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A Systematic Review of Treatment for Acute Interstitial Nephritis

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Introduction: Acute interstitial nephritis (AIN) is a common cause of acute kidney injury. It is characterized by tubular inflammation with eosinophils histologically. The mainstay treatment for AIN includes early diagnosis; underlying infection or systemic disease treatment; cessation of the offending agent; and corticosteroid therapy, when indicated. This systematic review aims to evaluate the efficacy and safety of pharmacotherapy treatments for AIN by assessing treatment outcomes and adverse effects.

Methods: PubMed, Embase, Cochrane Library, and other major databases were systematically searched in June 2024 after registration with the International Prospective Register of Systematic Reviews. Manual searches of the references in relevant articles were conducted. Studies focusing on the treatment of AIN cases that were diagnosed histologically were included. A fixed-effects meta-analysis and meta-regression were performed using Stata SE 16.

Results: A total of 3597 articles were eligible for screening. Twenty-three articles were included in the systematic review. There were 3 randomized controlled trials, 4 case series, and 16 retrospective cohort studies. Corticosteroids were the primary treatment in most of the studies, with 1 study evaluating the use of mycophenolate mofetil (MMF) in steroid-refractory patients. A meta-analysis of 3 studies showed that prednisolone use improved renal outcomes. There was significant variability across studies in dosing, treatment duration, and timing of initiation. Adverse events associated with corticosteroids were likely underreported.

Conclusion: Consistent evidence supporting the use of corticosteroids for treating AIN needs to be more comprehensive. There needs to be a clear consensus on the optimal treatment regimen. High-quality randomized controlled trials are required to help establish evidence-based guidelines for treating AIN.

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AIN is one of the common causes of acute kidney injury. Among patients who underwent renal biopsy for acute kidney disease, the incidence can be up to 10% to 30%.[1] Histologically, AIN is characterized by interstitial infiltrate and edema, with relatively preserved glomerulus and vasculature. There are many etiologies for AIN, including medicines, infections, autoimmune disease, and idiopathic causes.[2] AIN causes prolonged hospital admission, long-term kidney function damage, and, in severe cases, dependence on kidney replacement therapy.[3] It is essential to recognize AIN and initiate treatment promptly. The mainstay treatment of AIN remains early diagnosis, treatment of underlying infection or systemic disease, cessation of the offending agent, and corticosteroid therapy when there are no signs of recovery after supportive therapy.[2] In cases where patients may not tolerate or may fail to respond to steroids, immunomodulatory therapy such as MMF has also shown beneficial effects.[4] Nevertheless, the benefits of pharmacotherapy and the optimal timing, dosage, and duration of treatment still need to be determined. The latest systematic review by Quinto *et al*.[5] found that evidence needs to be provided to support the use of corticosteroids in drug-induced AIN (DI-AIN) and highlights the shortage of more extensive, well-designed clinical trials. In this systematic review, we sought to evaluate pharmacological options for AIN of various etiologies and identify any associated adverse effects.

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METHODS

This systematic review was registered with the International Prospective Register of Systematic Reviews and the protocol ID is CRD42024545318. The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[6]

Eligibility Criteria

We included studies that met the following inclusion criteria: (i) cohort studies, case series, and randomized controlled trials that focused on treating AIN and reported associated renal outcomes and (ii) studies in which AIN was diagnosed by renal biopsy. We excluded studies based on the following criteria: (i) studies involving patients aged < 16 years, (ii) studies focusing on renal transplant patients, (iii) diagnosis of AIN made based on clinical suspicion, (iv) non-English studies lacking available English full texts, and (v) case series with < 4 cases.

Search Strategy

PubMed, Embase, Cochrane Library, Web of Science, CINAHL Complete, Scopus, and Education Resources Information Center were systematically searched in June 2024. The detailed search strategy is listed in Supplementary Table S1. Manual searches of the references in relevant articles were conducted. We did not contact the study authors. Two reviewers agreed upon the search strategies. One reviewer searched and extracted eligible studies. Two reviewers screened the articles for eligibility. In instances of any uncertainty regarding inclusion, a third reviewer was consulted.

Data Extraction

Two reviewers performed data extraction independently. Data were extracted in a Microsoft Excel spreadsheet and included publication year, study period, study type, inclusion and exclusion criteria of the study, types of AIN, patient demographics, compared alternatives, treatment dosage and duration, timing of treatment initiation, renal function before and after treatment, follow-up duration, long-term renal outcome, and adverse reactions associated with treatment.

Bias Assessment

Two reviewers performed the risk of bias assessments. A third reviewer was consulted to resolve any disagreement. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)[7] was used to assess the risk of bias in randomized controlled trials. The Newcastle-Ottawa Scale[8] was used to evaluate the risk of bias in the cohort studies and case series. The quality of evidence of the studies included was assessed using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).[9]

Meta-Analysis With Meta-Regression

We conducted a meta-analysis to evaluate the effects of prednisolone on kidney function, explicitly targeting mean serum creatinine levels measured before and after treatment. Using a fixed-effects inverse-variance model, the analysis combined effect sizes from different studies while assuming a common effect across all included research. Each study contributed key data, including mean values, SDs, and sample sizes, facilitating the calculation of Cohen's d effect sizes and 95% confidence intervals.

Following the meta-analysis, a fixed-effects meta-regression was conducted to assess the influence of covariates, including patient age and treatment duration on the observed effect sizes. Statistical significance was set at the conventional 5% threshold. All analyses and computations were performed using Stata SE 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) statistical software.

RESULTS

This systematic review identified a total of 3597 articles for screening. The PRISMA flow diagram is illustrated in Supplementary Figure S1. After duplicate removal and preliminary title and abstract review, 208 studies were selected for full-text assessment.

Included Studies

Twenty-three articles were included in the systematic review (Table 1).[4,10-30] Years of publication ranged from 1983 to 2024. There were 3 randomized controlled trials, 4 case series and 16 retrospective cohort studies. A total of 1205 patients were included, among whom 952 received pharmacotherapy treatment for AIN. Corticosteroids were the primary treatment in most of the studies, with 1 study evaluating the use of MMF in patients who are steroid-irresponsive or steroid-resistant. Thirteen studies focused on the treatment for DI-AIN only, whereas the other studies included AIN of different etiologies, such as idiopathic AIN, autoimmune AIN, and tubulointerstitial nephritis with uveitis.

Interventions

Most studies evaluated the effect of corticosteroids in treating AIN (Table 2). Only 1 study used MMF in patients who had failed corticosteroid therapy for > 6 months.[4] The dosing and duration of corticosteroids were different across studies. Most studies used either oral prednisolone 1 mg/kg/d for a period

Table 1. Characteristics of the included studies

Authors	Study type Study period	Causes of AIN	Intervention	Control	Patient number (total/ intervention)	Age (intervention/control)
Pusey *et al.*,[10] 1983	Case series, single center. 1972–1980	DI-AIN	i.v. methylprednisolone	No medication	7/5	36 ± 14.3/41.5
Shibasaki *et al.*,[10] 1991	Cohort study, single center. N/A	DI-AIN	Corticosteroids	No medication	11/6	57 ± 7.1/53 ± 17.3
Eapen & Hall,[11] 1992	Cohort study, single center. 1980–1988	DI-AIN, idiopathic, infection	Oral prednisolone	Withdrawal of offending agent	11/8	47.4 ± 17.7/37.3 ± 25.1
Bhaumik *et al.*,[12] 1996	Cohort study, single center. N/A	DI-AIN	Oral prednisolone	Withdrawal of offending agent	16/6	41 ± 12.9/36 ± 15.8
Torpey *et al.*,[13] 2004	Cohort study, single center. 1995–1999	DI-AIN, idiopathic, TINU, sarcoidosis	i.v. methylprednisolone or oral prednisolone	No medication	23/20	55.4 ± 18.7/81.3 ± 7.6
Preddie *et al.*,[4] 2006	Cohort study, single center. N/A	DI-AIN, idiopathic, sarcoidosis, perinuclear antineutrophil cytoplasmic antibody seropositivity	Mycophenolate mofetil	N/A	8/8	60
Gonzalez *et al.*,[14] 2008	Cohort study, multicenter 1975–2006	DI-AIN	i.v. methylprednisolone and oral prednisolone	Withdrawal of offending agent	61/52	57.6 ± 17.9/58.1 ± 18
Raza *et al.*,[15] 2012	Cohort study, single center. N/A	DI-AIN, TINU, sarcoidosis, idiopathic.	Oral prednisolone	Not reported	49/37	64/66
Sampathkumar *et al.*,[16] 2013	Case series N/A	DI-AIN	i.v. methylprednisolone or oral prednisolone	N/A	4/4	48.0 ± 18.3
Muriithi *et al.*,[17] 2014[a]	Case series, single center. 1993–2011	DI-AIN, autoimmune, infection	Oral prednisolone	Not reported	95/83	64 (49–73)/58 (43–62)
Valluri *et al.*,[18] 2014[a]	Cohort study, multicenter, 2000–2012	DI-AIN	Corticosteroids	Not reported	124/73	67.8 (56.1–75.2)/65.4 (57.8–74.4)
Cortazar *et al.*,[19] 2016	Cohort study, multicenter, N/A	DI-AIN	i.v. methylprednisolone or oral prednisolone	Withdrawal of offending agent	12/10	66.9 ± 9.9/48
Legendre *et al.*,[20] 2016	Cohort study, multicenter, 1999–2015	TINU	i.v. methylprednisolone or oral prednisolone	No medication	41/35	44.9 ± 16.1/48.6 ± 18.1
Prendecki *et al.*,[21] 2017[a]	Cohort study, single center, N/A	DI-AIN, TINU, infection, sarcoidosis, Sjogren's, idiopathic	Oral prednisolone	Not reported	187/158	52.2 (16.4–85.3)/53.8 (19.2–87.8)
Fadrid *et al.*,[22] 2018	Cohort study, single center, 1993–2016	DI-AIN	Oral prednisolone	Not reported	24/14	61.7 ± 14.5/63 ± 5.5
Fernandez-Juarez *et al.*,[23] 2018	Cohort study, multicenter, 1996–2015	DI-AIN	i.v. methylprednisolone or oral prednisolone	N/A	182/182	66 ± 14
Yun *et al.*,[24] 2019	Cohort study, multicenter, 2000–2017	DI-AIN, idiopathic, autoimmune, malignancy and infection	Oral prednisolone	No medication	113/92	58.1 ± 15.4/60.6 ± 13.0
Oleas *et al.*,[25] 2020[a]	Cohort study, single center, N/A	DI-AIN	i.v. methylprednisolone or oral prednisolone	N/A	8/8	67
Duque *et al.*,[26] 2021	Case series, single center, 2014–2018	DI-AIN	i.v. methylprednisolone	N/A	8/8	61.3 ± 6
Zakiyanov *et al.*,[27] 2024[a]	Cohort study, single center, 1994–2016	DI-AIN, idiopathic, autoimmune, infection and toxins	i.v. methylprednisolone or oral prednisolone	No medication	103/68	54.0 (36.1–65.4)/52.2 (40.2–61.1)
Ramachandran *et al.*,[28] 2015	Randomized controlled trials, single center, N/A	DI-AIN	i.v. methylprednisolone and oral prednisolone	Oral prednisolone	29/29	41.5 ± 15.2
Chowdry *et al.*,[29] 2018	Randomized controlled trial, single center, N/A	DI-AIN	i.v. methylprednisolone and oral prednisolone	Oral prednisolone	31/31	39.5 ± 14.9
Badurdeen *et al.*,[30] 2023[a]	Randomized controlled trial, single center, N/A	Idiopathic	Oral prednisolone	No medication	59/15	44 (36-52)/47 (38–52)

AIN, acute interstitial nephritis; DI-AIN, drug-induced AIN; IQR, interquartile range; TINU, tubulointerstitial nephritis with uveitis.
[a]Values are reported in median (IQR). The rest of the studies are reported in means and SDs.

followed by a slow taper over several weeks or i.v. methylprednisolone pulse therapy for 2 to 3 days before stepping down to oral prednisolone.

Outcomes

The renal outcomes of pharmacotherapy treatment are outlined in Table 2. They were measured using different metrics. Sixteen studies documented changes in serum creatinine level,[4,10-17,20,22,26-29] 1 study reported changes in estimated glomerular filtration rate,[21] and 6 studies classified the degree of kidney function recovery as "complete recovery," "partial recovery," or "no recovery."[18,23-25,28,30] The definitions for these terms were not standardized across studies.

Eight studies found that corticosteroid treatment led to better renal function or a higher degree of kidney function improvement at the end of follow-up,[10,14,15,19-21,23,27] whereas 8 studies found no significant difference in renal function at follow-up between patients who received pharmacotherapy and patients who did not.[11-13,17,18,22,24,30] Five studies did not draw clear conclusions.[4,10,16,25,26]

Only 10 of the studies included statistical analysis results such as P-values or confidence intervals.[14,15,17,20-24,27,30] Apart from the 5 studies that did not conclude the effect of pharmacotherapy, the studies that did not report statistical outcomes were mainly older studies conducted before 2005. Of the 10 studies that reported statistics, 6 reported statistical differences in renal outcomes between the corticosteroid-treated group and untreated groups (P-values: < 0.001 to < 0.05),[14,15,20,21,23,27] and 4 studies did not observe a statistical significance (P-values: 0.2–0.49).[17,22,24,30] One study that evaluated the use of MMF for the treatment of AIN suggested that MMF could be a useful option in patients with steroid resistance or intolerance.[4] Four studies compared i.v. methylprednisolone to oral prednisolone and did not find a significant difference in treatment outcomes (P-values: 0.22–0.65).[24,27-29]

Seven studies assessed the impact of treatment initiation timing on renal function recovery.[14,15,17,18,22-24] Of these, 3 studies found that delays in initiating corticosteroid treatment worsen renal outcomes (odds ratio: 1.02–6.6, $P = 0.5$),[14,17,23] whereas the other 4 studies did not observe a significant impact (odds ratio: 1.0, $P = 0.45$–0.59).[15,18,22,24] The variability in how studies reported the timing of treatment initiation (symptoms onset vs. renal biopsy diagnosis vs. withdrawal of offending agent) should be considered when interpreting these findings.

Five studies evaluated the effect of corticosteroid treatment on long-term renal outcomes regarding dependence on renal replacement therapy or progression to kidney failure.[14,17,21,24,27] Of these, 3 studies observed that corticosteroid treatment benefits long-term renal outcomes ($P = 0.001$–0.0019),[14,21,27] whereas 2 other studies found no correlation ($P = 0.292$ and 0.4).[17,24] It should be noted that while the average follow-up duration was > 6 months in all 5 studies, each study's follow-up duration varied significantly, ranging from 6 to 34 months. Studies with longer follow-ups did not necessarily produce worse long-term outcomes. In addition, 4 studies identified that a higher degree of tubular atrophy and interstitial fibrosis on renal biopsy was correlated with poorer renal outcomes ($P = 0.005$–0.04, odds ratio $= 8.7$).[12,17,18,23]

Adverse Effects

Adverse reactions related to corticosteroid therapy, such as diabetes mellitus, infectious complications, gastritis and psychosis, were discussed in 4 studies involving a total of 38 patients.[21,28-30] These events were likely underreported, because more than half of the studies did not report adverse reactions, possibly because of the limitations of retrospective study designs or inadequate follow-up. The adverse events included infectious complications ($n = 11$), diabetes mellitus ($n = 10$), gastric side effects ($n = 8$), worsening hypertension ($n = 8$), and psychosis ($n = 1$). These adverse reactions were seen in both oral prednisolone and i.v. methylprednisolone regimens. No clear pattern was observed across the studies to suggest a greater risk of complications associated with specific regimens.

Risk of Bias

The risk of bias assessment for cohort studies and case series was performed using the Newcastle-Ottawa Scale,[8] which evaluates studies across the following 3 domains: selection of study groups, comparability of cohorts, and outcome ascertainment. Three of the 20 nonrandomized studies were classified as low quality, 12 as moderate quality, and 5 as high quality. Most studies failed to demonstrate adequate control for important confounders, causing downgrading in the comparability domain. In addition, some studies needed to be more precise in their ascertainment of patient data, leading to downgrades in the selection domain. Randomized controlled studies were evaluated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2),[7] which assesses 5 bias domains. Two of the 3 randomized studies were considered to have a moderate risk of bias because of concerns in the randomization process or selection reporting of outcomes. One randomized study was deemed to have a low risk of bias. All 3 randomized studies performed well regarding missing data documentation, outcome measurements, and adherence to the

Table 2. Summary of treatment and renal outcomes across included studies

Authors	Treatment	Renal function before treatment (intervention/control)	Final renal function (intervention/control)	Follow-up duration (intervention/control)	Statistics
Pusey *et al.*,[10] 1983	i.v. methylprednisolone 500 mg to 1 g for 1–2 d	1174 ± 524.0 μmol/l 1350 μmol/l	Creatinine clearance: 76.2 ± 7.5 ml/min 43.5 ml/min	2.7 ± 1.9 wks 1 mo	Not reported
Shibasaki *et al.*,[10] 1991	Corticosteroids	7.7 ± 6.5 mg/dl 9.6 ± 4.2 mg/dl	1.6 ± 1.2 mg/dl 4.1 ± 4.9 mg/dl	Not reported	No outcome
Eapen & Hall,[11] 1992	Oral prednisolone	7.8 ± 5.1 mg/dl 3.5 ± 1.3 mg/dl	2.0 ± 1.3 mg/dl 1.5 ± 0.4 mg/dl	1.9 ± 1.5 mos 3 mos	Not reported
Bhaumik *et al.*,[12] 1996	Oral prednisolone 1 mg/kg/d for 6 wks–3 mos	11.8 ± 4.8 mg/dl 9.6 ± 3.9 mg/dl	1.8 ± 0.13 mg/dl 1.6 ± 0.39 mg/dl	7.7 ± 3.4 mos 6.1 ± 6.5 mos	Not reported
Torpey *et al.*,[13] 2004	i.v. methylprednisolone 500 mg daily for 3 d then oral prednisolone OR oral prednisolone 0.5 mg/kg/d with tapering over 2–3 wks	At presentation: 467 ± 169.9 μmol/l 404 ± 199.4 μmol/l	138.9 ± 71.9 μmol/l 144.5 ± 21.9 μmol/l	19.5 ± 15.8 mos 47.7 ± 11.0 mos	Not reported
Preddie *et al.*,[4] 2006	Mycophenolate mofetil. Dosage ranged from 500 mg–1000 mg twice/d, mean duration of therapy: 24.3 mos	At start of treatment: 2.3 mg/dl	1.6 mg/dl	14–40 mos	Not reported
Gonzalez *et al.*,[14] 2008	i.v. methylprednisolone pulses 250–500 mg daily for 3–4 consecutive days, followed by oral prednisolone 1 mg/kg/d tapering off 8–12 wks. Duration: 23 ± 17 d	5.9 ± 3.4 mg/dl 4.9 ± 2.1 mg/dl	2.1 ± 2.1 mg/dl 3.7 ± 2.9 mg/dl	6 mos 18 ± 18 mos	$P < 0.05$
Raza *et al.*,[15] 2012	Oral prednisolone 1 mg/kg/d, mean duration of therapy: 5 mos	650 μmol/l 563 μmol/l	247 μmol/l 301 μmol/l	14.8 mos 34.9 mos	$P < 0.05$
Sampathkumar *et al.*,[16] 2013	i.v. methylprednisolone followed by oral prednisolone for 3 patients, oral prednisolone for 1 patient	At admission: 5.0 ± 4.0 mg/dl	1.3 ± 0.3 mg/dl	4 mos–1 yr	No outcome
Muriithi *et al.*,[17] 2014[a]	Oral prednisolone with starting dose of 60 mg daily, duration: 5 wks.	4.5 (3.3–8.4) mg/dl 3.0 (1.7–4.7) mg/dl	1.4 (1.1–1.8) mg/dl 1.5 (1.1–2.6) mg/dl	> 6 mos > 6 mos	$P = 0.3$
Valluri *et al.*,[18] 2014[a,b]	Corticosteroids	At biopsy: 356 (274–590) μmol/l 280 (216–500) μmol/l	48% achieved CR 41% achieved CR	12 mos	Not reported
Cortazar *et al.*,[19] 2016[c]	4 patients received i.v. methylprednisolone followed by oral prednisolone; 5 patients received oral prednisolone, 1 patient received i.v. methylprednisolone followed by oral prednisolone and MMF	6.6 ± 3.8 mg/dl Not reported	7 PR, 2 CR, 1 no recovery No recovery	Not reported	Not reported
Legendre *et al.*,[20] 2016	7 patients received i.v. methylprednisolone for 3 d followed by oral prednisolone, remaining patients received oral prednisolone with a median dose of 1mg/kg/d	At presentation 332.8 ± 319.0 μmol/l 207.8 ± 139.0 μmol/l	106.3 ± 48.2 μmol/l 121.2 ± 44.1 μmol/l	21.6 ± 27.4 mos 18.3 ± 9.2 mos	$P = 0.02$
Prendecki *et al.*,[21] 2017[a]	Oral prednisolone 40 mg–60 mg daily. Median duration: 6 mos	Median eGFR at biopsy: 20.5 (5–110) ml/min per 1.73 m^2 25 (5–59) ml/min per 1.73 m^2	Median eGFR in treated group: +13 ml/min per 1.73 m^2 compared with the nontreated group	39.9 mos 35 mos	$P < 0.0001$
Fadrid *et al.*,[22] 2018	Oral prednisolone 20 mg–60 mg daily. Duration range: 10 d–12 wks	7.8 ± 2.4 mg/dl 6.6 ± 3.7 mg/dl	1.7 ± 1.0 mg/dl 1.2 ± 0.5 mg/dl	6 mos 6 mos	$P = 0.38$
Fernandez-Juarez *et al.*,[23] 2018[d]	Oral corticosteroid starting dose: 0.8 ± 0.2 mg/kg/d. 42% of patients received i.v. methylprednisolone prior to oral therapy. Median treatment duration: 9 wks	5.7 ± 3.5 mg/dl	75 patients achieved CR, 83 patients achieved PR, 24 patients did not recover	6 mos	$P = 0.008$
Yun *et al.*,[24] 2019[a,e]	Oral prednisolone. Median dosage: 30 mg/d. Median duration of treatment: 14 wks	4.67 (3.00–7.46) mg/dl 4.43 (4.06–6.05) mg/dl	Renal recovery at 6 mos: 58.5% in the treated group, 50% in the nontreated group	34 (18–54) mos 27 (21–69) mos	$P = 0.49$
Oleas *et al.*,[25] 2020[f]	3 patients received i.v. methylprednisolone 250 mg–500 mg daily for 3 d; 5 patients received oral prednisolone 1 mg/kg/d. Mean duration of treatment: 4 mos	At presentation: 3.9 mg/dl	at 3-month follow-up: 7 patients achieved CR, 1 patient progressed to chronic kidney disease	> 3 mos	No outcome
Duque *et al.*,[26] 2021	i.v. methylprednisolone 500 mg daily for 3 d followed by tapering	At time of biopsy: 2.3 ± 1.4 mg/dl	3.1 ± 1.5 mg/dl	6 mos	No outcome
Zakiyanov *et al.*,[27] 2024[a]	12 patients received i.v. methylprednisolone 250 mg–500 mg daily for 3 d followed by oral prednisolone; Remaining patients received oral prednisolone 1 mg/kg/d tapered over 6–12 wks	At presentation: 374 (248–558) μmol/l 280 (169–569) μmol/l	153 (95–282) μmol/l 230 (113–306) μmol/l	12 mos	$P = 0.001$

(Continued on following page)

Table 2. (Continued) Summary of treatment and renal outcomes across included studies

Authors	Treatment	Renal function before treatment (intervention/control)	Final renal function (intervention/control)	Follow-up duration (intervention/control)	Statistics
Ramachandran *et al.*,[28] 2015	13 patients received i.v. methylprednisolone before oral prednisolone; 16 patients received oral prednisolone 1 mg/kg/d for 3 wks	At diagnosis: 9.3 ± 4.8 mg/dl	1.3 ± 0.52 mg/dl	3 mos	$P = 0.22$
Chowdry *et al.*,[29] 2018	Oral prednisolone 1 mg/kg/d or i.v. methylprednisolone for 3 d, then oral prednisolone. Duration of treatment: 4 wks	10.1 ± 4.2 mg/dl	1.4 ± 0.4 mg/dl	3 mos	$P = 0.65$
Badurdeen *et al.*,[30] 2023[a,g]	Oral prednisolone 1 mg/kg/d for 1 mo, then taper over 5–12 wks	eGFR at baseline: 47 (37–52) ml/min per 1.73 m^2 44 (29–52) ml/min per 1.73 m^2	3 CR, 8 PR, 2 no response 8 CR, 5 PR, 2 no response	6 mos	$P = 0.2$

CR, complete recovery; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MMF, mycophenolate mofetil; PR, partial recovery.
[a]Values are reported in median (IQR). The rest of the studies are reported in means and SDs.
[b]CR: complete renal recovery was defined as a return to baseline serum creatinine (SCr) within 1 yr; incomplete renal recovery was defined as nadir SCr over 12 mos >26 μmol/l above baseline.
[c]CR: complete recovery is return of SCr to < 0.35 mg/dl above the baseline value; PR: partial recovery is a return of SCr to > 0.35 mg/dl but less than twice the baseline value.
[d]CR: complete recovery is SCr level at 6 mos did not exceed baseline level by > 25%; PR: partial recovery is SCr level at 6 mos exceeded baseline level by 25%–75%; No recovery is SCr level at 6 mos exceeded baseline level by > 75% or maintenance dialysis was required.
[e]Renal recovery was defined as a decrease in SCr to < 1.3 mg/dl or ≥ 50% from its peak value.
[f]There was no clear definition made for renal recovery.
[g]CR: complete recovery is defined as eGFRof 61–90 ml/min per 1.73 m^2; PR: partial recovery is defined as eGFR of 31–60 ml/min per 1.73 m^2; No response is defined as eGFR of 0–30 ml/min per 1.73 m^2.
Unless specified, renal function before treatment was the maximum serum creatinine level reported.

intended study protocols. The detailed risk of bias assessment is presented in Tables 3 and 4. The quality of evidence for the 5 outcomes in this systematic review was assessed using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation),[9] as summarized in Table 5. Unfortunately, the quality of evidence was rated very low for all outcomes among the included studies, given the high risk of bias, inconsistent conclusions, significant variabilities among studies, and the lack of robust statistical analysis.

Meta-Analysis

A meta-analysis was conducted on a specific subset of studies that evaluated the same treatment at the exact dosage for a minimum duration and provided pretreatment and posttreatment data on kidney function, specifically mean serum creatinine and SD. We were able to select only 3 studies that met these criteria and assessed prednisolone at 1 mg/kg/d for at least 2 weeks: Ramachandran *et al*.[28] (Study 2), Chowdry *et al*.[29] (Study 4), and Bhaumik *et al*.[12] (Study 6). The forest plot presents a meta-analysis using a fixed-effects inverse-variance model based on 3 studies examining treatment effects using before- and after-intervention serum creatinine readings (Figure 1a). Each study includes mean values, SDs, and sample sizes, leading to Cohen's d effect sizes with 95% confidence intervals. All 3 studies show significant effects on serum creatinine, with Cohen's d values of −2.16, −3.60, and −2.95, respectively. Study 2 holds the most weight in the analysis (44.04%). The overall effect size is −2.24, with a confidence interval of −2.82 to −1.67, indicating significant treatment effects. The I^2 value of 0.00% suggests no variability among study results, and a z test score of −7.64 ($P = 0.00$) confirms effective treatment. However, results should be interpreted cautiously because of the limited number of studies ($n = 3$) and the specific treatment (prednisolone at 1 mg/kg/d for at least 2 weeks).

The fixed-effects meta-regression was performed to investigate the effect of covariates, including patient age and treatment duration on effect size (Figure 1b). The Wald chi-square statistic is 0.81 with a P-value of 0.6658, indicating no significant relationship between covariates and effect size.

DISCUSSION

This systematic review evaluated the efficacy and safety of pharmacotherapy treatment for AIN. Corticosteroids remain the cornerstone of AIN treatment; however, the quality of evidence supporting this practice could be better. Although our meta-analysis indicates a positive effect of prednisolone on kidney function in AIN, these findings should be interpreted with caution. The limited number of studies in our analysis required the use of a fixed-effects model, which assumes that all studies estimate the same underlying effect and does not account for variability among them. This can lead to an underestimation of the actual treatment effect and restricts the generalizability of the findings.[31] Four studies that compared i.v. methylprednisolone to oral prednisolone found no superiority of one regimen. One study that explored the use of immunomodulatory therapy suggested possible benefits of MMF. However, because no statistical analysis was conducted to validate the therapeutic effect, more investigations are needed to confirm the findings. To explore whether DI-AIN responds

Table 3. Risk of bias assessment for cohort studies and case series using Newcastle-Ottawa scale

Authors	Selection (Max 4)	Comparability (Max 2)	Outcome (Max 3)	Total	Quality
Pusey *et al.*,[10] 1983	★	0	★	2/9	Low
Shibasaki *et al.*,[10] 1991	0	0	★	1/9	Low
Eapen & Hall,[11] 1992	★★★	★	★	5/9	Moderate
Bhaumik *et al.*,[12] 1996	★★★	0	★★★	6/9	Moderate
Torpey *et al.*,[13] 2004	★★★	★	★★★	7/9	High
Preddie *et al.*,[4] 2006	★★★	★	★	5/9	Moderate
Gonzalez *et al.*,[14] 2008	★★★	★★	★★	7/9	High
Raza *et al.*,[15] 2012	★★	★	★★★	6/9	Moderate
Sampathkumar *et al.*,[16] 2013	0	0	★★★	3/9	Low
Muriithi *et al.*,[17] 2014	★★★	★	★★	6/9	Moderate
Valluri *et al.*,[18] 2014	★★★	0	★★	5/9	Moderate
Cortazar *et al.*,[19] 2016	★★★	★	★	5/9	Moderate
Legendre *et al.*,[20] 2016	★★	0	★★★	5/9	Moderate
Prendecki *et al.*,[21] 2017	★★★	★	★★★	7/9	High
Fadrid *et al.*,[22] 2018	★★★	0	★★★	6/9	Moderate
Fernandez-Juarez *et al.*,[23] 2018	★★★	★	★★★	7/9	High
Yun *et al.*,[24] 2019	★★	★	★★★	6/9	Moderate
Oleas *et al.*,[25] 2020	★	★	★★	4/9	Moderate
Duque *et al.*,[26] 2021	★	★	★★★	5/9	Moderate
Zakiyanov *et al.*,[27] 2024	★★★	★★	★★★	8/9	High

differently to corticosteroids, studies focusing exclusively on DI-AIN were analyzed separately. Of the 7 studies in this group, 4 showed beneficial effect,[10,14,19,23] and 3 did not.[12,18,22] The quality of evidence supporting the use of corticosteroids in DI-AIN remains low because of the limitations noted earlier: high risk of bias, inconsistent results, and small study populations.

The strengths of this systematic review include comprehensive coverage of treatments for AIN across a wide range of etiologies. We employed a rigorous search strategy across major medical databases, strictly adhered to PRISMA guidelines, and used standardized risk-of-bias tools to ensure a thorough evaluation of the current evidence. Before our study, the most recent systematic review on the treatment of AIN was completed by Quinto *et al*.[5] Our study included 8 additional cohort studies and 3 randomized controlled trials completed after the study period covered by Quinto *et al*.[5] By including a large number of studies, we expanded the data set available for analysis and we were able to perform a meta-analysis, which demonstrated benefits of oral prednisolone treatment in AIN. Nevertheless, this systematic review has limitations. Although a meta-analysis was performed, the fixed-effect models that were used are more suitable when the studies being analyzed are homogeneous, which may not accurately reflect the broader clinical reality, where patient characteristics and treatment responses differ significantly. To arrive at a more definitive conclusion regarding the efficacy of prednisolone in AIN, it is essential to conduct additional large-scale studies that encompass a diverse range of populations and settings. This would allow for the potential use of random-effects models for meta-analysis, which could better account for interstudy variability and enhance the generalizability of the results. In addition, the meta-analysis was only able to study the effect of a particular prednisolone treatment regimen on kidney function. Considerable heterogeneity among studies in treatment regimens (i.v. vs. oral prednisolone), follow-up duration and outcome measures precludes the possibility of a meta-analysis to quantify many other outcomes. The long-term kidney outcomes and adverse events captured were possibly confounded by the variable follow-up periods, which ranged from 2.7 weeks to 47.7 months. The predominance of retrospective cohort studies and case series and the lack of robust randomized controlled trials weaken the overall quality of the evidence. In addition, only 10 studies provided statistical analysis to support their conclusions, whereas the rest made observations without statistical validation. The scarcity of statistical analysis

Table 4. Risk of bias assessment for randomized controlled studies using Cochrane risk of bias tool (RoB2)

Author	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of the reported result	Risk of bias
Ramachandran *et al.*,[28] 2015	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns
Chowdry *et al.*,[29] 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Badurdeen *et al.*,[30] 2023	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns

Table 5. Quality of evidence assessment using the GRADE approach

Evidence area	Risk of bias	Inconsistency	Indirectness	imprecision	Publication bias	Quality
Effect of corticosteroid on renal outcomes (16)[a]	Downgraded by 1 level: moderate risk of bias in most studies	Downgraded by 1 level: significant inconsistency (8 studies showed positive outcomes, 8 studies showed negative outcomes)	Downgraded by 1 level: differences in populations and treatments	Downgraded by 1 level: small sample sizes and 6 studies without statistical data	No concerns	Very low
Timing of corticosteroid initiation (7)[a]	Downgraded by 1 level: moderate risk of bias in most studies	Downgraded by 1 level: significant inconsistency (3 studies showed positive outcomes, 4 studies showed negative outcomes)	Downgraded by 1 level: differences in timing calculations and follow-up periods	Downgraded by 1 level: for small sample sizes in most studies	No concerns	Very low
Adverse effects associated with corticosteroids (4)[a]	Downgraded by 1 level due to moderate risk of bias in cohort studies	Downgraded by 1 level for inconsistency in findings	No downgrade	Downgraded by 1 level for small sample sizes and inconsistent reporting of adverse events	No concerns	Very low
Efficacy of IV methylprednisolone vs oral prednisolone (4)[a]	Downgraded by 1 level: 1 RCT had some concerns, 1 cohort study was moderate quality	No downgrade for consistent results across studies	Downgraded by 1 level: differences in dosage and duration introducing indirectness	Downgraded by 1 level: small sample sizes and lack of reported confidence intervals	No concerns	Very low
Long term renal outcomes (5)[a]	Downgraded by 1 level: moderate risk of bias (all cohort studies, some moderate quality)	Downgraded by 1 level: inconsistency in results	Downgraded by 1 level: differences in follow-up duration	Downgraded by 1 level: lack of confidence intervals in most studies	No concerns	Very low

RCT, randomized controlled trial.
[a]Number of studies that investigated the listed outcome.

reduces the reliability of some conclusions drawn in the studies.

Overall, the review findings highlight the ongoing uncertainty in the clinical management of AIN and reinforce the need for high-quality randomized controlled trials with standardized study protocols. There are many challenges associated with conducting high-quality trials, including patient recruitment and heterogeneity of AIN as a condition. Moving forward, measures such as multicenter

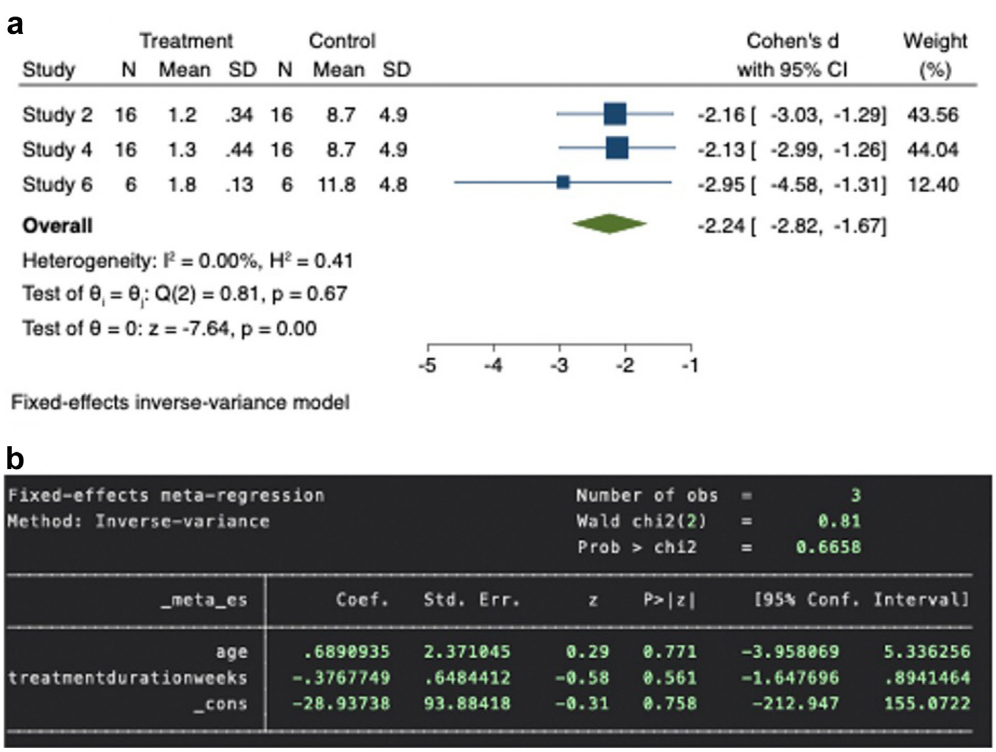

Figure 1. (a) The forest plot displays the results from 3 studies, comparing treatment outcomes measured as Cohen's *d*, which indicates the effect size. (b) The fixed-effects meta-regression output examines how certain covariates impact the effect size across studies. "treatmentdurationweeks," is the duration of the treatment measured in weeks. CI, confidence interval.

collaborations, establishing registries to pool cases, and focusing on subgroups of patients can be considered to increase feasibility of high-quality randomized controlled trials. At the time of this review, the PRAISE trial[32] is being conducted with a focus on the evaluation of prednisolone use in AIN, which will hopefully improve our understanding of this topic.

CONCLUSION

Conclusive evidence supporting the use of corticosteroids in treating AIN still needs to be provided. Decisions cannot be made regarding the optimal dosage, therapy duration, or treatment initiation timing. In addition, there is inadequate evidence comparing the efficacy of i.v. methylprednisolone versus oral prednisolone. Priority should be given to high-quality randomized controlled trials to help establish evidence-based guidelines and clinical practice for the management of AIN.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

AM, YY, and EB conceptualized the study and developed the protocol. YY and XC conducted the literature search and study selection. YY and XC undertook data extraction. YY and EB undertook data analysis. YY drafted the manuscript with all coauthors providing input, review and edits. AM supervised the review process. All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. PRISMA flow diagram.

Table S1. Search strategy.

PRISMA 2020 checklist.

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