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Comparative study in safety and efficacy of maintenance therapies for patients with anti-neutrophil cytoplasmic antibody small vessel vasculitis: A network meta-analysis

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ABSTRACT

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis represents a potentially life-threatening disease. Induction of remission is achieved in the vast majority of patients by high-dose glucocorticoid therapy combined with cyclophosphamide or rituximab, followed by oral glucocorticoid tapering; however, relapses are common. The present network meta-analysis is aiming to accumulate current literature knowledge and compare the efficacy and safety of different regimens used for maintenance of remission in patients with ANCA vasculitis. Adult patients with ANCA-associated vasculitis in complete remission including clinical the phenotypes of granulomatosis with polyangiitis, microscopic polyangiitis, and renal-limited disease will be included. All potential maintenance treatments will be simultaneously compared. Only randomized controlled trials will be included. A random-effects frequentist network meta-analytic model will be fitted and interventions will be ranked according to their P-scores.

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KEYWORDS

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1 Background Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis represents a potentially life-threatening disease characterized by vascular inflammation, endothelial and tissue injury. In most patients, ANCAs against

leukocyte proteinase 3 (PR3) or myeloperoxidase (MPO) are detected. Necrotizing vasculitis predominantly affects small vessels, leading to inflammation in various tissues and organs, such as lungs and glomeruli. Timely diagnosis is essential to enable prompt treatment initiation and improve prognosis by limitation of irreversible organ damage. Induction of remission is achieved in the vast majority of patients by high-dose glucocorticoid therapy combined with cyclophosphamide or rituximab, followed by oral glucocorticoid tapering. However, relapses are common, with reported rates ranging from 10 to 60%. Certain factors have been associated with increased risk of relapse, including PR3-ANCA seropositivity, lung or upper respiratory involvement, prior history of relapsing disease, persistence of elevated ANCA titers, particularly PR3-ANCA, and rising ANCA titers. Nonetheless, the optimal immunosuppressant regimen for remission maintenance remains under investigation. The present network meta-analysis is aiming to accumulate current literature knowledge and compare the efficacy and safety of different regimens used for maintenance of remission in patients with ANCA vasculitis.

2 Study design The network meta-analysis will be conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses (PRISMA-NMA) guidelines.

3 Eligibility criteria Population: Adult patients with ANCA-associated vasculitis in complete remission including clinical the phenotypes of granulomatosis with polyangiitis, microscopic polyangiitis, and renal-limited disease. Exclusions: Patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), patients who have ended up in end-stage kidney disease and are on renal replacement therapies. Interventions: Azathioprine, cyclophosphamide, rituximab, methotrexate, mycophenolate mofetil, leflunomide, belimumab with azathioprine Outcomes: Relapse (any/major), relapse-free survival, overall survival, adverse effects (any serious, any serious infections, any cancer) Study type: Randomized controlled trials Exclusions: Observational studies, review articles, in vitro studies, animal studies

4 Search strategy Medline, Scopus, CENTRAL, Web of Science and Clinicaltrials.gov will be systematically searched from inception. Google Scholar will be searched to provide grey literature coverage. The full reference list of the retrieved studies will also be searched to identify potential additional sources (“snowball” method). Search will be based on Medical Subject Headings (MeSH) terms ("Antibodies, Antineutrophil Cytoplasmic"[Mesh], "Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis"[Mesh], "Granulomatosis with Polyangiitis"[Mesh], "Microscopic Polyangiitis"[Mesh]) combined with a list of key-terms (“anca”, “vasculitis”, “granulomatosis with polyangiitis”, “microscopic polyangiitis”, “Wegener”, “pauci-immune”, “azathioprine”, “cyclophosphamide”, “rituximab”, “methotrexate”, “mycophenolate mofetil”, ”leflunomide”, “belimumab”, “maintenance”). No date or language restriction will be applied.

5 Study selection The studies will be selected following 3 consecutive stages. Firstly, the titles and abstracts of the articles identified by database search will be screened to assess for potential eligibility. Subsequently, all studies that will be presumed to meet the pre-specified inclusion criteria will be retrieved as full-texts. Then, studies that will meet any of the exclusion criteria will be identified and will not be included in the review.

6 Data extraction Data extraction will be performed independently by two researchers. The following data will be extracted: name of first author, publication date, country, study design, inclusion and exclusion criteria, vasculitis clinical phenotype, MPO/PR-3 positivity, patients’ number, sex, serum creatinine or estimated glomerular filtration rate, BVAS score, organ involvement, type of induction treatment as well as the necessary data for outcomes of interest.

7 Quality assessment The quality of studies will be assessed with the RoB-2 tool for randomized controlled trials, which takes into account the following domains: randomization, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. The credibility of evidence will be evaluated with the Confidence In Network Meta-Analysis (CINeMA) approach, which is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and evaluates the potential presence of within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence.

8 Data analysis A random-effects frequentist network meta-analytic model will be fitted to provide pooled estimates of odds or hazard ratios. Confidence intervals (CI) will be set at 95%. League tables will be created, depicting the relative effects for all comparisons. Treatments will be ranked according to their P-scores, which range from 0 to 1. Heterogeneity will be quantified by calculating the inconsistency index (I2), while its impact on outcomes will be assessed by estimating the 95% prediction intervals (PI). Publication bias will be assessed by examining the possible

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presence of small-study effects through the visual inspection of comparison-adjusted funnel plots. The plausibility of the transitivity assumption will be tested by comparing the distributions of potential confounders across studies grouped by comparison. The global consistency of network will be statistically assessed with the design-by-treatment interaction test.

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