discontinued after considering a possible adverse drug reaction due to the development cardiac failure. In a real-life study by Bagnasco et al. (7), one case required hospitalization for paroxysmal supraventricular tachycardia which started a few days after the second dose of mepolizumab treatment. However, mepolizumab treatment was continued, assuming that this event was not related to treatment. To the best of our knowledge, no other serious cardiovascular adverse events were reported in other real-life studies. In a real-life study, adverse events that required mepolizumab discontinuation were evaluated in 61 severe eosinophilic asthma patients and no adverse events indicated discontinuing the treatment were reported (14). In another study evaluated 143 patients who received at least one dose of mepolizumab, the rate of mepolizumab discontinuation was 6/143 (4.2%), while the reason for the discontinuation was an inadequate response to the treatment in five of the six patients and probable treatment-related urticaria in one patient (13). Our study and other real-life studies show that the rates of discontinuation of mepolizumab treatment are lower. The tolerability of mepolizumab seems better in real-life studies, for adverse events that require mepolizumab discontinuation are lower when compared to clinical studies.

Herpes infection or other opportunistic infections were not observed in any of our cases during treatment. In the DREAM study, herpes zoster was detected in two patients in the mepolizumab group while it was not detected in the placebo group (4,16). In the COSMEX extension trial, 8 patients with herpes infection were reported (5). In the COLUMBA extension study, herpes zoster infection was detected in 8 (2%) patients (6). In real-life studies, herpes zoster infection was reported only in one study and in one patient; however, this event was not found to be associated with mepolizumab and the patients continued mepolizumab treatment uneventfully (17). Both our study and the real-life studies revealed that the patients who would be treated with mepolizumab may not need herpes vaccination. Further large-scale studies with longer follow-up are needed to prove this relationship.

The main limitations of our study were the small sample size and the retrospective design. Another limitation was that an interpretation for clinical comparison could not be made because of the absence of a placebo arm.

In conclusion, the most common drug-related adverse events in our study were myalgia/arthralgia, headache, and local injection site reactions. Adverse drug reactions that required discontinuation of mepolizumab treatment were observed in two (2.4%) cases but their association with the drug could not be clearly defined. These outcomes reveal that mepolizumab is a well-tolerated drug in real-life. However, further large-scale real-life studies with long-term follow-up are still needed.

Conflicts of Interest

İnsu Yılmaz reports advisory board and speaker fees from Novartis, GSK, Chiesi. Murat Türk reports congress travel support from Novartis. Sakine Nazik Bahçecioğlu, Emel Atayık, Gülden Çetin Paçacı, Bahar Arslan, İnci Gülmez, report no conflict of interest.

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Authorship Contributions

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REFERENCES

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43(2):343-73.
2. Assaf SM, Hanania NA. Biological treatments for severe asthma. Curr Opin Allergy Clin Immunol 2019;19(4):379-86.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020. https://ginasthma.org/gina-reports
4. Mitchell P, Leigh R. A drug safety review of treating eosinophilic asthma with monoclonal antibodies. Expert Opin Drug Saf 2019;18(12):1161-70.
5. Khurana S, Brusselle GG, Bel EH,Fitz Gerald JM, Masoli M, Korn S, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: The COSMEX study. Clin Ther 2019;41(10):2041-56.
6. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol 2019;143:1742-51.
7. Bagnasco D, Caminati M, Menzella F, Milanese M, Rolla G, Lombardi C, et al. One year of mepolizumab. Efficacy and safety in real-life in Italy. Pulm Pharmacol Ther 2019;58:101836.
8. Aronson JK, Ferner RE. Clarification of terminology in drug safety. Drug Saf 2005;28(10):851-70.
9. Aronson JK. Distinguishing hazards and harms, adverse drug effects and adverse drug reactions. Drug Saf 2013;36:147-53.
10. Safety of Medicines. A guide to detecting and reporting adverse drug reactions. World Health Organization 2002. http://archives.who.int/tbs/safety/esd_safety.pdf
11. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, classification, diagnosis, management, surveillance. Lancet 2000;356:1255-60.
12. Pelaia C, Busceti MT, Solinas S, Terracciano R, Pelaia G. Real-life evaluation of the clinical, functional, and hematological effects of mepolizumab in patients with severe eosinophilic asthma: Results of a single-centre observational study. Pulm Pharmacol Ther 2018;53:1-5.
13. Lombardi C, Bagnasco D, Caruso C, D'Amato M, Menzella F, Milanese M, et al. Analysis of the drop-out rate in patients receiving mepolizumab for severe asthma in real life. Pulm Pharmacol Ther 2019;54:87-9.
14. Pertzov B, Unterman A, Shtraichman O, Shitenberg D, Rosengarten D, Kramer MR. Efficacy and safety of mepolizumab in a real-world cohort of patients with severe eosinophilic asthma. J Asthma 2019;3:1-6.
15. Enríquez-Rodríguez AI, Hermida Valverde T, Romero Álvarez P, López-González FJ, Gullón Blanco JA, Expósito Villegas AR, et al. Results in clinical practice in the treatment of severe eosinophilic asthma with mepolizumab: A real-life study. J Asthma 2021;27:1-7.
16. Pavord ID, Korn S, Howarth P,Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo- controlled trial. Lancet 2012;380:651-9.
17. Strauss RA, Jawhari N. Mepolizumab in thetreatment of severe eosinophilic asthma: Resultsfrom a physician in thefield. Ann Allergy Asthma Immunol 2018;121:121-3.