INPLASY

Efficacy and Safety of Mycophenolate Mofetil (MMF) vs Azathioprine (AZA) for Treatment Naive Autoimmune Hepatitis: A Systematic Review and Meta-analysis

INPLASY202510018

doi: 10.37766/inplasy2025.1.0018

Received: 6 January 2025

Published: 6 January 2025

Anwar, MT; Shahzil, M; Arif, TB; Khaqan, MA; Co, EL; Hasan, F; Tarar, R; Naeem, H; Farooq, S; Jaan, A; Chaudhary, AJ; Jahagirdar, V; Salgia, R.

Corresponding author:
Muhammad Shahzil

shahzilm7@gmail.com

Author Affiliation:
Penn State Health Milton S Hershey Medical Center.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202510018

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 January 2025 and was last updated on 6 January 2025.

INTRODUCTION

Review question / Objective Evaluation of Efficacy and Safety of Mycophenolate Mofetil versus Azathioprine in Treatment-Naïve Autoimmune Hepatitis Patients age > 18 years of age.

Condition being studied Autoimmune Hepatitis, which is characterized by autoimmune attack on liver cells.

METHODS

Participant or population Treatment-Naïve Autoimmune Hepatitis Patients age > 18 years of age.

Intervention Mycophenolate Mofetil.

Comparator Azathioprine.

Study designs to be included RCT, Case Cohort studies.

Eligibility criteria Inclusion criteria were meticulously defined to include all comparative studies, including Randomized Controlled Trials (RCTs) and observational studies, which compared MMF vs AZA for AIH in treatment-naïve patients. Eligible studies had to meet the following criteria: (1) Adult participants (≥18 years); (2) Intervention: Mycophenolate Mofetil regimen for AIH patients; (3) Control: Azathioprine regimen for AIH patients; (4) Outcomes: Complete Biochemical Response (CBR), corticosteroid withdrawal rates, relapse rates, treatment response, and safety outcomes. Excluded were case reports, case series with fewer than ten patients, single-arm studies, guidelines, and non-comparative studies. Priority was given to the most comprehensive and recent publications in cases of overlapping data. Additionally, literature reviews, duplicates, conference proceedings, animal studies, and unpublished articles were excluded.

Information sources A thorough literature search was performed across multiple databases,

including the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE (via Ovid), Embase (Elsevier), and Web of Science. The search covered the period from each database's inception until May 2024, focusing on studies comparing MMF and AZA for AIH in treatment-naïve patients. Both Medical Subject Headings (MeSH) and free-text terms were utilized, such as "Autoimmune Hepatitis", "AIH", "Mycophenolate Mofetil", "MMF", "Azathioprine", and "AZA".

Main outcome(s) Complete Biochemical Response (CBR), corticosteroid withdrawal rates, relapse rates, treatment response, and safety outcomes.

Quality assessment / Risk of bias analysis The risk of bias in the RCTs included in our analysis was evaluated using the revised Cochrane Risk of Bias Tool for RCTs (RoB 2.0). This tool scrutinizes bias in five domains: (1) bias resulting from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in the measurement of the outcome; and (5) bias in the selection of the reported result.
For the included cohort and case-control studies, we employed the Newcastle-Ottawa Scale tool. Each study underwent assessment based on eight items in three categories: selection of study groups, comparability of groups, and ascertainment of exposure or outcome of interest. Studies receiving seven, eight, or nine points were classified as high quality, while those receiving four, five, or seven points were deemed fair quality (high risk of bias), and those with three or fewer points were considered low quality (very high risk of bias). To determine the certainty of evidence for each outcome, we used the five grades of recommendation, assessment, development, and evaluation (GRADE) considerations. These considerations include evaluating study limitations, consistency of effect, imprecision, indirectness, and publication bias.

Strategy of data synthesis We adhered to the Cochrane Handbook and PRISMA guidelines, analyzing data from previously published studies, comparing mycophnolate mofetil (MMF) and azathioprine (AZA) in treatment-naïve autoimmune hepatitis (AIH) patients. A comprehensive search across major databases was conducted up to May 2024 using both MeSH and free-text terms. Strict inclusion criteria allowed comparative studies (RCTs and observational) with adult participants assessing outcomes like biochemical response, corticosteroid withdrawal, and safety. Case reports, single-arm studies, guidelines, and non-comparative research were excluded.
Study selection and data extraction were performed independently by two reviews, resolving discrepancies through discussion or a third reviewer. Data included patient characteristics, interventions, outcomes, and study details based on the PICO framework.
Primary outcomes were complete biochemical response (CBR) and corticosteroid-related measures, while secondary outcomes included relapse rates, treatment changes, and safety. Risk of bias in RCTs was assessed using the Cochrane Risk of Bias Tool, which cohort and case-control studies were evaluated using the Newcastle-Ottawa Scale. Evidence certainty was graded using the GRADE framework.
Meta-Analysis employed a random-effects model in RevMan 5.4, reporting results as odds ratios (ORs) or mean differences with 95% confidence intervals. Heterogeneity was assessed using Chi-square and Higgins I2 statistics, with subgroup and sensitivity analyses conducted for high heterogeneity. Funnel and DOI plots evaluated publication bias. Statistical significance was set at $p < 0.05$.

Subgroup analysis None.

Sensitivity analysis Meta-analysis was performed using RevMan 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) employing a random-effects model to account for clinical heterogeneity. Dichotomous outcomes were expressed as odd ratios (OR), and continuous outcomes as mean differences with 95% confidence intervals (CIs). Statistical significance was set at $p<0.05$. Heterogeneity was evaluated using the Chi-square test and the Higgins I^2 statistic. For outcomes with more than ten studies, funnel plots were used to assess publication bias, while DOI plots in MetaXL were used for outcomes with 3-10 studies. Heterogeneity among studies was assessed using the Chi-square test (significance set at $p < 0.10$) and quantified with the Higgins I^2 statistic. I^2 values of 25%, 50%, and 75% were interpreted as representing low, moderate, and high heterogeneity, respectively. In cases of substantial heterogeneity ($I^2 > 50\%$), potential sources were explored through subgroup and sensitivity analyses.

Country(ies) involved United States, Philippines, Pakistan.

Keywords Hepatitis, Autoimmune, Immunosuppressive agents, Azathioprine, Mycophenolate Mofetil, Prednisolone, Drugs-

related side effects and adverse reactions, Hepatitis, chronic, Morbidity, recurrence.

Contributions of each author

Author 1 - Muhammad Tayyab Anwar.
Email: muhammadtayyabanwar264@gmail.com
Author 2 - Muhammad Shahzil.
Author 3 - Taha Bin Arif.
Author 4 - Muhammad Ali Khaqan.
Author 5 - Edzel Lorraine Co.
Author 6 - Fariha Hasan.
Author 7 - Rameez Tarar.
Author 8 - Hamza Naeem.
Author 9 - Sibgha Farooq.
Author 10 - Ali Jaan.
Author 11 - Ammad Javaid Chaudhary.
Author 12 - Vinay Jahagirdar.
Author 13 - Reena Salgia.