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Burden of corticosteroid therapy in patients with immunoglobulin A nephropathy (IgAN): a systematic literature review

Sarah N. Ali[1*], Nicole Fusco[2], Dilip Makhija[1], Vakaramoko Diaby[1], Tosin Oladapo[4], Darsh Devani[2], Cibele Pinto[1], Mohit Mathur[3] and Ancilla W. Fernandes[1]

Abstract

Background Immunoglobulin A nephropathy (IgAN) is one of the most common forms of primary glomerulonephritis (GN) worldwide. While specific treatment differs regionally, treatment usually focuses on background therapy, with short-term (≤ 6 months) corticosteroids recommended as an add-on treatment for patients at high risk of progressive chronic kidney disease. Although corticosteroids can help to manage IgAN, treatment with corticosteroids may lead to undesirable adverse outcomes.

Objective To highlight corticosteroid treatment burden in patients with IgAN globally.

Methods Embase, MEDLINE, and Cochrane CENTRAL were searched for articles published in any language from January 1, 2013 to August 24, 2023. Eligible studies reported ≥ 1 outcome related to the clinical, humanistic, or economic burden of corticosteroids in patients with IgAN. Articles were independently screened by 2 reviewers. Data extraction and quality assessment were completed by 1 researcher and validated by a second. Results are reported among the number of studies with data on each outcome.

Results Of 1,024 records screened, 64 studies were included. Of 37 studies reporting treatment duration, 68% found that corticosteroids were used long-term (range: 8–24 months). In studies reporting data for long-term use (> 6 months), there were more overall AEs and serious AEs with corticosteroids than with comparator treatments (e.g., background therapy alone, tonsillectomy, placebo). Rates of metabolic AEs, Cushing's syndrome, edema and sleep disorders were also higher with long-term corticosteroids than with comparator treatments; however, most studies did not report the statistical significance of these results. Infection rates were similar between corticosteroids and comparator treatments.

Conclusions Current guidelines recommend short-term corticosteroid treatment for patients at high risk of progression but long-term use appears to be widespread. Corticosteroids may lead to adverse outcomes and should therefore be reserved only for IgAN patients most at risk of rapid progression to end-stage kidney disease and for limited duration. Novel corticosteroid-sparing therapies are necessary to supplement the current treatment landscape.

*Correspondence:
Sarah N. Ali
Sarah.Ali@otsuka-us.com

Full list of author information is available at the end of the article

Keywords Immunoglobulin A nephropathy, Corticosteroids, Safety, Treatment burden, Treatment patterns

Introduction

Immunoglobulin A nephropathy (IgAN) is one of the most common forms of primary glomerulonephritis (GN) worldwide with an annual global incidence of 2.5 per 100,000 people [1]. IgAN affects the glomeruli and occurs due to the mesangial deposition of nephritogenic immune complexes and activation of the inflammatory cascade [2, 3]. Diagnosis requires a kidney biopsy, and the symptoms and disease course are variable [2, 3]. Early stages may have no notable symptoms, but IgAN is progressive in most cases; it is estimated that at least 50% of patients reach end-stage kidney disease (ESKD) within 12 years [3, 4]. Patients present with signs of hematuria, proteinuria, and/or peripheral edema. Progressive disease often leads to hypertension, high cholesterol, and kidney failure [5].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines published in 2021 recommended optimized background therapy as the primary focus of treatment [6]. This includes angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) to treat both high blood pressure and proteinuria. Corticosteroids for up to 6 months were recommended as add-on treatment for patients at high risk of progressive chronic kidney disease (CKD) despite previously prescribed background therapy. Tonsillectomy, sometimes combined with corticosteroid pulses, is frequently used in Japan, where it is associated with improved remission rates [7, 8]; however, 2021 KDIGO guidelines recommend against tonsillectomy for IgAN in Caucasian patients [6]. Some studies show that both mycophenolate mofetil (MMF) [8] and hydroxychloroquine [9] are effective in Chinese patients, but these results have not been replicated in Caucasian patients.

The 2021 KDIGO guidelines recommended avoiding the use of corticosteroids, or using only with extreme caution, in patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, diabetes, obesity, latent infections, secondary disease, peptic ulceration, osteoporosis, and uncontrolled psychiatric illness [6]. The next update of the KDIGO guidelines, in draft form at the time of writing, is anticipated to recommend a reduced initial dose of corticosteroids for a shorter duration of 2 months, followed by monthly dose tapering for 6–9 months in total in patients at risk of progressive kidney function loss. Alternative IgAN therapies, including antiplatelet agents, anticoagulants, azathioprine, cyclophosphamide, calcineurin inhibitors, rituximab, and fish oil were not endorsed by KDIGO guidelines due to the lack of documented efficacy. The 2021 guidelines also highlight the uncertainty over the safety and efficacy of immunosuppressive treatments and an unmet need for new treatments, recommending that patients at high risk of CKD progression, despite maximal supportive care, be offered participation in clinical trials investigating new IgAN therapies [6].

Since the last full KDIGO guidelines update, several medications have been approved for the treatment of IgAN. Budesonide targeted-release received full approval from the United States (US) Food and Drug Administration (FDA) in December 2023 for primary IgAN at risk of rapid disease progression [10] and in the European Union (EU) [11] in July 2024 for primary IgAN. Iptacopan was granted accelerated approval in the US by the FDA in August 2024 [12] and Atrasentan in April 2025. Sparsentan received full approval from the FDA in September 2024 [13] and received conditional authorization in IgAN in the EU [14] in April 2024. The 2024 draft KDIGO guidelines is built upon the 2021 framework and reflects the evolving landscape of IgAN management. However, it is important to note that the guidelines are currently in draft form and are subject to change based on feedback received during the period of public consultation.

Notwithstanding these new therapies, treatment options for primary IgAN are limited. Many patients still receive corticosteroids for IgAN despite safety concerns about corticosteroid use from other conditions. Evidence from systematic literature reviews (SLRs) and meta-analyses indicated that short courses (3–7 days) of systemic corticosteroids for bronchial asthma were associated with an increased risk of osteoporosis, bone fracture, hypertension, gastrointestinal complications, mental illness, pneumonia, opportunistic infections, diabetes, hypertension, and cataracts [15, 16]. An SLR investigating treatment for the skin condition pemphigoid reported statistically significantly more adverse events (AEs) with systemic steroids than with biologic agents [17]. Another SLR reported a strong association between systemic steroids and hyperglycemia and hypertension, compared with placebo, in people treated for a range of diseases [18]. Recent trials in IgAN patients have also reported safety concerns with corticosteroid use, such as the Therapeutic Effects of Steroids in IgA Nephropathy Global (TESTING) trial, which was initially paused due to an excess number of AEs in people treated with corticosteroids [19–21].

In addition to the clinical burden of AEs associated with corticosteroids, there are important cost implications to take into consideration. A dose-related increase in healthcare costs was reported in patients with asthma or chronic rhinosinusitis who experienced AEs while being treated with corticosteroids [16, 22]. A similar

association was reported in an SLR investigating corticosteroids in a broad range of diseases, where annual incremental costs in people using corticosteroids ranged from $5,700 for low doses to $29,000 for high doses, compared to non-corticosteroid users [23].

Because of the potential risks of corticosteroids and the limitations of the current evidence to establish clear recommendations, it is important to understand how corticosteroids are currently used for IgAN and how this treatment affects patients. To date, SLRs conducted on the safety of corticosteroids in IgAN have included only randomized controlled trials (RCTs), not real-world observational studies, and many of these SLRs either did not report any safety data at all or reported only overall rates of AEs. To our knowledge, this is the first SLR with the objective of summarizing evidence on the clinical, economic, and humanistic burden of corticosteroids in IgAN patients from both observational studies and RCTs.

Methods

This SLR was conducted according to Cochrane guidance for SLRs and meta-analyses (protocol available in supplemental materials) [24]. Embase, Medline, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched via Ovid.com to identify articles published between 2013 and August 24, 2023 (date of search), on the clinical, humanistic, or economic burden of corticosteroids in IgAN (search strategy available in S1 Table). The National Kidney Foundation Spring Clinical Meeting (2022 and 2023) was manually searched to identify additional abstracts not indexed in bibliographic databases. Two reviewers independently screened the titles and abstracts of the records identified by the literature searches using the eligibility criteria presented in Table 1. Eligible full text studies were screened independently by 2 reviewers, with conflicts resolved by a third reviewer. The reference lists of any relevant SLRs and meta-analyses were checked against the final list of studies to ensure that all eligible publications were identified.

Data extraction and methodological quality assessment were completed by one researcher with complete validation of data conducted by a second researcher and any discrepancies resolved by a third researcher. Methodological quality was assessed with validated tools specific to different study designs:

- RCTs: Cochrane Risk of Bias tool [24].
- Non-randomized interventional studies: Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) [25].
- Retrospective cohort/database studies: Motheral Scale [26].
- Prospective cohort studies: Newcastle-Ottawa Scale [27].
- Case-control studies: Newcastle-Ottawa Scale [27].
- Cross-sectional studies: Joanna Briggs Institute Appraisal [28].
- Economic evaluations and cost-effectiveness analyses: Drummond Economic Evaluation [29] and Philip's Checklist [30].

Results of the included studies were systematically extracted and organized using tabulation, with results summarized separately for long-term (>6 months) and short-term (≤6 months or duration not specified) corticosteroid use. Narrative synthesis was used to highlight patterns, themes, and variations in the findings to provide a comprehensive understanding of the overall evidence landscape.

Results

Search results and summary of included studies

The literature searches returned 1,024 unique records. After title/abstract and full-text screening, 63 studies (76 publications) met the inclusion criteria (Fig. 1). AE data were reported in 35/63 (56%) studies while 44/63 (70%) studies reported treatment pattern data. One study reported economic data on budesonide targeted-release. No studies were identified that reported the humanistic burden of corticosteroids in IgAN patients. Most studies were conducted in Asia (45/63; 71%), with others in Europe (10/63; 16%), North and South America (4/63, 6%), internationally (4/63; 6%), or unreported locations (1/63; 2%). Most studies were retrospective cohort studies (47/63; 75%). Detailed study characteristics are available in S2 Table.

Across the 63 included studies there was a diverse range of ages. The mean or median age in the 17 studies that reported including only adults ranged from 25 to 65 [31–47]; 2 of these studies had a lower age limit of 60 and the median age in both studies was 65 [41, 44]. In 12 studies the lower age limit was 14, 15, or 16 [20, 48–58]; these studies did not report the range of ages so it is not clear if they included any adolescents but the median reported age across the 12 studies ranged from 29 to 47. Two studies included children only, with a median age of 10 in both studies [59]. Two studies with mixed populations of children and adults, without specifying any age limits, reported median ages of 22 [60] and 38 [61]. In 19 studies no information was reported about whether inclusion was restricted to any particular age group but the range of median ages was 30 to 50 [60, 62–79]. The remaining 11 studies did not report any information at all about patients' age.

Duration of corticosteroid treatment and safety outcomes

Here we summarize findings from the included studies regarding the duration of corticosteroid treatment and

Table 1 PICOS eligibility criteria for study selection

Domain	Inclusion criteria	Exclusion criteria
Population	Adults and children with primary IgAN	• Studies not including patients with primary IgAN • Studies not reporting data separately for patients with primary IgAN
Interventions	Corticosteroids	No patients receiving corticosteroids
Comparators	• For clinical burden and treatment pattern outcomes: Any comparator (other doses, other corticosteroids, other treatments, etc.) • For humanistic and economic burden outcomes: Any/none	No restriction
Outcomes	Outcomes of interest include (all measures, all time points): • Clinical burden o Efficacy and effectiveness (or ineffectiveness) of current treatments o Safety or other adverse outcomes of current treatments • Treatment patterns • Humanistic burden o Quality of life o PROs • Economic burden o Healthcare resource use/burden o Direct costs o Indirect costs o Cost-effectiveness	No outcomes of interest
Study design	• Interventional studies • Observational studies • Economic analyses • Systematic reviews of non-English articles[a]	• Case reports/series • Pharmacodynamic studies • Letters, editorials, comments • Systematic reviews of English language articles[a] • Non-systematic or narrative reviews
Time	2013–2023 for articles; 2020–2023 for conference abstracts	
Language	Any	No restriction

[a] Publications of systematic reviews of English-language articles were tagged for manual reference checks but excluded from the list of final included studies. English-language articles identified during reference checks were retrieved. Systematic reviews that included hard-to-find non-English articles were included in our review via the data available in the SLR, but the non-English articles were not retrieved

Key: IgAN – immunoglobulin A nephropathy; PRO – patient-reported outcome

AE data. Data for overall AEs, serious adverse events (SAEs), and metabolic AEs are presented in Tables 2, 3 and 4. Data relating to specific AEs are summarized in the text, with accompanying tables in supplementary materials; Tables S3–S9 cover Cushing's syndrome, edema, infections, osteoporosis, fractures, glaucoma, and sleep disorders.

Duration of corticosteroid treatment

The duration of corticosteroid treatment was reported in 39 studies, of which 14 (36%) reported that corticosteroids were used for 6 months [33, 39, 43, 46, 50, 53, 61, 66, 68, 79–83]. and 2 (5%) studies reported a duration less than 6 months (range: 3–8 weeks) [60, 64]. The remaining 23 (59%) studies reported a duration longer than 6 months (range: 8–24 months) [20, 31, 32, 35, 37, 41, 45, 48, 49, 54–58, 63, 65, 67, 71, 74, 77, 78, 84, 85].

Overall AEs

Safety was assessed in a variety of ways: number of patients experiencing ≥ 1 AE, number of patients experiencing ≥ 1 SAE, and specific adverse outcomes of interest (e.g., Cushing's syndrome, diabetes). Twelve studies reported the number of patients experiencing any ≥ 1 AE (Table 2). In 3 studies of short-term corticosteroid use (≤ 6 months) there was no statically significant difference in AE rates between patients treated with daily corticosteroids compared with the comparator groups [39, 46, 50]. Of the 2 studies that did not report the duration of corticosteroid use, 1 found that patients treated with TSP and corticosteroids experienced significantly more AEs

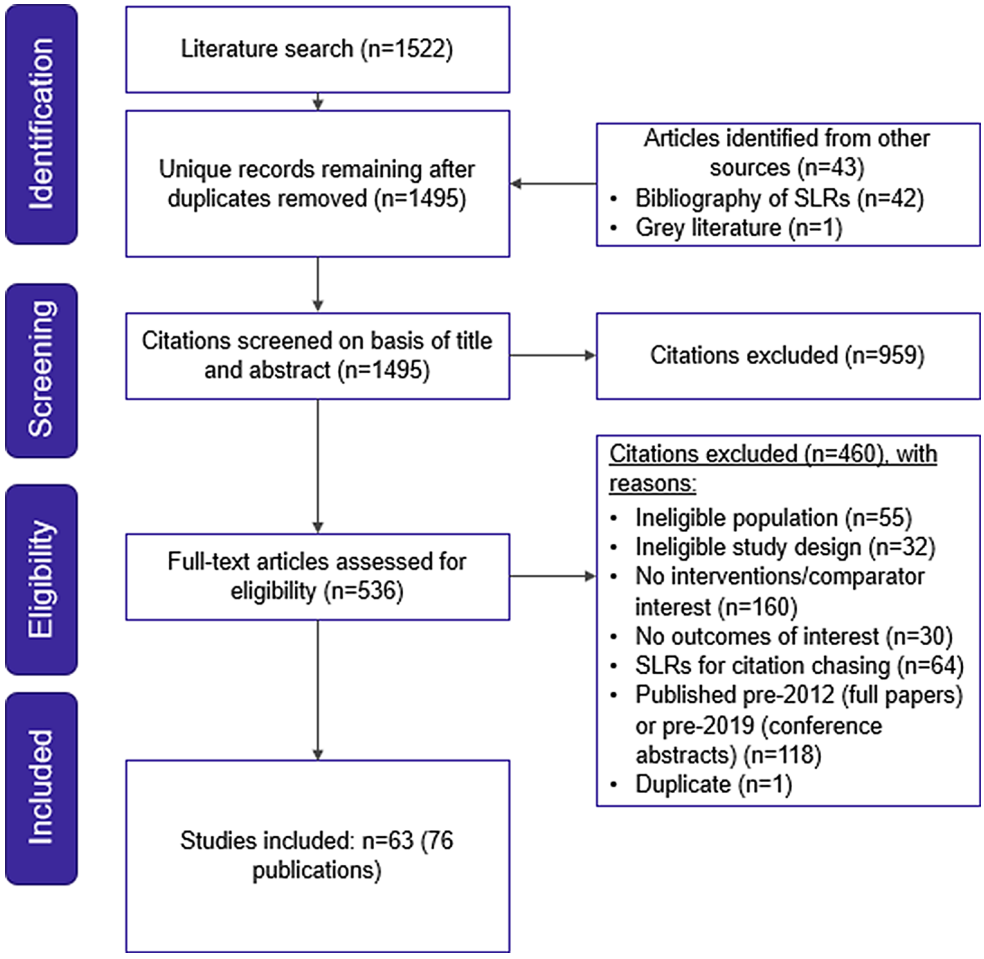

Fig. 1 PRISMA diagram. Key: SLR – systematic literature review. Key: PRISMA – preferred reporting items for systematic reviews and meta-analyses; SLR – systematic literature review

than patients treated with TSP alone [86] and the other did not report statistical significance but 35% of patients treated with corticosteroids experienced AEs compared to none in the background therapy group [47].

In all 7 studies reporting data for long-term corticosteroid use (>6 months), there were numerically more AEs in the corticosteroid group than the comparator group. In the studies that reported statistical significance, corticosteroids were associated with significantly more overall AEs than hydroxychloroquine (1/2 studies [71, 78]), tonsillectomy plus steroid pulse (TSP) (2/2 studies [49, 54]), and no additional treatment (2/2 studies [31, 49]).

SAEs

Nine studies reported the number of IgAN patients who experienced SAEs (Table 3). In 3 studies of short-term corticosteroid use (≤6 months), and 2 studies that did not report details of treatment duration, there was either no statically significant difference in SAE rates between corticosteroids and a comparator treatment [40, 46] or statistical significance was not assessed [59, 80, 83]. In the 2 short-term studies that did not assess statistical significance, there were numerically more SAEs in patients receiving glucocorticoids plus immunosuppressive therapy (16%) compared with either glucocorticoids alone (7%) or background therapy alone (2%) [80] and numerically more SAEs in patients with suboptimal kidney function (eGFR < 60 mL/min/1.73 m^2) receiving corticosteroids (63%) than in those receiving background therapy only (26%) [83]. However, in patients with eGFR ≥ 60 mL/min/1.73 m^2 there fewer SAEs in patients treated with corticosteroids (22%) than in those treated with background therapy only (26%) [83].

In all 4 studies reporting long-term corticosteroid use (>6 months) there were more SAEs in patients treated with corticosteroids than in the comparator groups. In the 3 studies that reported statistical significance, corticosteroid use was associated with significantly more SAEs than hydroxychloroquine (1/1 study [78]), placebo (1/1 study [20]), and either TSP or background therapy only (1/1 study) [49]. In the study that did not report statistical significance, SAEs occurred in 10% of patients

Table 2 Number and percent of IgAN patients with any AE[a]

Study	Duration of treatment	Intervention description	Total AEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤ 6 months) or treatment duration not reported				
Li 2022 [39, 87]	6 months	Oral prednisone (0.8-1.0 mg/kg/day [maximum 70 mg/day], then tapered by 5 mg every 10 days for the next 4 months)	30 (71)	0.363
		Methylprednisolone pulse + alternative low-dose (0.5 g) prednisone at baseline and month 3, followed by oral prednisone [15 mg] every other day for 6 months)	28 (62)	
Liang 2022 [50]	6 months	Group 1-2-3: IV methylprednisolone (0.25 g/d) for 3 consecutive days in the 1st-2nd-5th month, and oral prednisone (0.5 mg/kg/d) on consecutive days for 6 months	4 (11)	0.737
		Group 1-3-5: IV methylprednisolone (0.25 g/d) for 3 consecutive days in the 1st-3rd-5th month, and oral prednisone (0.5 mg/kg/d) on consecutive days for 6 months	6 (16)	
Yan 2022 [46]	6 months	Glucocorticoid (0.8-1.0 mg per day/kg in initial 2 months, then decreased by 20% every month for the next 4 months)	14 (47)	0.4
		Tacrolimus (0.05 mg/kg per day)	7 (35)	
Fujii 2023 [86]	NR	TSP plus follow-up steroid administration[b, c]	14 (54)	0.005
		TSP without follow-up steroid administration[c]	2 (13)	
Luo 2023 [47]	NR	Prednisone (0.5–1 mg/kg/d, decreasing by 10–20% after 2–3 months, then maintained at 2.5–10 mg/d)	7 (35)	NR
		Background therapy	0 (0)	
Long-term corticosteroid treatment (> 6 months)				
Si 2023 [71]	6–8 months	Corticosteroid (prednisone or prednisolone; 0.5-1 mg/kg/d; maximum 60 mg/d, for 2 months, then tapered to 5 mg every 2 weeks)	12 (31)	0.055
		Hydroxychloroquine	5 (13)	
Yang 2019 [78]	6–8 months	Corticosteroid - Oral prednisone or prednisolone (0.8-1.0 mg/kg/d, maximum 60 mg/d for 2 months, then tapered by 5 mg every 2 weeks Or - IV methylprednisolone (500 mg) for 3 days at 1, 3 and 5 months, followed by oral prednisone (15 mg/d) for 6 months	1 AE: 19 (21) ≥ 2 AEs: 15 (16)	< 0.001
		Hydroxychloroquine	1 AE: 6 (7) ≥ 2 AEs: 3 (3)	
Chen 2020 [31]	6–12 months	Group treated with corticosteroid (0.5-1.0 mg/kg/day for first 6–8 weeks, then tapered by 2.5-5 mg each month)[c]	21 (35)	< 0.001
		Untreated group[c]	3 (5)	
Lafayette 2023 (NefIgArd trial) [37, 88, 89]	9 months	Budesonide targeted release 16 mg/day	159 (87)	NR
		Placebo	125 (69)	
Fellstrom 2017 (NEFIGAN trial) [34, 84, 90]	9 months	Budesonide targeted release 16 mg/day	43 (88)	NR
		Budesonide targeted release 8 mg/day	48 (94)	
		Placebo	42 (84)	

Table 2 (continued)

Study	Duration of treatment	Intervention description	Total AEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤ 6 months) or treatment duration not reported				
Kumon 2020 [49]	24 months	Oral prednisolone: 0.5–0.8 mg/kg for first 4 weeks then gradual tapering by 2.5-5 mg every 4 weeks) TSP (methylprednisolone pulses 500 mg/day for 3 consecutive days and 2 additional pulses within the next 6 months) Background therapy	52 in 41 patients[d] 6 in 23 patients[d] 18 in 51 patients[d]	< 0.01 for oral prednisolone versus TSP, and for oral prednisolone versus background therapy 0.43 for TSP versus background therapy
Ogura 2021 [54]	24 months	Oral prednisolone (0.5–0.8 mg/kg/d for the first month, then tapered by 2.5-5 mg/month) TSP (IV methylprednisolone 0.5 g/d for 3 consecutive days and 2 additional pulses within the next 6 months at a 2 to 3-month interval) Tonsillectomy was performed during the corticosteroid treatment and within 6 months after the third SP; 0.5 mg/kg body weight of oral prednisolone was administered every other day for these 6 months; after the third SP, oral prednisolone dosage was gradually tapered by 5 mg.	26 (79) 6 (19)	< 0.001

[a] Unless otherwise stated all patients in all groups received background therapy (ACEI and/or ARB)

[b] Dosage not reported

[c] Does not state if patients also received background therapy

[d] Data reported are total number of AEs, not number of patients with ≥ 1 AE

Key: ACEI – angiotensin-converting enzyme inhibitor; AE – adverse event; ARB – angiotensin receptor blocker; IgAN – immunoglobulin A nephropathy; IV – intravenous; NR – not reported; TSP – tonsillectomy plus steroid pulse

receiving corticosteroids compared to 5% of those receiving placebo [37]. Of note the TESTING trial reported lower SAE rates when the corticosteroid dose was reduced, although the rate was still higher than in the placebo group [20, 91, 92].

Metabolic AEs

Twenty-three studies reported rates of diabetes and/or hyperglycemia (Table 4). In 8 studies of short-term corticosteroid use (≤ 6 months), and 2 studies that did not report details of treatment duration, there was either no statically significant difference in overall metabolic AE rates between corticosteroids and a comparator treatment [39, 46, 50, 66, 79] or statistical significance was not assessed [43, 53, 83]. Similarly, in 13 long-term studies of long-term corticosteroid use (> 6 months) 4 reported no statically significant difference in overall metabolic AE rates between corticosteroids and a comparator treatment [32, 45, 49, 54, 67] and 7 did not assess statistical significance [31, 34, 37, 48, 56, 65, 71].

With regard to specific metabolic events, in 2 studies of long-term corticosteroid use there were statistically significantly higher rates of dyslipidemia in corticosteroid-treated patients than in the comparator groups.[54,77] There were numerically more diabetes events with corticosteroids in 3/4 studies of long-term corticosteroid use [31, 37, 65, 71] (range: 3–5% with corticosteroids versus 0% with comparator therapy) but statistical significance was not assessed in these 4 studies.

Hypertension was reported in 2 studies of short-term corticosteroid use and 3 studies of long-term use (Table 4). In all 5 studies, there were numerically higher rates of hypertension in the groups receiving corticosteroids than in the comparator groups; statistical significance was not assessed in 4/5 studies [34, 37, 53, 62] while there was no statistically significant difference in the other study [54, 77]. The proportion of corticosteroid-treated patients with hypertension ranged from 3% [54] to 17% [53] contrasted with 0% [53, 54] to 4% [62] in the comparator groups. In 4/5 studies, > 5% of

Table 3 Number and percent of IgAN patients with any SAE[a]

Study	Duration of treatment	Intervention description	SAEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤ 6 months) or treatment duration not reported				
Alberici 2020 [80]	6 months	Glucocorticoid[b]	41 (7)	NR
		Glucocorticoid[b] + immunosuppressive therapy (no further details reported)	27 (16)	
		Background therapy	4 (2)	
Rauen 2018 (STOP IgAN trial) [83]	6 months	High eGFR (≥ 60 mL/min/1.73 m^2), corticosteroid monotherapy[b]	12 (22)	NR
		High eGFR (≥ 60 mL/min/1.73 m^2), background therapy only	14 (26)	
		Low eGFR (< 60 mL/min/1.73 m^2), cyclophosphamide for 3 months followed by azathioprine + oral prednisolone[b]	17 (63)	NR
		Low eGFR (< 60 mL/min/1.73 m^2), background therapy only	6 (23)	
Yan 2022 [46]	6 months	Glucocorticoid (0.8-1.0 mg per day/kg in initial 2 months, then decreased by 20% every month for the next 4 months)	1 (3)	NS
		Tacrolimus (0.05 mg/kg per day)	1 (5)	
Mao 2023 [59]	NR	Corticosteroid (prednisone 1–2 mg/kg/d, maximum 60 mg 1 month, then tapered by 5–10 mg every2 weeks)	0 (0)	NR
		Background therapy	0 (0)	
Moriyama 2021 [40]	NR	TSP1: tonsillectomy + 1 steroid pulse + oral prednisolone (0.54 mg/kg) [c]	0 (0)	NS
		TSP2: tonsillectomy + 2 steroid pulses + oral prednisolone[b, c]	0 (0)	
		TSP3: tonsillectomy + 3 steroid pulses + oral prednisolone (0.50 mg/kg) [c]	0 (0)	
		TSP0: tonsillectomy alone[c]	0 (0)	
Long-term corticosteroid treatment (> 6 months)				
Yang 2019 [78]	6–8 months	Corticosteroid - Oral prednisone or prednisolone (0.8-1.0 mg/kg/d, maximum 60 mg/d for 2 months, then tapered by 5 mg every 2 weeks Or - Intravenous methylprednisolone (500 mg) for 3 days at 1, 3 and 5 months, followed by oral prednisone (15 mg/d) for 6 months	Total SAEs: 6 (7) 1 SAEs: 5 (5) ≥ 2 SAEs: 1 (1)	0.03
		Hydroxychloroquine	0 (0)	
Lafayette 2023 (NefIgArd trial) [37, 88, 89]	9 months	Budesonide targeted release 16 mg/day	18 (10)	NR
		Placebo	9 (5)	
Lv 2022 (TESTING trial) [20, 91–93]	8–10 months	Methylprednisolone overall combined results	28 (11)	NR
		Placebo overall combined results	7 (3)	
		Methylprednisolone full dose regimen (0.6–0.8 mg/kg/d for 2 months, maximum 48 mg/d, then tapered by 8 mg per day)	20 (15)	0.001[d]
		Placebo full dose regimen	4 (3)	
		Methylprednisolone reduced dose regimen (0.4 mg/kg/d, maximum 32 mg/d)	6 (5)	NR
		Placebo reduced dose regimen	3 (3)	

Table 3 (continued)

Study	Duration of treatment	Intervention description	SAEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤ 6 months) or treatment duration not reported				
Kumon 2020 [49]	24 months	Oral prednisolone: 0.5–0.8 mg/kg for first 4 weeks then gradual tapering by 2.5-5 mg every 4 weeks)	30 (73)	< 0.01 for oral prednisolone versus TSP, and for oral prednisolone versus background therapy 0.79 (for TSP versus background therapy)
		TSP (methylprednisolone pulses 500 mg/day for 3 consecutive days and 2 additional pulses within the next 6 months)	6 (26)	
		Background therapy	12 (24)	

[a] Unless otherwise stated all patients in all groups received background therapy (RAAS blocker)

[b] Dosage not reported

[c] Does not state if patients also received background therapy

[d] Number of people with SAEs in the methylprednisolone full dose group was reported as 20 in the 2017 paper and 22 in the 2022 paper. The numerator in the placebo group was the same in both publications and the denominators for both groups also remained the same. The 2017 paper reported a p-value of 0.001 whereas the 2022 paper did not report any statistical testing for the difference between groups in SAEs

Key: eGFR – estimated glomerular filtration rate; IgAN – immunoglobulin A nephropathy; NR – not reported; NS – not significant; RAAS – renin-angiotensin-aldosterone system; SAE – serious adverse event; TSP – tonsillectomy plus steroid pulse

corticosteroid-treated patients had hypertension [37, 53, 62, 84].

Cushing's syndrome

In the 4 studies that reported rates of Cushing's syndrome, there were more cases of Cushing's with oral corticosteroids than steroid pulse or placebo (S3 Table). Corticosteroid treatment duration was 6 months in 2 studies [39, 66], 9 months in a third [84], and was not reported in the fourth [94].

Edema

Two RCTs investigating a 9 month course of budesonide 16 mg/day versus placebo reported numerically higher rates of edema in the corticosteroid groups (S4 Table). For peripheral edema, the rates in the budesonide groups taking budesonide 16 mg/day were 12% [95] and 17% [37] compared to 4% in each of the placebo groups [37, 95]. One RCT also reported face edema, which occurred in 8% and 1% of the budesonide and placebo groups, respectively [37].

Infections

Twenty studies reported rates of a variety of infections (pneumonia, upper respiratory tract infections, urinary tract infections, gastrointestinal infection, bronchitis, hospitalizations due to infection, and unspecified infections) (S5 Table). In 6 studies of short-term corticosteroid use (≤ 6 months), 1 reported statistically significantly higher rates of infections in patients treated with daily steroids compared with steroid pulse [39], 4 found no statistically significant difference between groups [46, 50, 79, 82] and the other 2 did not assess statistical significance [43]. In 4 studies that did not report the duration of corticosteroid use there was either no statically significant difference in infection rates between corticosteroids and a comparator treatment [40, 46, 62, 94] or statistical significance was not assessed [47, 59, 62, 94].

Results were similar in the 10 long-term studies (> 6 months). One study reported significantly more hospitalizations with severe infections in people receiving corticosteroids compared with placebo [20] and 6 studies found no statistically significant differences between groups [31, 45, 48, 54, 67, 78]. Of the 3 that did not assess statistical significance, 2 studies reported almost identical rates of infection across the treatment groups [34, 37] and the other reported 1 occurrence of pneumonia and 1 of gastrointestinal infection in the corticosteroid group compared with no occurrences of either type of infection in the Hydroxychloroquine group [71].

Other AEs

Rates of osteoporosis were low, and there was no significant impact of corticosteroids in the studies identified [31, 49, 54, 62] (S6 Table). However, patients treated with corticosteroids long-term were significantly more likely to experience fractures than either TSP or conservative therapy (1/1 long-term use study) [49] (S7 Table).

Long-term use of oral corticosteroids was associated with significantly higher rates of cataracts than either

Table 4 Number and percentage of IgAN patients with metabolic AEs[a]

Study	Duration of treatment	Intervention description	Metabolic AEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤6 months) or treatment duration not reported				
Yan 2022 [46]	6 months	Tacrolimus (0.05 mg/kg per day)	Abnormal blood glucose: 1 (5)	NS
		Glucocorticoid (0.8-1.0 mg per day/kg in initial 2 months, then decreased by 20% every month for the next 4 months)	Abnormal blood glucose: 1 (3)	
Laranjinha 2018 [66, 118]	6 months	Oral prednisolone (1 mg/kg/day)[b]	De novo or worsening diabetes: 2 (14)	NS
		Steroid pulses (1 g/day methylprednisolone pulses for 3 consecutive days at the beginning of months 1, 3 and 5, followed by 0.5 mg/kg prednisolone on alternate days)[b]	De novo or worsening diabetes: 2 (8)	
Li 2022 [39, 87]	6 months	Oral prednisone (0.8-1.0 mg/kg/day [maximum 70 mg/day], then tapered by 5 mg every 10 days for the next 4 months)	Impaired glucose tolerance: 3 (7) Newly diagnosed diabetes: 1 (2) Dyslipidemia 29 (69)	NS
		Methylprednisolone pulse + alternative low-dose (0.5 g) prednisone at baseline and month 3, followed by oral prednisone [15 mg] every other day for 6 months)	Impaired glucose tolerance: 7 (16) Newly diagnosed diabetes: 0 (0) Dyslipidemia: 22 (49)	
Liang 2022 [50]	6 months	Group 1-2-3: MP (0.25 g/d) for 3 consecutive days in the 1st-2nd-5th month, and oral prednisone (0.5 mg/kg/d) on consecutive days for 6 months	Steroid diabetes: 2 (6)	NS
		Group 1-3-5: MP (0.25 g/d) for 3 consecutive days in the 1st-3rd-5th month, and oral prednisone (0.5 mg/kg/d) on consecutive days for 6 months	Steroid diabetes: 0 (0)	
Novaretti 2013 [53]	6 months	Corticosteroids (1 g/day intravenous methylprednisolone for 3 consecutive days at the beginning of months 1, 3, and 5 plus 0.5 mg/kg oral prednisone on alternate days for 6 months)	Hypertension: 2 (17)	NR
		Background therapy	Hypertension: 0 (0)	
Rauen 2018 (STOP IgAN trial) [83]	6 months	High GFR (≥ 60 mL/min/1.73 m^2), corticosteroid monotherapy[c]	Impaired glucose tolerance/DM 9 (17)	NR
		High GFR (≥ 60 mL/min/1.73 m^2), background therapy only	Impaired glucose tolerance/DM: 1 (2)	
		Low GFR (< 60 mL/min/1.73 m^2), cyclophosphamide for 3 months followed by azathioprine + oral prednisolone[c]	Impaired glucose tolerance/DM 1 (4)	
		Low GFR (< 60 mL/min/1.73 m^2), background therapy only	Impaired glucose tolerance/DM 1 (4)	
Stefan 2022 [43, 119]	6 months	Corticosteroids: - Intravenous methylprednisolone 1 g/day for 3 consecutive days at the beginning of months 1, 3, and 5, + oral prednisone 0.5 mg/kg on alternate days for 6 months Or - 6-month course of prednisone 1.0 mg/kg/day for 2 months, then tapered by 0.2 mg/kg/day every month	Diabetes related to corticotherapy: 0 (0)	NR
		Uncontrolled background therapy	Diabetes related to corticotherapy: 0 (0)	
Zhao 2021 [79]	6 months	Corticosteroid: prednisone 50 mg/d for 2 months, and tapered by 20% each month for the next 4 months	Hyperglycemia: 2 (8.0)	NS
		Corticosteroid + MMF: prednisone 30–40 mg/d for 2 months, then tapered by 20% each month for the next 4 months. MMF was prescribed for 6 months at 1.0–1.5 g/day in patients with a BW of < 50 or ≥ 50 kg	Hyperglycemia: 9 (18)	
		Background therapy	Hyperglycemia: 3 (7)	
Li 2020 [94]	NR	Low-dose oral prednisolone[b, c]	Impaired fasting glucose: 3 (9) Dyslipidemia: 17 (50)	NS
		Methylprednisolone pulse[b, c]	Impaired fasting glucose: 2 (7) Dyslipidemia 14 (50)	

Table 4 (continued)

Study	Duration of treatment	Intervention description	Metabolic AEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤6 months) or treatment duration not reported				
Aldworth 2022 [62]	NR	Corticosteroids[b, c]	Diabetes: 4.8 (16)[d] Hypertension: 9.6 (16)[d]	NR
		Not on corticosteroids[b, c]	Diabetes: 1.8 (6)[d] Hypertension: 3.8 (6)[d]	
Long-term corticosteroid treatment (> 6 months)				
Si 2023 [71]	6–8 months	Corticosteroid (prednisone or prednisolone; 0.5-1 mg/kg/d; maximum 60 mg/d, for 2 months, then tapered to 5 mg every 2 weeks)	Newly diagnosed diabetes: 1 (3)	NR
		Hydroxychloroquine	Newly diagnosed diabetes: 0 (0)	
Ma 2020 [67]	8 months	Corticosteroid (oral prednisone 0.6-1.0 mg/kg/day for 2 months, then 5 mg/day for 1 month, tapered to 10 mg for 6 months)	DM: 2 (9)	NS
		Corticosteroid (oral prednisone 30 mg/day for 3 months, then 5 mg/day for 1 month, tapered to 10 mg for 6 months) + oral cyclophosphamide (50 mg/day for 5 months)	DM: 7 (10)	
		Uncontrolled background therapy	DM: 3 (7)	
Chen 2018 [32]	6–12 months	Prednisone (0.8-1.0 mg/kg/day, maximum 60 mg, for 8 weeks, then tapered to stop within 6–9 months)	Steroid diabetes: 3 (4)	NS
		Prednisone (0.8-1.0 mg/kg/day, maximum 60 mg, for 8 weeks, then tapered to stop within 6–9 months) + cyclophosphamide (0.5–0.75 g/m^2 body surface area twice a month)	Steroid diabetes: 0 (0)	
		Prednisone (0.8-1.0 mg/kg/day, maximum 60 mg, for 8 weeks, then tapered to stop within 6–9 months) + leflunomide (50 mg/day for 3 days, reduced to 20 mg/day for 3–6 months, and subsequently tapered)	Steroid diabetes: 0 (0)	
		ACEI/ARB	Steroid diabetes: 0 (0)	
Chen 2020 [31]	6–12 months	Group treated with corticosteroid (0.5-1.0 mg/kg/day for first 6–8 weeks, then tapered by 2.5-5 mg each month)[b]	Hyperglycemia: 3 (5)	NR
		Untreated group[b]	Hyperglycemia: 0	
Lafayette 2023 (NeflgArd trial) [37, 88, 89]	9 months	Budesonide targeted release 16 mg/day	Diabetes events: 4 (2) Hypertension: 22 (12)	NR
		Placebo	Diabetes events: 0 (0) Hypertension: 6 (3)	
Fellstrom 2017 (NEFIGAN trial) [34, 84, 90]	9 months	Budesonide targeted release 16 mg/day	Hypertension: 5 (10)	NR
		Budesonide targeted release 8 mg/day	Hypertension: 3 (6)	
		Placebo	Hypertension: 1 (2)	
Yamamoto 2013 [56]	12 months	Tonsillectomy + 40 mg/day of oral prednisolone, gradually tapered over 2 years	Diabetes requiring insulin: 1 (3)	NR
		TSP: tonsillectomy + IV methylprednisolone 500 mg/day for 3 consecutive days, generally for 4 courses every 2 months, which was discontinued at 3 courses if urinary findings showed remission, followed by oral prednisolone at an initial dose of 20 mg/day	Diabetes requiring insulin: 2 (4)	
Kamei 2014 [65]	12 months	Tonsillectomy plus ISP therapy (IV methylprednisolone pulses of 0.5 g/day for 3 consecutive days at the start of the steroid course, and a further 2 pulses within 6 months after the initial pulse. Oral prednisone 0.5 mg/kg on every alternate day for 6 months. After the third pulse, oral prednisone was gradually withdrawn over a period of 1 month)	Steroid-induced diabetes: 1 (3) Hyperglycemia: 0 (0)	NR
		Tonsillectomy plus CSP therapy (IV methylprednisolone pulses of 0.5 g/day for 3 consecutive days weekly, repeated 3 times for 3 consecutive weeks. After final pulse, oral prednisone 0.5 mg/kg on every alternate day was administered and gradually withdrawn over a period of 1 year)	Steroid-induced diabetes: 0 (0) Hyperglycemia: 2 (4)	

Table 4 (continued)

Study	Duration of treatment	Intervention description	Metabolic AEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤6 months) or treatment duration not reported				
Watanabe 2017 [77]	12 months	Group 3 A: Tonsillectomy plus 3 courses of steroid pulse therapy with oral prednisolone on alternate days (IV methylprednisolone pulses of 0.5 g/day for 3 consecutive days followed by oral prednisolone 30 mg/day on 4 consecutive days, all repeated three times for 3 consecutive weeks. After final pulse therapy, oral prednisolone 30 mg on alternate days, decreased by 5 mg every 8 weeks)	Dyslipidemia • Treated with statin at 12 months: 6 (24) • Treated with statin at 24 months: 6 (24) • Treated with statin at final observation: 5 (20)	12 months: 0.26 24 months: 0.02 Final observation: 0.19
		Group 1 C: Tonsillectomy plus 1 course of steroid pulse therapy with oral prednisolone on consecutive days (intravenous methylprednisolone pulses of 0.5 g/day for 3 consecutive days then oral prednisolone 30 mg/day and gradually withdrawn).	Dyslipidemia • Treated with statin at 12 months: 2 (10) • Treated with statin at 24 months: 0 (0) • Treated with statin at final observation: 1 (5)	
Yamatani 2022 [45]	12 months	ISP with methylprednisolone pulses + prednisolone (0.5 g/day of IV methylprednisolone pulse for 3 consecutive days, repeated 3 times in alternate months. During the interval between each treatment course, oral prednisolone was given at 30 mg every other day. After the last methylprednisolone pulse, oral prednisolone at 30 mg every other day for 2 months, then tapered every 2 months as follows: 20 mg, 10 mg, and 5 mg)	Impaired glucose intolerance: NR (7)	NS
		CSP with methylprednisolone pulses + prednisolone (0.5 g/day of IV methylprednisolone pulse for 3 consecutive days and oral prednisolone 30 mg /day for 4 consecutive days, repeated 3 times for 3 consecutive weeks. After the last methylprednisolone pulse, oral prednisolone at 30 mg every other day, then tapered by 5 mg every 2 months as follows: 25 mg, 20 mg, 15 mg, 10 mg, and 5 mg)	Impaired glucose intolerance: NR (6)	
Komatsu 2016 [48]	12–18 months	Corticosteroid without tonsillectomy (1–3 steroid pulse: IV methylprednisolone 0.5 g/day for 3 consecutive days as one course of pulse therapy. Initial dose of oral corticosteroid after steroid pulse therapy was 20–30 mg/day and continued for about 12–18 months)	Hyperglycemia: 1 (11)	NR
		TSP (1–3 steroid pulse: IV methylprednisolone 0.5 g/day for 3 consecutive days as one course of pulse therapy. Initial dose of oral corticosteroid after steroid pulse therapy was 20–30 mg/day and continued for about 12–18 months)	Hyperglycemia: 6 (13)	
		Non-steroid therapy[b]	Hyperglycemia: 0 (0)	
Kumon 2020 [49]	24 months	Oral prednisolone: 0.5–0.8 mg/kg for the first 4 weeks followed by gradual tapering by 2.5-5 mg every 4 weeks, with continued administration for at least 2 years	Impaired glucose tolerance or diabetes: 6 (15)	NS
		TSP (methylprednisolone pulses of 500 mg/day for 3 consecutive days + 2 additional pulses within the next 6 months)	Impaired glucose tolerance or diabetes: 3 (13)	
		Background therapy	Impaired glucose tolerance or diabetes: 2 (4)	
Ogura 2021 [54]	24 months	Oral prednisolone (0.5–0.8 mg/kg/d for the first month, then tapered by 2.5-5 mg/month)	Diabetes/abnormal glucose tolerance: 3 (9) Hypertension: 1 (3)	NS
		TSP (IV methylprednisolone 0.5 g/d for 3 consecutive days and 2 additional pulses within the next 6 months at a 2 to 3-month interval) Tonsillectomy was performed during the corticosteroid treatment and within 6 months after the third SP; 0.5 mg/kg body weight of oral prednisolone was administered every other day for these 6 months; after the third SP, oral prednisolone dosage was gradually tapered by 5 mg.	Diabetes/abnormal glucose tolerance: 1 (3) Hypertension: 0 (0)	

Table 4 (continued)

Study	Duration of treatment	Intervention description	Metabolic AEs, *n* (%)	*P*-value
Short-term corticosteroid treatment (≤6 months) or treatment duration not reported				
		Oral prednisolone (0.5–0.8 mg/kg/d for the first month, then tapered by 2.5-5 mg/month)	Dyslipidemia 8 (24)	0.043
		TSP (IV methylprednisolone 0.5 g/d for 3 consecutive days and 2 additional pulses within the next 6 months at a 2 to 3-month interval) Tonsillectomy was performed during the corticosteroid treatment and within 6 months after the third SP; 0.5 mg/kg body weight of oral prednisolone was administered every other day for these 6 months; after the third SP, oral prednisolone dosage was gradually tapered by 5 mg.	Dyslipidemia 2 (6)	

[a] Unless otherwise stated all patients in all groups received background therapy (RAAS blocker)

[b] Non-steroid background therapy not specified

[c] Dosage not reported

[d] Annualized rate per patient for patients with all prescription information – n (SD)

Key: AE – adverse event; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; BW – body weight; CSP – consecutive steroid pulse; DM – diabetes mellitus; GFR – glomerular filtration rate; IgAN – immunoglobulin A nephropathy; ISP – intermittent steroid pulse; IV – intravenous; MMF – mycophenolate mofetil; NR – not reported; NS – not significant; RAAS – renin-angiotensin-aldosterone system; TSP – tonsillectomy plus steroid pulse

TSP or conservative therapy [49]. However, neither long-term nor short-term use appeared to be associated with significant differences in rates of glaucoma [82] (S8 Table).

Two short-term use studies did not report any significant association between corticosteroid use and sleep-related disorders [39, 46], and 1 additional short-term use study and 3 long-term use studies did not assess statistical significance [48, 65, 71, 84] (S9 Table). However, all 6 studies reported numerically higher rates of sleep-related disorders, which occurred in >5% of patients receiving corticosteroids (5/6 studies) [39, 46, 48, 65, 84].

Economic and humanistic burden

No studies were identified that reported humanistic burden data related to corticosteroid use for IgAN. One study (2 publications) reported on the cost-effectiveness of corticosteroids in IgAN patients, using efficacy data from the NefIgArd trial, which compared 16 mg of budesonide targeted-release with placebo [96, 97]. The results showed that the incremental cost-effectiveness ratio of budesonide targeted-release plus standard of care compared with standard of care alone was $15,427 per quality-adjusted life-year gained [97]. No other economic analysis studies met our inclusion criteria.

Methodological quality of the included studies

Risk of bias assessment of the included RCTs indicated some concerns due to lack of blinding and lack of reporting of allocation concealment methods. The methodological quality of the observational studies was moderate, given the inherent limitations of these study designs, where causation cannot be established. Studies published only as conference abstracts contained limited detail regarding study methodology. Complete details of the methodological quality assessment for each study are available in Tables S10, S11, S12, S13, S14, S15, and S16.

Discussion

The 2021 KDIGO guidelines recommended corticosteroids as an add-on therapy for up to 6 months for IgAN in patients at high risk of progressive CKD where previously prescribed background therapy was ineffective [6, 98]. However, based on the evidence identified here from RCTs and observational studies, corticosteroids are frequently administered to patients with IgAN for longer than 6 months [31, 32, 35, 36, 41, 44, 45, 48, 49, 51, 54–58, 63, 65, 67, 70–72, 76–78, 85]. Evidence from a Cochrane review of RCTs indicated that short-term (2–4 months) corticosteroid treatment helps to prevent progression to ESKD [99, 100]. In our review, which included evidence from real-world studies as well as RCTs, we examined evidence relating to longer-term use of corticosteroids.

The studies identified for inclusion in this review suggest that AEs can occur frequently with long-term use of corticosteroids. There were statistically significantly higher rates of dyslipidemia [54, 77], fracture [49], and cataracts [49] in patients treated with corticosteroids for longer than 6 months, relative to those not treated with corticosteroids. In studies of short- and long-term corticosteroids where statistical significance was either not reached or not reported, >5% of corticosteroid-treated patients experienced a wide range of burdensome AEs including hyperglycemia [31, 39, 45, 48, 49, 79, 83, 94], edema [37, 95], Cushing's syndrome [39, 66, 84, 94], diabetes [50, 54, 62, 66, 67], infections [47, 62, 67, 79, 82], and sleep disorders [47, 62, 67, 79, 82]. There is limited evidence that corticosteroids may be more harmful to some subgroups of patients. Our findings with regard to higher rates of SAEs in patients with lower eGFR receiving corticosteroids than those receiving only background

therapy are in line with meta-analyses of RCT data, where decreasing eGFR was associated with higher risk of AEs in patients taking corticosteroids [101].

However, due to the limitations inherent in retrospective studies—from which the majority of these data come—and to the lack of statistical power for detecting differences in AE rates between groups in RCTs, it is important to acknowledge some remaining uncertainty about the true risk of AEs with long-term corticosteroid treatment balanced against the potential benefits for people with IgAN. Evidence from the TESTING trial suggests that reducing corticosteroid dosages, combined with antibiotic prophylaxis to protect against serious infections, may help to reduce the risk of AEs [20, 91–93], however the extent to which risk reduction is attributable to the lower corticosteroid dose versus the antibiotic prophylaxis remains uncertain. Additionally, despite the dosage reduction, the rate of SAEs in the corticosteroid-treated group remained higher than in the placebo group.

The AE-related findings presented here are broadly in line with those from other SLRs and meta-analyses investigating corticosteroids for IgAN. Five meta-analyses of RCTs showed a statistically significant difference in the rate of AEs with corticosteroids compared with control groups [99, 102–105]. Other SLRs of RCTs either did not report any safety data [106–109], found only trends in AE rates between corticosteroids and control groups [100, 110, 111], or reported more AEs with corticosteroids without assessing statistical significance [112]. Although meta-analyses of RCTs provide valuable insight, our inclusion of observational studies in addition to RCTs provides a more representative estimate of the clinical burden associated with corticosteroids in real-world settings. Since RCTs are not powered to detect differences between groups in rates of AEs, and often do not follow up participants for long enough to be informative about long-term safety [113], our review of evidence from trials and real-world settings enhances the evidence base regarding the safety of corticosteroids in IgAN.

Safety concerns should be considered in the context of the clinical benefit that may be gained from corticosteroids in terms of kidney function. There is evidence from RCTs indicating that corticosteroids are effective for reducing proteinuria, thereby slowing the decline of kidney function [20, 83], however, the same RCTs also reported that long-term use of corticosteroids led to higher rates of AEs compared to the supportive care or placebo groups. These data suggest a clear need for novel IgAN treatment approaches that balance efficacy with long-term safety.

The completeness of our findings is limited by the paucity of humanistic and economic burden data available for corticosteroid-treated IgAN patients. Despite our comprehensive literature searches we did not identify any studies that reported quality of life data for IgAN patients treated with corticosteroids, which is indicative of an important evidence gap. Economic evidence from the NeflgArd trial suggests that budesonide plus background therapy may be cost-effective compared to background therapy alone. This appears to be supported by a budget impact model, also using data from NeflgArd, which projected that the adoption of budesonide targeted-release over 3 years would increase costs by only $0.09 per member per month [114]. However, given the absence of economic evidence for corticosteroids for IgAN from any other sources, only limited conclusions can be drawn from the economic analysis of the NeflgArd trial, and it is difficult to generalize the findings to other corticosteroids. Furthermore, the economic evidence from NefIgArd should be considered in the context of the high number of studies reporting AE rates that are statistically significant and numerically higher in corticosteroid-treated patients than in patients not treated with corticosteroids. Evidence from patient populations with similar characteristics indicates there may be a correlation between corticosteroids and higher costs and lower quality of life. A study of 78,704 patients with select systemic immune disorders, central nervous system conditions, specific rare diseases, or nephrotic conditions, comparing intermittent corticosteroid use (< 60 days in 1 year) versus low, medium, or daily dosages reported that increasing doses of corticosteroids were associated with significantly higher healthcare costs [115]. Additionally, for all dosages, AE-related medical costs accounted for more of the total healthcare costs than either disease-related medical costs or disease-related prescription costs.

Notwithstanding the comprehensive literature searches underpinning this systematic review, the findings are limited by the availability of published data. Although the NEFIGAN and NefIgArd trials have been completed and published, there remains uncertainty regarding the impact of budesonide targeted-release on safety outcomes. Statistical significance of the comparative data on AEs was not reported in NEFIGAN or NefIgArd, but there were higher rates of new-onset diabetes (2% [37, 88, 89]) and hypertension (> 5% [34, 84, 90]) with budesonide compared to placebo. To date there are no published safety data from observational studies on budesonide targeted-release. Moreover, cumulative exposure to corticosteroids may contribute to the risk of AEs, however, calculation of cumulative exposure would require individual patient level data, detailing amount and duration of use as well as previous exposure to corticosteroids before the index therapy [116]. None of the included studies provided this level of detail, limiting the ability to account for cumulative exposure in this systematic review. Furthermore, statistical significance for AE rates

was often not reported or not presented across studies, making it challenging to interpret the results and quantify the risk of AEs with corticosteroid use. Notably, findings from key RCTs, including the STOP IgAN and TESTING trials, reinforce concerns regarding corticosteroid-associated AEs. The STOP IgAN trial reported a numerically higher incidence of SAEs related to corticosteroid use (63%) in patients with suboptimal kidney function (eGFR < 60 mL/min/1.73 m^2) compared to patients receiving background therapy only (23%) [83]. In the TESTING trial, dose reductions were required due to reported safety concerns with the initial regimen (0.6–0.8 mg/kg per day for 2 months [maximum 48 mg per day] adjusted to a lower dose (0.4 mg/kg per day [maximum 32 mg per day] alongside antibiotic prophylaxis to mitigate the risk of serious infections [20, 91–93]. In the full dose regimen, the TESTING trial reported higher SAEs in the corticosteroid group compared to the placebo group (15% vs. 3%, $p = 0.001$). Although the TESTING trial reported lower SAE rates when the corticosteroid dose was reduced, the rate remained elevated (5% corticosteroid group vs. 3% placebo group). Despite the limitations regarding the lack of statistically significant data, the current review is consistent with findings reported from these RCTs in the literature.

Methodological limitations should be considered. The reliance on retrospective cohort studies introduces potential bias and limitations in the evidence base like selection bias, missing data, variations in clinical practice over time, and variability in data reporting. Although methodological quality was assessed using appropriate tools, these factors should be considered when interpreting the findings.

Geographical bias may limit the extrapolation of data. Most included studies were conducted in Asia where differences in treatment practices, healthcare infrastructure, and disease presentation exist. While these studies provide important contributions to the field, future research across diverse populations should be considered to ensure a more comprehensive understanding of corticosteroid-related safety. While a component of this review was to summarize the humanistic and economic burden, no studies explicitly reported on these aspects of corticosteroid therapy. This is a gap in the literature and limits the understanding of the patient experience and costs related to corticosteroid therapy. Future research should consider incorporating qualitative, patient-reported outcomes, and quantify the monetary impact of corticosteroid use in IgAN to better capture these attributes.

Another limitation of this systematic review is the absence of a meta-analysis. The original scope of this work aimed to summarize the clinical, economic, and humanistic burden of corticosteroid-treated IgAN but did not include plans for conducting a meta-analysis. This limits the ability to draw firm conclusions regarding the strength and direction of effects. However, meaningful meta-analysis may not have been feasible due to the heterogeneity in study designs, populations, and treatment regimens of the included studies. Given the heterogeneity, future research should consider separate meta-analyses for RCTs and observational studies to address these differences. Despite this limitation, our findings are based on rigorous systematic review methods presented as a narrative synthesis, which provides a foundation for future updates as more data become available that may support meta-analysis.

Historically, treatment options for IgAN have been limited and AE data from the current body of evidence, comprising interventional trials and observational studies, suggest that novel corticosteroid-sparing therapies are needed to supplement the current treatment landscape. Recent developments in IgAN therapies, such as the approvals granted to budesonide-targeted release, iptacopan, and sparsentan, may be reflected in the next update of the KDIGO guideline, which is currently in draft form only and is undergoing a period of public consultation. Ongoing clinical trials, investigating the effectiveness of new molecular-targeted agents that inhibit the BAFF and APRIL systems and endothelin and complement pathways [117], may help to further address the unmet needs of IgAN patients.

Conclusion

Our review of the existing evidence from clinical trial and real-world settings highlights that IgAN treated with long-term corticosteroids may lead to adverse outcomes that increase clinical burden. Corticosteroids should therefore be reserved for IgAN patients most at risk of rapid progression to ESKD and should be used for limited duration(s). The lack of evidence specific to IgAN is an important knowledge gap and provides direction for future research. Primary studies that measure QoL and other patient-reported outcomes, healthcare resource utilization, long-term indirect and direct costs, and costs due to AEs, will help to decrease uncertainty about the benefit of therapies for patients with IgAN.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
AE	Adverse event
ARB	Angiotensin receptor blocker
CENTRAL	Cochrane central register of controlled trials
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESKD	End-stage kidney disease
FDA	Food and drug administration
IgAN	Immunoglobulin A nephropathy
KDIGO	Kidney disease: improving global outcomes
MMF	Mycophenolate mofetil
NR	Not reported
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

PRO	Patient-reported outcome
RAAS	Renin-angiotensin-aldosterone system
RCT	Randomized controlled trial
ROBINS-I	Risk of Bias in Non-randomised Studies of Interventions
SAE	Serious adverse event
SLR	Systematic literature review
TESTING	Therapeutic effects of steroids in IgA nephropathy global
TSP	Tonsillectomy plus steroid pulse
US	United States

Supplementary Information

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Supplementary Material 1

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Author contributions
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Data availability
All data relevant to the study are included in the article or uploaded as supplementary information.

Declarations

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Not applicable.

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Not applicable.

Competing interests
Authors SA, DM, VD, CP, and AF are employees of Otsuka Pharmaceutical. Author MM is an employee of Visterra, a wholly owned subsidiary of Otsuka Pharmaceutical. At the time of conducting the study, authors NF, TO and DD were employees of Cencora, which received funding to develop this manuscript.

Author details
[1]Otsuka Pharmaceutical Development and Commercialization, 508 Carnegie Center, Princeton, NJ 08540, USA
[2]Cencora, Conshohocken, PA, USA
[3]Visterra, Inc, Waltham, MA, USA
[4]Cencora, London, UK

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