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Efficacy and Safety of Anti-Interleukin-1 Therapy in Familial Mediterranean Fever Patients: Protocol for a Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 July 2023 and was last updated on 13 July 2023.

INTRODUCTION

Review question / Objective How efficient and safe are anti-interleukin-1 treatment options in the treatment of familial mediterranean fever? Population (P): Pediatric or adult familial mediterranean fever patients with active disease. Intervention (I): Anti-interleukin-1 agents: anakinra, canakinumab, rilonacept. Comparison (C): Placebo or post treatment. Outcomes (O): Complete remission*, >50% reduction in attack frequency, acute phase response, disease activity scores, adverse events. Study design (S): Randomized controlled trials (RCTs) , non-RCTs, observational studies.

Rationale Familial Mediterranean Fever (FMF) is the most common hereditary monogenic fever syndrome characterized by recurrent attacks of fever and polyserositis. Anti-inflammatory drugs, with colchicine being the first-line therapy, have been used in FMF treatment to provide improvement in attacks and prevent amyloidosis, the most severe complication of the disease. The IL-1 blocking agents are indicated for patients with colchicine resistance or colchicine intolerance.

Condition being studied FMF is a hereditary autoinflammatory disorder characterized by recurrent episodes of fever accompanied by inflammation in the abdomen, joints, and chest. The cause of the disease are mutations in the MEFV gene, which provides instructions for the synthesis of a protein called pyrin. Pyrin is primarily expressed in immune cells and plays a role in the regulation of inflammation. In FMF patients, the normal function of pyrin is disrupted and this leads to excessive inflammation in various parts of the body and recurrent episodes of fever. Colchicinr and anti-IL-1 agents are used in the management

of FMF, aiming to modulate the exaggerated inflammatory response and reduce the frequency and severity of FMF attacks.

METHODS

Search strategy The electronic databases MEDLINE (PubMed), EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), and Web of Science were screened with the following search strategy: #1: ((((((familial mediterranean fever) OR (fmf)) OR (hereditary periodic fever syndromes)) OR (recurrent fever syndromes)) OR (systemic autoinflammatory diseases)))
#2: ((((((((((((((anakinra) OR (kineret)) OR (canakinumab)) OR (ilaris)) OR (rilonacept)) OR ("anti interleukin 1")) OR ("anti il 1")) OR ("il 1 inhibit*")) OR ("interleukin 1 inhibit*")) OR ("il 1 block*")) OR ("interleukin 1 block*")) OR ("il 1 receptor antagonist")) OR ("interleukin 1 receptor antagonist")) OR ("il 1 antagonist")) OR ("interleukin 1 antagonist”))).
#3: #1 AND #2

Participant or population We included pediatric and adult patients with a confirmed FMF diagnosis and indications for anti-il-1 treatment. We included patients with active disease to be able to evaluate the efficacy of anti-il-1 agents on attack frequency and severity. In order to prevent manipulations in efficacy and safety effect sizes, we excluded studies focusing on patients with additional conditions (eg. pregnants, renal transplant recipients), patients diagnosed with other hereditary periodic fever syndromes, patients with accompanying diseases, and patients with severe complications related to FMF (eg. amyloidosis). We also excluded animal studies and in vitro studies.

Intervention We included patients continuously treated with at least one of the following anti-il-1 agents: anakinra, canakinumab, and rilonacept. On-demand and prophylactic usages were excluded. A certain threshold for dosage or treatment duration were not determined.

Comparator Results of the placebo group (RCTs) or post treatment outcomes of the enrolled patients (observational studies) were used as comparators.

Study designs to be included We included RCTs, non-RCTs, prospective and retrospective observational studies (case series). Case reports were excluded from the study.

Eligibility criteria We included studies which didn't specify the outcomes for anti-il-1 drugs seperately and evaluated the effect as a whole under the title of "anti-il-1 treatment". We excluded studies with insufficient data on study methods and results. Studies with contradictory results were also excluded. We didn't exclude conference abstracts with clear and eligible methodology, to increase our systematic reviews comprehensiveness and precision, and decrease the potential risk of publication bias.

Information sources We screened MEDLINE, EMBASE, CENTRAL, and Web of Science for eligible studies. If necessary, the authors of the studies were consulted to obtain further information.

Main outcome(s) Our primary efficacy outcome was the proportion of patients who achieved complete remission of attacks (clinical complete response). Our primary safety outcome was the proportion of patients who experienced at least one adverse event.

Additional outcome(s) Secondary outcomes are: proportion of patients who achieved >50% reduction in the frequency of attacks, effects on the level of acute phase reactants (CRP and ESR), and changes in disease activity scores.

Data management Two reviewers independently performed the literature screening, data extraction and crosscheck. The reviewers screened the studies manually. Data were extracted and recorded manually, in table form. Disagreements were resolved through discussion and reaching consensus, or consulting a third reviewer.

Quality assessment / Risk of bias analysis Two researches independently evaluated the risk of bias in the included studies and crosschecked the results. Disagreements were resolved through discussion and reaching consensus, or consulting a third reviewer. Risk of bias analysis for RCTs were made through Cochrane recommendations ,and Newcastle-Ottawa Scale for observational studies.

Strategy of data synthesis The statistical software STATA (Statacorp, USA) was used for quantitative analysis. Outcome measures were determined as proportions with 95% CIs for binary outcomes and mean differences and 95% CIs for continuous outcomes. Our findings were visualised in forest plots. Estimation of the mean and standard deviation values of the study results presented in median and interquartile range were

made with the method suggested by Wan et al. in 2014. Study results presented in median and range were excluded from the quantitative analysis to prevent uncertainities derived from high data skewness. Statistical heterogeneity among the studies was assessed through I-squared and Q statistics. The random effects model was used in the meta-analysis due to the detection of high heterogeneity.

Subgroup analysis Outcomes of pediatric and adult cohorts were analysed separately. The subgroup analysis was performed for anakinra, canakinumab, rilonacept and "Anti-IL-1" subgroups. The last stands for studies evaluated both anakinra and canakinumab without reporting the results specifically for each drug.

Sensitivity analysis None.

Country(ies) involved Turkey.

Keywords Familial mediterranean fever; FMF; il-1; interleukin-1; anakinra; canakinumab; rilonacept; colchicine resistance; colchicine intolerance.

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