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Impact of Obesity on Response Rate for Biological Agents in Rheumatoid Arthritis：a systematic review and meta-analysis of cohort studies

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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 07 November 2023 and was last updated on 07 November 2023.

INTRODUCTION

Review question / Objective We further provide evidence-based medical evidence for the impact of obesity on the response rate of biological agents in RA patients through systematic review and meta-analysis.

Rationale Currently, BMI is mostly considered to be related to chronic inflammation and immune responses .Adipose tissue of patients with obesity secretes inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α) and leptin,followed by an inflammatory reaction. The levels of these inflammatory markers are elevated before the onset of RA . Body mass index (BMI)≥25 kg/m2 is considered an independent risk factor for RA. An increase in BMI significantly increases RA risk. Compared to controls, patients with obesity and RA have a lower remission rate as shown by the Disease Activity Score in 28 joints (DAS28) . Thus, BMI has a causal relationship with the increased risk of RA.

At present, some studies have focused on exploring whether obesity affects the use rate of bDMARDs, and the results are somewhat controversial. Some studies have shown that obesity reduces the response rate of RA patients using bDMARDs, while others suggest that obesity is not a factor affecting clinical response rate.Therefore, we conducted a systematic review and meta-analysis, as well as a subgroup analysis of the types of bDMARDs, to reveal the impact of obesity, and to analyze whether the heterogeneity source is the type of bDMARDs.

Condition being studied Rheumatoid arthritis (RA) can be defined as a chronic, autoimmune disease which characterized by persistent joint destruction. It manifests as pain and swelling of the hand and foot joints, accompanied by morning stiffness of the affected joints.With a high rate of disability, it seriously affects lifequality. Disease-modifying anti-rheumatic drugs (DMARDs) are considered to be the first-line drugs to treat RA worldwide. Biological DMARDs(bDMARDs) have various targets, thereby providing various treatment

options for patients who fail to meet the treatment standards.Currently, bDMARDs used for targeted treatment of RA mainly include:tumor necrosis factor inhibitors (TNFi), IL-6 receptor antagonist(anti-IL6), T cell co-stimulation inhibitor and Anti-CD20 monoclonal antibody.Adipose tissue in patients with obesity is involved in immune and inflammatory reactions caused by metabolic disorders and chronic inflammatory and autoimmune diseases, respectively, thereby increasing the risk of RA . Currently, BMI is mostly considered to be related to chronic inflammation and immune responses .Adipose tissue of patients with obesity secretes inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α) and leptin,followed by an inflammatory reaction. The levels of these inflammatory markers are elevated before the onset of RA . Body mass index (BMI)≥25 kg/m2 is considered an independent risk factor for RA. An increase in BMI significantly increases RA risk. Compared to controls, patients with obesity and RA have a lower remission rate as shown by the Disease Activity Score in 28 joints (DAS28) . Thus, BMI has a causal relationship with the increased risk of RA.

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METHODS

Search strategy The systematic literature review and meta-analysis was conducted according to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines .Two researchers independently conducted search using the PICO strategy.We searched electronic databases to identify relevant trials.Pubmed, Medline, Web of science,Scopus and Cochrane Central Register of Clinical Trials were searched, database dates to June 2023.We used Medical Subject Headings (MeSH) and predefined keywords:“obesity” “RA” and “bDMARDs”. Then, by manually selecting a reference list, eligible studies are included and supplemented.Then, by manually selecting a reference list, eligible studies are included and supplemented.Redundant articles, meeting abstracts,conference proceedings, reviews, letters, editorials, comments were excluded.

Participant or population Patients: 1987 American College of Rheumatology ACR or 2010 European League Against Rheumatism EULAR criteria for RA.

Intervention bDMARDs: TNFi(Infliximab (IFX), Adalimumab(ADA),Etanercept(ETA)),anti-IL6(Tocilizumab(TCZ)),T cell co-stimulation inhibitor (Abatacept(ABA)) and Anti-CD20 monoclonal antibody (rituximab(RTX)).

Comparator bDMARDs: TNFi(Infliximab(IFX), Adalimumab(ADA),Etanercept(ETA)),anti-IL6(Tocilizumab(TCZ)),T cell co-stimulation inhibitor(Abatacept (ABA)) and Anti-CD20 monoclonal antibody (rituximab(RTX)).

Study designs to be included Cohort studies.

Eligibility criteria 1. The research type is cohort study(prospective or/and retrospective);2. Patients: 1987 American College of Rheumatology ACR [14] or 2010 European League Against Rheumatism EULAR criteria for RA [15]; 3. Therapy: bDMARDs: TNFi(Infliximab(IFX),Adalimumab(ADA),Etanercept(ETA)),anti-IL6(Tocilizumab(TCZ)),T cell co-stimulation inhibitor(Abatacept(ABA)) and Anti-CD20 monoclonal antibody(rituximab(RTX)). 4. The definition of obesity is BMI＞30 kg/m2; 5. Outcomes: We choose the following indicators for evaluation.(a):DAS28<2.6;(b)Response:decrease in DAS28＞1.2;(c)Good EULAR response:defined.

Information sources Electronic databases, contact with authors, trial registers.

Main outcome(s) (a):DAS28<2.6.

Additional outcome(s) (b)Response:decrease in DAS28＞1.2;(c)Good EULAR response:defined as decrease in DAS28＞1.2, and with low disease activity (DAS28≤3.2);(d)Moderate EULAR response: defined as decrease in 0.6<DAS28≤1.2 and with moderate disease activity (3.2<DAS28≤5.1);(e)Retention Rate;(f) CDAI Clinical Disease Activity Index (CDAI≤2.8).

Data management Two researchers (YT.L. and Y.Z.) independently extracted the data from the article, and cross-checked the results. The data conclude: the name of first author name, year of publication,sample size,the number of subjects(n), number of patients with obesity and non-obesity(n),type of study,duration and outcomes.

Quality assessment / Risk of bias analysis Methodological quality of included studies and risk of bias was evaluated by The NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE for Cohort Studies.
The scoring system covers three main areas (selection of exposed and non-exposed cohorts, comparability, and evaluation of outcomes) with a total of eight items.

Strategy of data synthesis Use Review Manager 5.3 and StataSE17 software to analyze extracted data.Pooled statistics were calculated as pooled odds ratios (ORs) with 95% confident intervals (CIs). Assessment of statistical heterogeneity was conducted using Cochran's Q statistic or I2 value size.The selection of fixed-effects model or random models was based on the P-value≥0.10 and I2≤50% value of statistical tests. P values<0.05 were considered statistically significant.

Subgroup analysis Use Review Manager 5.3 and StataSE17 software to analyze extracted data.Pooled statistics were calculated as pooled odds ratios (ORs) with 95% confident intervals (CIs). Assessment of statistical heterogeneity was conducted using Cochran's Q statistic or I2 value size.The selection of fixed-effects model or random models was based on the P-value≥0.10 and I2≤50% value of statistical tests.

Sensitivity analysis The stability of the research results was proved by sensitivity analysis.

Country(ies) involved China.

Other relevant information None.

Keywords Obesity;Biological Agents; rheumatoid arthritis; meta-analysis; systematic review.

Dissemination plans Paper publication.

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