KI REPORTS
KIReports.org
CLINICAL RESEARCH

Exploring Novel Adverse Events of Nefecon

Jingyu Wang[1,2,3,4,5], Zhao Zhang[1,2,3,4,5], Xingzi Liu[1,2,3,4,5], Sufang Shi[1,2,3,4,5], Jicheng Lv[1,2,3,4,5], Yuemiao Zhang[1,2,3,4,5] and Hong Zhang[1,2,3,4,5]

[1]Renal Division, Peking University First Hospital, Beijing, China; [2]Peking University Institute of Nephrology, Beijing, China; [3]Key Laboratory of Renal Disease, Ministry of Health of China, Beijing, China; [4]Key Laboratory of Chronic Kidney Disease Prevention and Treatment, Peking University, Ministry of Education, Beijing, China; and [5]Research Units of Diagnosis and Treatment of Immune-mediated Kidney Diseases, Chinese Academy of Medical Sciences, Beijing, China

Introduction: Nefecon, the first innovative drug approved by both the US Food and Drug Administration (FDA) and European Medicines Agency for IgA nephropathy (IgAN), lacked comprehensive real-world assessments of its adverse events (AEs).

Methods: We leveraged postmarketing data of Nefecon from the US FDA Adverse Event Reporting System (FAERS), employing disproportionate analysis (DPA) to detect positive signals at the system organ class (SOC) and preferred terms (PTs) levels. Duplicate AEs related to budesonide and those previously reported in studies were excluded through the use of the Medical Dictionary of Regulatory Activities (MedDRA). Our analysis encompassed time-to-onset (TTO), Weibull shape parameter (WSP) evaluation, cumulative incidence, clinical prioritization evaluation, and subgroup analysis based on gender and age.

Results: A total of 1515 individuals with IgAN were included. Five positive SOC signals and 23 positive PT signals were identified, including 4 PTs (asthenia, malaise, product dose omission issue, and anxiety) representing novel AEs newly identified in this study. None of the positive PTs were classified as high clinical priority, with only acne, hypertension, swelling face, and weight increased considered as moderate clinical priority events. The median time to TTO was 31 days. All WSP test results indicated an early failure type profile. Lastly, subgroup analysis provided further insights into the relative risk of specific AEs.

Conclusion: Nefecon demonstrates a favorable safety profile, with no high-priority clinical events identified. The identification of novel AEs and subgroup-specific relative high-risk events fills a gap in existing studies and offers valuable insights for early clinical vigilance.

Kidney Int Rep (2024) **9,** 2705–2717; https://doi.org/10.1016/j.ekir.2024.07.006
KEYWORDS: adverse events; budesonide; FAERS; IgA nephropathy; Nefecon; pharmacovigilance

IgAN is the most common primary glomerulonephritis on a global scale, distinguished by the accumulation of IgA1, specifically the galactose-deficient IgA1 (Gd-IgA1), in the mesangial area of the glomerulus.[1] About 40% of patients advance to end-stage renal disease within a span of 2 decades postdiagnosis.[1-4]

In the Kidney Disease Improving Global Outcomes 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, a void persists concerning the availability of IgAN-specific therapies,[5] and this is more than half a century after IgAN was first discovered. Consequently, the primary focus of IgAN treatment has traditionally centered on supportive measures such as managing blood pressure and reducing proteinuria.[6] Regrettably, these approaches fall short of meeting the complex needs of both patients with IgAN and nephrology specialists. For example, the use of renin-angiotensin system inhibitors may be met with challenges in terms of patient tolerance, particularly among those at a heightened risk of progression.[7] Even with optimal utilization of these interventions, the overall risk of disease advancement persists.[5] This predicament is largely attributed to the fact that the fundamental pathogenic mechanisms triggering IgAN have yet to be adequately addressed.[8]

Drawing on fresh revelations regarding the pathophysiology of IgAN, particularly the mucosal source of Gd-IgA1, has significantly engendered novel approaches for the care of IgAN. Evidence has demonstrated that the origin of circulating Gd-IgA1 can be traced back to the mucosal immune system, whereas aberrations in gut-associated lymphoid tissue result in heightened levels of pathogen-specific IgA.[9,10] In

Correspondence: Yuemiao Zhang, Renal Division, Peking University First Hospital, Xishiku Street No. 8, Xicheng District, Beijing 100034, China. E-mail: zhangyuemiao@bjmu.edu.cn

Received 19 June 2024; revised 25 June 2024; accepted 2 July 2024; published online 6 July 2024

addition, IgA derived from mucosal sources exhibits similarities with the physicochemical properties of immune complexes within the mesangium, including polymerization, affinity, and *O*-galactosylation deficiency.[9] Therefore, targeting sites of mucosal immune hyper-responsiveness and reducing the activity of Gd-IgA1–producing immune cells is expected to reduce the levels of anti-Gd-IgA1 antibodies as well as the intensity of subsequent hits, thereby inhibiting IgAN progression.

Nefecon (referred to as targeted release-budesonide, marketed as Tarpeyo and Kinpeygo) comprises budesonide enclosed in a pH-sensitive encapsulation. Through the customization with TARGIT technology,[11] the capsule has been designed to dispense the medication at its maximum levels precisely at Peyer's patches in the terminal ileum, a pivotal site for antigen sampling and priming within gut-associated lymphoid tissue.[12] The targeted-release mode of administration enables the oral corticosteroid to undergo thorough first-pass metabolism, thereby minimizing systemic side effects. The NEFIGAN and the NefIgArd studies presented a compelling demonstration of the benefits in terms of estimated glomerular filtration rate, urine protein-to-creatinine ratio, proteinuria, and microscopic hematuria in participants. Common AEs included peripheral edema, hypertension, muscle cramps, and acne.[13-15] Consequently, Nefecon became the inaugural and exclusive medication globally to obtain complete approval from the US FDA (December 2021) and the European Medicines Agency (July 2022) for the allopathic management of IgAN, and to be marketed in the US and Europe.[16]

We have not avoided discussing the benefits that Nefecon has shown thus far; however, we have acknowledged the constraints of clinical trials in terms of follow-up duration and sample size,[17-19] along with the paucity of safety data on Nefecon in real-world populations. This study aimed to comprehensively characterize the postmarket emerging AEs and safety profile of Nefecon through the DPA using FAERS database, thereby furnishing a valuable reference.

METHODS

Data Source

Developed in compliance with the E2B (R3) specifications of the International Safety Reporting Guidelines established by the International Council for Harmonisation,[20] the FAERS database stands as the largest pharmacovigilance database globally.[21] It houses reports of AEs, medication errors, and product quality complaints, with the reported AEs being standardized and classified based on the PTs outlined in the MedDRA.[22] The FAERS dataset includes 7 datasets encompassing patient demographics and management information (file descriptor: Demo), drug information (file descriptor: Drug), AE information (file descriptor: Reac), patient outcomes (file descriptor: Outc), reporting source (file descriptor: Rpsr), treatment initiation and cessation dates for reported drugs (file descriptor: Ther), as well as indications for drug administration (file descriptor: Indi).

Data Processing

The continuous updating of the database may result in duplication with previous reports. Following FDA guidelines, duplicates were carefully reviewed and eliminated before statistical analysis based on the following criteria: (i) In cases where CASEIDs matched, the most recent FDA_DT was chosen. (ii) If CASEIDs and FDA_DTs were identical, the higher PRIMARYID was prioritized.[21,23,24]

A postmarketing survey on AEs and pharmacovigilance study of Nefecon (indication for administration is IgAN) was commenced using data from quarter 4, 2021 through quarter 4, 2023. The search encompassed both generic and brand names of target drugs, including "Nefecon", "Tarpeyo", "Kinpeygo", "targeted-release formulation-budesonide", and "TRF-budesonide." The FAERS database displayed 4 categories of drug effects: primary suspect, secondary suspect, concomitant, and interacting. To enhance analysis accuracy and mitigate the influence of confounding variables, the AEs role codes were limited to cases identified as "primary suspect" through the above-mentioned drug search names. After eliminating duplicate reports, the total number of reports was reduced to 2340, and 1515 cases with Nefecon as the primary suspect drug was finally identified. Refer to Figure 1a for an illustration of the survey process.

DPA and Signal Mining

DPA involves comparing observed and expected numbers of reports for a specific drug and AEs, aiming to hypothesize a correlation between them. This method is commonly employed for vigilance analysis of AEs within vast, spontaneously reported databases.[25,26] Widely used algorithms for DPA include the reporting odds ratio (ROR) and proportional reporting ratio (PRR) (Supplementary Table S1), which have been extensively employed by various regulatory bodies, such as the World Health Organization and the US FDA. Here, we combined these 2 algorithms to reveal robust signals.

It is crucial to emphasize that though budesonide serves as the active ingredient in Nefecon, its unique

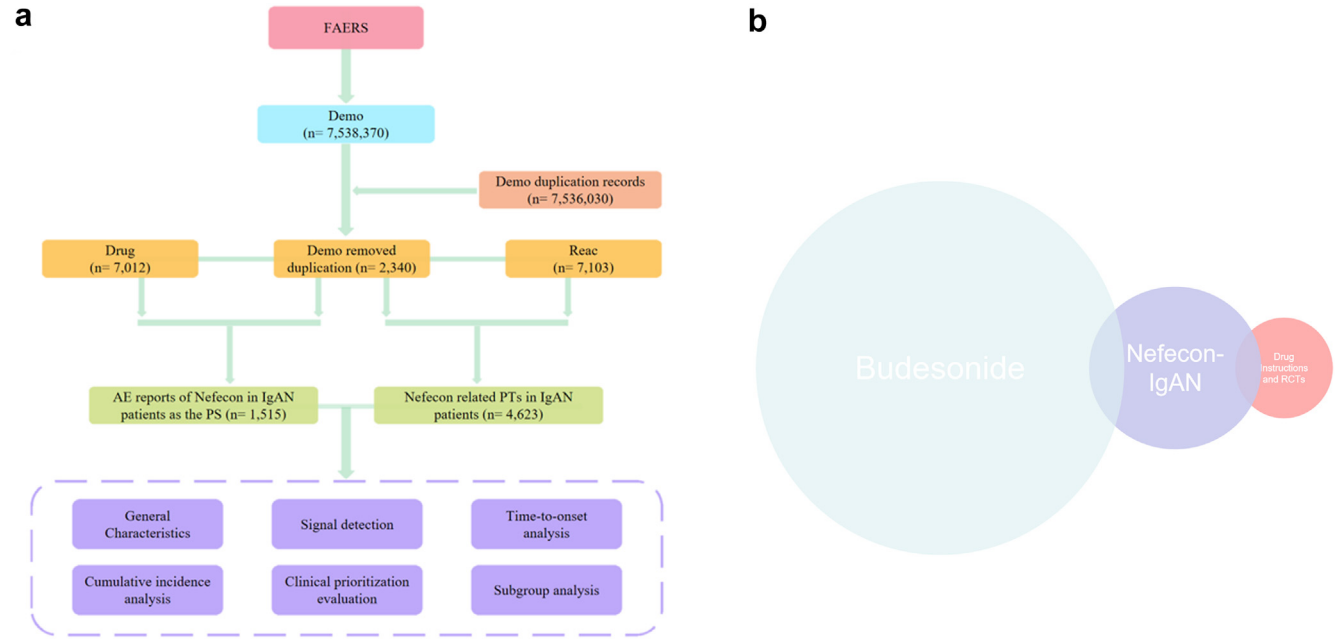

Figure 1. Data processing procedures. (a) The process of selecting Nefecon-associated AEs from FAERS. (b) Novel AEs associated with Nefecon were screened by excluding intersections. AEs, adverse events; FAERS, US Food and Drug Administration Adverse Event Reporting System; IgAN, IgA nephropathy.

targeted release design positions it as the first anti-IgAN drug to specifically target the etiology of the disease. In this context, its mechanism that appears to inhibit the progression of IgAN by blocking the production of Gd-IgA1.[16,27] This sets Nefecon apart from generic budesonide. Furthermore, budesonide was not prescribed as a first-line option for IgAN before the advent of Nefecon. To accurately pinpoint the unreported novel signal of Nefecon in the IgAN population, AEs documented in drug inserts, as well as those observed in the NEFIGAN and NefIgArd trials and those overlapping with budesonide, were also excluded (Figure 1b, Supplementary Tables S2–S4).[13–15,28,29]

The above exclusion procedure was executed utilizing MedDRA. PTs searchable by MedDRA as synonyms of each other are also excluded, such as "contusion" (code: 10050584) and "increased tendency to bruise" (code: 10063580). If AEs cannot be queried through PT in MedDRA, synonymous terms are removed. For example, "peripheral swelling," "peripheral edema," and "peripheral oedema" are considered synonymous AEs; "swelling face" and "face oedema" are also considered synonymous AEs. Similarly, "weight increased," "increased weight," and "increase in weight" are treated as synonymous AEs. Furthermore, a few specific terms, closely linked and showing significant overlap, were deliberately excluded to enhance the detection of novel signals. Examples include "blood pressure increased" and "hypertension," "swelling," and "peripheral edema," as well as "blood glucose increased" and "diabetes mellitus."

Clinical Prioritization Evaluation

We conducted a semiquantitative assessment of emerging signals within the PT tier, evaluating them across 5 dimensions, namely number of target events, lower limit of ROR, mortality proportion, adherence to important medical events or designated medical events criteria, and biological plausibility (Table 1).[30,31] Important medical events and designated medical events are established and standardized by the European Medicines Agency.[32,33] Important medical events encompass AEs with severity characteristics; whereas designated medical events represent rare, severe AEs with a high drug-attributable risk, potentially prompting safety concerns in specific scenarios. Each dimension is stratified into 3 levels and assigned scores

Table 1. A rating scale assessing clinical priority of disproportionality signals

Assessment items	2 points	1 point	0 point
Number of target events (a)	>50	10–50	<10
Lower limit of ROR	>5	2–5	1–2
Mortality proportion (%)	>50	25–50	<25
IMEs or DMEs	DME	IME	None
Biological plausibility	Recognized as AE in the drug inserts or within the NEFIGAN or NefIgArd studies	Overlap with AEs recorded in budesonide	Unreported

AE, adverse event; DME, designated medical event; EMA, European Medicines Agency; IME, important medical events; ROR, reporting odds ratio.
Mortality proportion: percentage of cases in which death was reported as an outcome in the overall cases report for a particular AE. IMEs and DMEs are developed and updated by EMA. Recognized as AE in the drug inserts or within the NEFIGAN or NefIgArd studies; please see Supplementary Tables S2 and S3. For overlap of AEs recorded with budesonide please, see Supplementary Table S4.

of 0, 1, or 2, respectively. In instances where an event aligns with multiple criteria within a dimension, the highest score is applied to ensure maximal attribution. AEs with cumulative scores falling within the ranges of 0 to 4, 5 to 7, or 8 to 10 are designated as low, moderate, or high clinical priorities, respectively.

TTO and Cumulative Incidence

TTO was delineated as the temporal span between the commencement of Nefecon and the emergence of AEs. To uphold the precision of the study, we omitted records featuring erroneous date entries, discrepancies, and omissions,[34] while incorporating the median, quartiles, minimum, maximum, and WSP evaluation for TTO. The WSP analysis discerns and anticipates variations in the incidence of AEs over time by utilizing the α-parameters and β- parameters. These parameters govern the scale and configuration of the distribution function, respectively. A shape parameter $\beta < 1$, with its 95% confidence interval < 1, signifies a decline in hazards over time (early failure type profile); a shape parameter β equal to or proximate to 1, with its confidence interval encompassing the value 1, points to a sustained occurrence of hazards over time (random failure-type profile); and a shape parameter $\beta > 1$, with its confidence interval excluding a value of 1, indicates an increase in hazards over time (wear-out failure type profile). The cumulative incidence of Nefecon-associated AEs in the IgAN cohort was graphically depicted utilizing the Kaplan-Meier approach and subjected to comparison via the log-rank test. A *P*-value lower than 0.05 was determined to be statistically significant.

Subgroup Analysis

Subgroup analysis can strengthen the association between Nefecon and AEs, while helping to mitigate the impact of demographic variables on the findings.[35] However, due to missing data (albeit in small proportions) on gender and age categories, it was not possible to directly classify subgroups into A and non-A groups, thereby limiting the use of precise algorithms such as relative ROR, etc., that are better suited to comparing 2 groups.[36,37] Therefore, we continue to apply the consistent DPA criteria to assess the relative risk of specific AEs in different subgroups.

Statistics

The statistical methods utilized have been meticulously delineated in the aforementioned sections. All processing, analysis, and visualization of exhibition data were executed using Microsoft Office 2019 or R 4.3.2 (https://posit.co/download/rstudio-desktop/). This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

RESULTS

General Characteristics

The clinical features of AEs associated with Nefecon in the IgAN cohort are depicted in Table 2. Within the current dataset, the incidence of AEs skewed higher among males (57.56%) compared to females (42.18%). Concerning age distribution, the proportion of patients aged 18 to 64 years (80.92%) surpassed that of other age brackets. We also counted the most severe outcome for each documented individual, with death prioritized over life-threatening events, which in turn were prioritized over hospitalization, and finally over other serious outcomes. The results indicated that the documented outcomes included 9 cases of death, 2 cases of life-threatening events, 86 cases of hospitalization, and 94 cases of other serious outcomes. Ultimately, the US reported the most cases, comprising 99.93% of the total instances.

Signal Detection at the SOC Level

In Table 3, we present the signal intensity and frequency of reports regarding Nefecon within the IgAN population at the SOC level. The positive SOCs meeting the criteria of both DPA algorithms simultaneously include endocrine disorders (ROR 4.05, PRR 4.02), psychiatric disorders (ROR 2.74, PRR 2.66),

Table 2. Clinical characteristics of patients treated for IgAN with Nefecon in the FAERS database, N = 1515

Characteristics	Case number, *n*	Case proportion, %
Gender		
Female	639	42.18
Male	872	57.56
Unknown	4	0.26
Age (yr)		
<18	8	0.53
18–64	1226	80.92
65–84	227	14.98
≥ 85	2	0.13
Unknown	52	3.43
Outcomes		
Death	9	0.59
Life-threatening	2	0.13
Hospitalization	86	5.68
Other serious outcome	94	6.20
Unknown	1324	87.39
Reported countries		
USA	1514	99.93
China	1	0.07
Reporting yr		
2022	340	22.44
2023	1175	77.56

IgAN, IgA nephropathy; FAERS, US Food and Drug Administration Adverse Event Reporting System.

Table 3. Signal detection results at the SOC level

SOC	a	ROR (95% CI)	PRR (χ^2)
Blood and lymphatic system disorders	15	0.25 (0.13–0.46)	0.25 (22.91)
Cardiac disorders	30	0.48 (0.29–0.8)	0.49 (8.53)
Congenital, familial and genetic disorders	1	0.18 (0.02–1.72)	0.18 (2.83)
Ear and labyrinth disorders	7	0.34 (0.13–0.88)	0.34 (5.45)
Endocrine disorders	45	4.05 (1.73–9.51)*	4.02 (12.11)*
Eye disorders	76	1.96 (1.2–3.18)*	1.94 (7.62)
Gastrointestinal disorders	447	1.01 (0.86–1.2)	1.01 (0.02)
General disorders and administration site conditions	880	0.96 (0.85–1.09)	0.97 (0.38)
Hepatobiliary disorders	8	0.1 (0.05–0.22)	0.1 (51.62)
Immune system disorders	20	0.27 (0.15–0.45)	0.27 (26.85)
Infections and infestations	202	0.62 (0.51–0.77)	0.64 (19.49)
Injury, poisoning and procedural complications	409	1.11 (0.93–1.32)	1.1 (1.26)
Investigations	558	1.15 (0.99–1.35)	1.13 (3.2)
Metabolism and nutrition disorders	123	0.72 (0.54–0.95)	0.73 (5.62)
Musculoskeletal and connective tissue disorders	309	1.32 (1.06–1.63)*	1.3 (6.48)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	6	0.64 (0.2–2.11)	0.64 (0.54)
Nervous system disorders	327	0.6 (0.5–0.7)	0.62 (37.38)
Product issues	4	1.07 (0.2–5.86)	1.07 (0.01)
Psychiatric disorders	223	2.74 (1.98–3.79)*	2.66 (40.26)*
Renal and urinary disorders	194	0.75 (0.6–0.94)	0.76 (6.41)
Reproductive system and breast disorders	48	5.19 (2.06–13.06)*	5.15 (15.26)*
Respiratory, thoracic, and mediastinal disorders	133	0.81 (0.62–1.07)	0.82 (2.14)
Skin and subcutaneous tissue disorders	262	2.23 (1.69–2.94)*	2.16 (34.11)*
Social circumstances	4	1.07 (0.2–5.86)	1.07 (0.01)
Surgical and medical procedures	101	9.21 (4.04–21.02)*	9.03 (41.06)*
Vascular disorders	191	1.46 (1.11–1.93)*	1.44 (7.31)

CI, confidence interval; PRR, proportional reporting ratio; ROR, reporting odds ratio; SOC, system organ class.
*Reports that adhered to the algorithm

reproductive system and breast disorders (ROR 5.19, PRR 5.15), skin and subcutaneous tissue disorders (ROR 2.23, PRR 2.16), as well as surgical and medical procedures (ROR 9.21, PRR 9.03). The SOCs that met at least 1 of the algorithmic criteria included eye disorders (ROR 1.96), musculoskeletal and connective tissue disorders (ROR 1.32), vascular disorders (ROR 1.46).

Signal Detection at the PT Level and Novel Signal Mining

The application of DPA algorithms revealed 23 positive PT signals linked to Nefecon (Table 4). In order to provide a more detailed description of the Nefecon's unique PTs, we excluded 23 PTs that overlapped with the drug instructions of Tarpeyo and Kinpeygo, the NEFIGAN and NefIgArd studies, and the established AEs of budesonide (Figure 1b, Supplementary Tables S2–S4, Supplementary Figure S1). Ultimately, 4 novel AEs of Nefecon were identified: asthenia (ROR 2.16, PRR 2.15), malaise (ROR 2.83, PRR 2.82), product dose omission issue (ROR 2.46, PRR 2.43), and anxiety (ROR 3.02, PRR 3) (Figure 2, Table 4).

Clinical Prioritization

Among the 23 PTs scrutinized, no fatalities were observed (Table 5). "End-stage renal disease" alone was attributed to important medical events. In the final synthesis analysis, a total of 19 events were classified as low clinical priorities, with 4 events identified as moderate clinical priority. This included acne, hypertension, swelling face, and weight increased. No events were established as high clinical priorities.

TTO and WSP

Of the 1515 reports, 470 contain TTO data with a median onset time of 31 days and an interquartile range (IQR) of 7 to 106 days (Table 6). The peak reporting of AEs was observed within the time intervals of days 0 to 30 ($n = 229$, 48.72%) and 91 to 180 ($n = 83$, 17.66%) posttreatment (Figure 3). The WSP result indicated an early failure type profile (Table 6).

Subgroup Analysis - Gender

The top 3 most frequently reported PTs in males were peripheral swelling (86 reports), hypertension (81 reports), and weight increased (67 reports); whereas in females, they were weight increased (57 reports), product dose omission issue (56 reports), and hypertension (52 reports) (Supplementary Table S5).

We further assessed the differences in Nefecon's AEs across genders by DPA analysis. The results showed that among the positive PT signals shared between genders, males had a higher relative risk of swelling face, whereas females had a higher relative risk of swelling, muscle spasms, and hypertension (Figure 4a). Both sexes had comparable risks of weight increased (Figure 4a).

Among the 470 cases with TTO data, 278 were male (with a median onset time of 34 days and an IQR of 7.25–119.25 days) and 192 were female (with a median onset time of 26.5 days and an IQR of 7–91 days) (Supplementary Table S6). Both genders exhibited similar onset times for AEs (Figure 5a and b), with the most reported timeframe for AEs being within 1 month; the WSP results for both genders indicated an early failure type profile (Supplementary Table S6). Furthermore, there was no difference in the cumulative incidence of AEs during Nefecon treatment between male and female patients (Figure 5c).

Subgroup Analysis - Age

After excluding subgroups with inadequate reporting, 2 subgroups were delineated: 18 to 64 years and 65 to 84 years. Within the 18 to 64 years subgroup, the top 3 frequently reported PTs were hypertension (102

Table 4. Signal detection at the PTs level with novel signal mining

SOC	PT	a	ROR (95% CI)	PRR (χ^2)
Endocrine disorders	Cushingoid˄˅	32	5.76 (1.76–18.81)	5.72 (10.74)
Gastrointestinal disorders	Abdominal distension˄	42	2.83 (1.33–6.04)	2.82 (7.93)
General disorders and administration site conditions	Swelling face˄˅	62	4.8 (2.19–10.51)	4.75 (18.81)
	Asthenia*	48	2.16 (1.14–4.07)	2.15 (5.92)
	Swelling˅	45	6.08 (2.19–16.94)	6.04 (15.54)
	Malaise*	42	2.83 (1.33–6.04)	2.82 (7.93)
	Hunger˄	31	4.18 (1.47–11.85)	4.16 (8.54)
	Energy increased˄	16	8.61 (1.14–64.96)	8.58 (6.32)
Injury, poisoning and procedural complications	Product dose omission issue*	86	2.46 (1.49–4.04)	2.43 (13.27)
	Contusion˄	50	27.1 (3.74–196.33)	26.82 (24.55)
Investigations	Weight increased˄˅	124	3.23 (2.03–5.14)	3.17 (27.19)
	Blood pressure increased˄˅	95	2.58 (1.59–4.19)	2.55 (15.8)
	Product residue present˄	60	32.6 (4.51–235.35)	32.19 (29.98)
	Blood glucose increased˅	37	3.33 (1.4–7.89)	3.31 (8.36)
Metabolism and nutrition disorders	Increased appetite˄	34	9.18 (2.2–38.24)	9.12 (13.72)
Musculoskeletal and connective tissue disorders	Muscle spasms˄˅	105	2.86 (1.77–4.62)	2.82 (20.03)
Psychiatric disorders	Insomnia˅	48	2.88 (1.41–5.88)	2.86 (9.25)
	Anxiety*	28	3.02 (1.16–7.82)	3 (5.7)
Renal and urinary disorders	End-stage renal disease˄	41	5.54 (1.98–15.48)	5.5 (13.5)
Skin and subcutaneous tissue disorders	Acne˄˅	56	30.4 (4.21–219.73)	30.04 (27.8)
	Alopecia˅	20	3.59 (1.06–12.08)	3.58 (4.86)
Surgical and medical procedures	Dialysis˄	26	14.02 (1.9–103.39)	13.95 (11.62)
Vascular disorders	Hypertension˄˅	133	6.09 (3.37–11.02)	5.95 (46.22)

AE, adverse event; CI, confidence interval; PRR, proportional reporting ratio; PT, preferred term; ROR, reporting odds ratio; SOC, system organ class.
˄Duplicate signal recorded with budesonide.
˅Signals explicitly recorded as AEs drug insert, NEFIGAN study, and NeflgArd study.
*Novel signals.

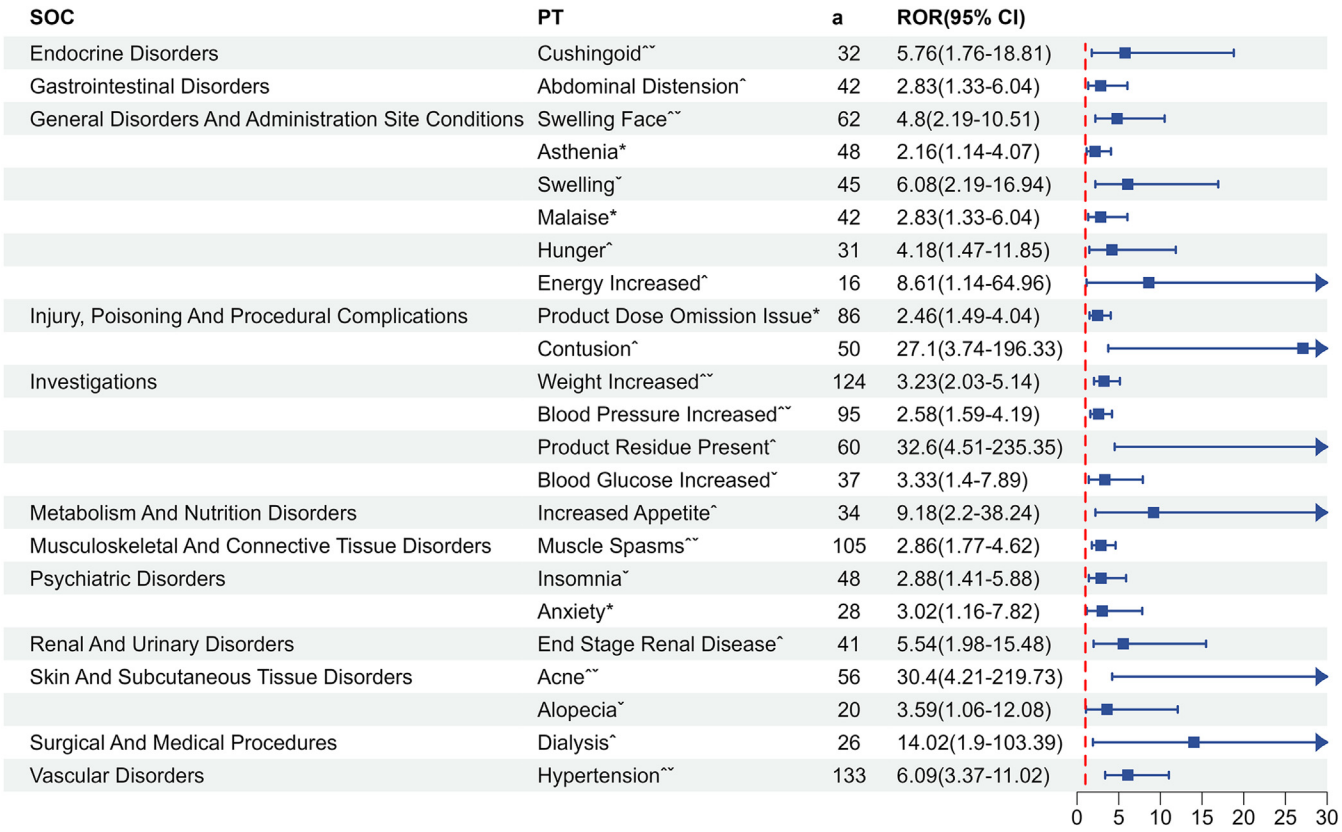

Figure 2. The forest plot of 23 positive signals associated with Nefecon at the preferred term level. ˄ Duplicate signal recorded with budesonide. ˅Signal explicitly recorded as AEs drug insert, NEFIGAN study, and NeflgArd study. * Novel signals. PT, preferred term; ROR, reporting odds ratio; SOC, system organ class.

Table 5. Clinical priority assessing results of disproportionality signals

PT	Number of target events (score)	Lower limit of ROR (score)	Death (score)	IMEs or DMEs (score)	Biological plausibility score	Priority level (score)
Abdominal distension	42 (1)	1.33 (0)	0 (0)	Neither (0)	1	Weak (2)
Acne	56 (2)	4.21 (1)	0 (0)	Neither (0)	2	Moderate (5)
Alopecia	20 (1)	1.06 (0)	0 (0)	Neither (0)	2	Weak (3)
Anxiety	28 (1)	1.16 (0)	0 (0)	Neither (0)	0	Weak (1)
Asthenia	48 (1)	1.14 (0)	0 (0)	Neither (0)	0	Weak (1)
Blood glucose increased	37 (1)	1.4 (0)	0 (0)	Neither (0)	2	Weak (3)
Blood pressure increased	95 (2)	1.59 (0)	0 (0)	Neither (0)	2	Weak (4)
Contusion	50 (2)	3.74 (1)	0 (0)	Neither (0)	1	Weak (4)
Cushingoid	32 (1)	1.76 (0)	0 (0)	Neither (0)	2	Weak (3)
Dialysis	26 (1)	1.9 (0)	0 (0)	Neither (0)	1	Weak (2)
End-stage renal disease	41 (1)	1.98 (0)	0 (0)	IME (1)	1	Weak (2)
Energy increased	16 (1)	1.14 (0)	0 (0)	Neither (0)	1	Weak (2)
Hunger	31 (1)	1.47 (0)	0 (0)	Neither (0)	1	Weak (2)
Hypertension	133 (2)	3.37 (1)	0 (0)	Neither (0)	2	Moderate (5)
Increased appetite	34 (1)	2.2 (1)	0 (0)	Neither (0)	1	Weak (3)
Insomnia	48 (1)	1.41 (0)	0 (0)	Neither (0)	2	Weak (3)
Malaise	42 (1)	1.33 (0)	0 (0)	Neither (0)	0	Weak (1)
Muscle spasms	105 (2)	1.77 (0)	0 (0)	Neither (0)	2	Weak (4)
Product dose omission issue	86 (2)	1.49 (0)	0 (0)	Neither (0)	0	Weak (2)
Product residue present	60 (2)	4.51 (1)	0 (0)	Neither (0)	1	Weak (4)
Swelling	45 (1)	2.19 (1)	0 (0)	Neither (0)	2	Weak (4)
Swelling face	62 (2)	2.19 (1)	0 (0)	Neither (0)	2	Moderate (5)
Weight increased	124 (2)	2.03 (1)	0 (0)	Neither (0)	2	Moderate (5)

DME, designated medical event; IME, important medical events; PT, preferred term; ROR, reporting odds ratio.

reports), peripheral swelling (101 reports), and weight increased (99 reports) (Supplementary Table S7). In the 65 to 84 years subgroup, only 2 positive PT signals were identified: hypertension and muscle spasms (Supplementary Table S7).

Further DPA analysis revealed that among the 2 positive PT signals shared by the 2 age subgroups, patients aged 18 to 64 years exhibited a higher relative risk of both muscle spasms and hypertension compared to those aged 65 to 84 years (Figure 4b).

Among the 464 cases with TTO data, 390 cases were between the ages of 18 and 64 years (with a median onset time of 31 days and an IQR of 7–111 days), whereas 74 cases were between the ages of 65 and 84 years (with a median onset time of 30 days and an IQR of 7–65.75 days) (Supplementary Table S6). Individuals aged 18 to 64 years frequently reported AEs primarily occurring on days 0 to 30 and 91 to 180, whereas individuals aged 65 to 84 years experienced AEs mostly within the first 2 months following treatment (Figure 6a and b). The WSP results for both subgroups exhibited an early failure type profile, with a statistically significant difference in the cumulative incidence of AEs ($P = 0.043$) (Figure 6c and Supplementary Table S6).

DISCUSSION

Given the paucity of premarketing preclinical data, and the stringent and explicit enrollment criteria and comorbidity screening in clinical trials, which are often more intricate in real-world scenarios, discrepancies may arise in the accuracy of clinical trials in depicting real-world data.[17-19] There is a necessity for structured postmarket surveillance of AE data following the launch of a drug to accurately capture its real-world impact.[38,39]

The findings from our investigation reveal a continued increase in documented AEs (Table 2), underscoring the critical need for ongoing surveillance of AEs. We observed a higher incidence of AEs among male patients with IgAN (57.56%). This observation

Table 6. In 470 out of the 1515 reports, TTO data was included. For these reports, median values, extreme values, and WSP results were also calculated

			Weibull distribution				
	TTO (d)		Scale parameter		Shape parameter		
Cases	Median (IQR)	Min–Max	α	95% CI	β	95% CI	Failure type
470	31 (7–106)	1–452	58.37	50.83–65.91	0.74	0.69–0.79	Early failure

CI, confidence interval; IQR, interquartile range; max, maximum; min, minimum; TTO, time-to-onset.

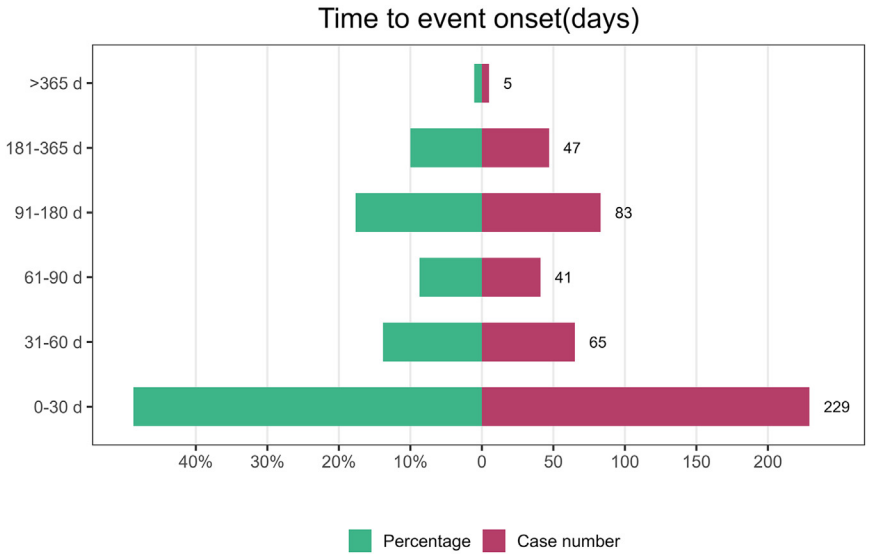

Figure 3. Time-to-onset data of Nefecon-related adverse events (470 reports).

may be attributed to 99.93% of the reports originating from the US, where the prevalence of IgAN between men and women in North America stands at 3:1.[2] A mortality outcome was observed in 9 patients as a result of this investigation (Table 2). In addition, these individuals reported COVID-19 pneumonia, cardiovascular accidents, organ failure, suicide, etc. (Supplementary Table S8). These events lie outside the scope of Table 4, suggesting that they were independent of the use of Nefecon therapy, a finding that resonates with previous literature reports.[15] The median age of the 9 patients was 77 years, with a mean age of 73 years (Supplementary Table S8), whereas the median age of the Nefecon-treated group was less than 45 years in both the NEFIGAN and NefIgArd studies. This underscores the potential significance of systematically documenting Nefecon-associated AEs in elderly patients with IgAN.

Kinpeygo's summary of product characteristics details 8 SOCs.[29] Intriguingly, our analysis results similarly reveal that 8 SOCs meet at least 1 algorithmic criterion (Table 3), with 5 SOCs overlapping. These include endocrine disorders, vascular disorders, skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, and eye disorders. To some extent, these SOCs offer preliminary directions for averting potential AEs.

At the PT level, we identified a total of 23 positive signals, with 19 of them having been previously reported or disclosed in past studies and/or drug labels. This high level of consistency underscores the robustness of the findings from this study. Among these events, the signal for "product residue present" was the strongest (ROR 32.6, PRR 32.19). Pharmacokinetics play a critical role in influencing drug residues.[40,41] Nefecon is primarily metabolized by the liver, with a small portion undergoing metabolism in the small intestine. Its plasma clearance rate ranges from 0.9 to 1.8 L/min, indicating hepatic clearance. Consequently, liver function is a significant factor

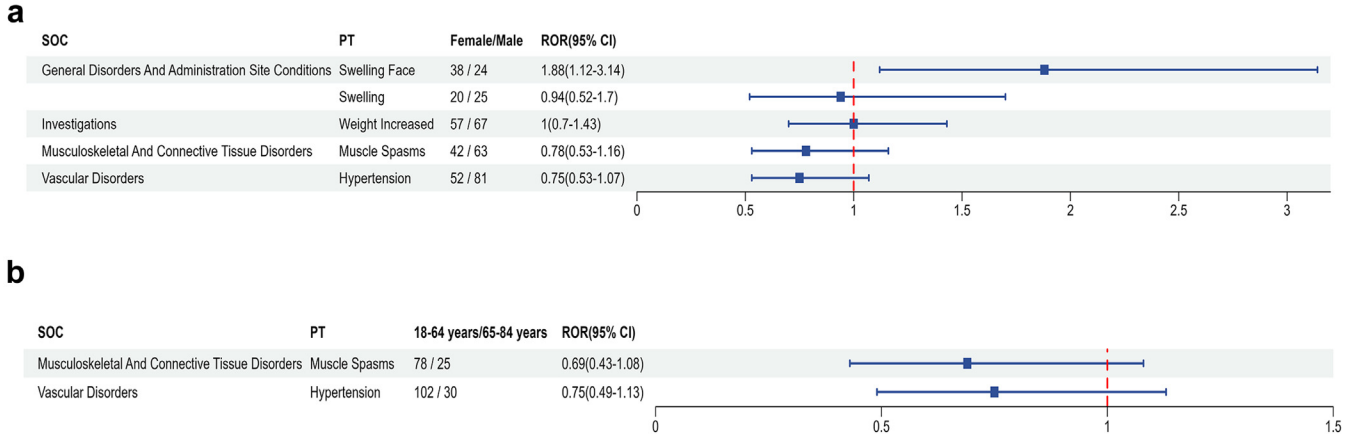

Figure 4. Analyzing risk differences in the signals of Nefecon in different populations. (a) gender difference; (b) age difference.

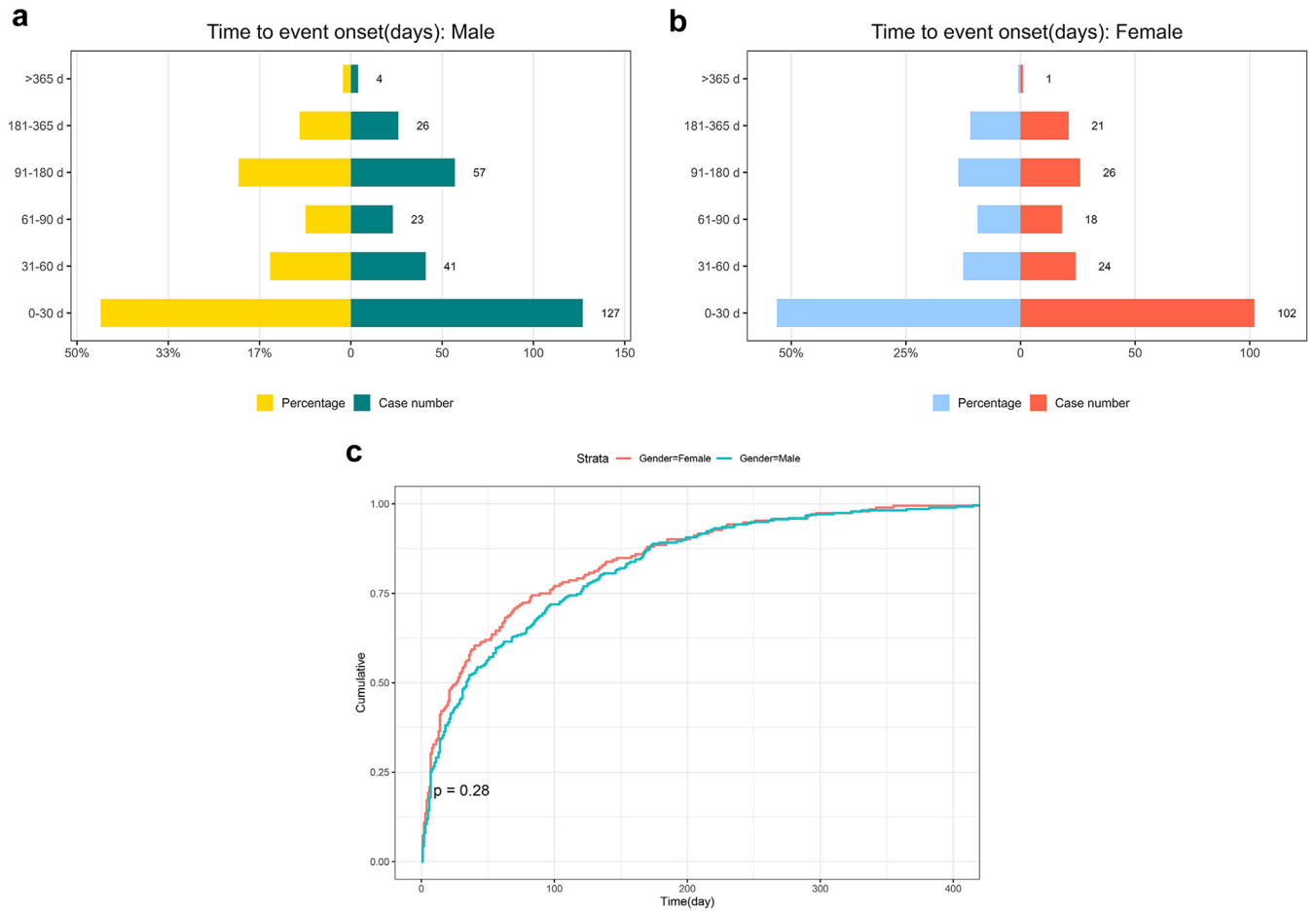

Figure 5. Time-to-onset data and cumulative incidence of adverse by gender subgroups. (a and b) Time-to-onset of Nefecon-related adverse events in males or females. (c) No significant difference was observed in the cumulative incidence of adverse events between male individuals receiving Nefecon treatment and their female counterparts (log-rank test, $P = 0.28$).

affecting the pharmacokinetics of Nefecon,[28] whereas renal function is not considered a factor affecting its metabolism.[29] In addition, Nefecon is metabolized via cytochrome P450 3A4. Therefore, cytochrome P450 3A4 inhibitors (excluding oral contraceptives containing ethinylestradiol) may increase plasma levels of budesonide, thus increasing the likelihood of drug residues. Moreover, Nefecon's impact on signals indicating "blood pressure increased" and "blood glucose increased" has been identified, suggesting that conducting appropriate physical and hematological examinations may be necessary. As for "dialysis" and "end-stage renal disease," they may be closely related to the natural progression of IgAN itself.

Some of the 19 PTs explicitly categorized as AEs in previous studies and/or drug inserts were indicative of corticosteroid-induced Cushing's syndrome, including cushingoid, swelling face, hunger, acne, weight increased, etc. Although both 16 mg of Nefecon and 8 mg of low-dose prednisolone exhibit similar efficacy in suppressing endogenous cortisol effects,[42] it is crucial to acknowledge the risk of iatrogenic Cushing's syndrome associated with nonoral glucocorticoids.[43–46] Therefore, there is a potential importance in enhancing the education of patients with IgAN regarding the standardized administration and cessation of Nefecon. Our findings similarly identified an AE related to medication regimen, namely product dose omission issue. However, due to the limited availability of relevant information from the FAERS database, investigating whether medication omission was intentional or not remains challenging. The substantial financial burden, totaling $14,160 for 1 month of treatment,[47,48] may be a consideration in this context.

The identification of product dose omission issue, along with PTs such as asthenia, anxiety, and malaise, has been established as novel AE signals associated with Nefecon. These signals were not reported in previous studies or documented within the positive signals related to budesonide (Supplementary Tables S3 and S4). These signals warrant appropriate attention in future clinical scenarios. Of greater interest to health care practitioners is the correlation of positive signals with clinical treatment, and the severity and

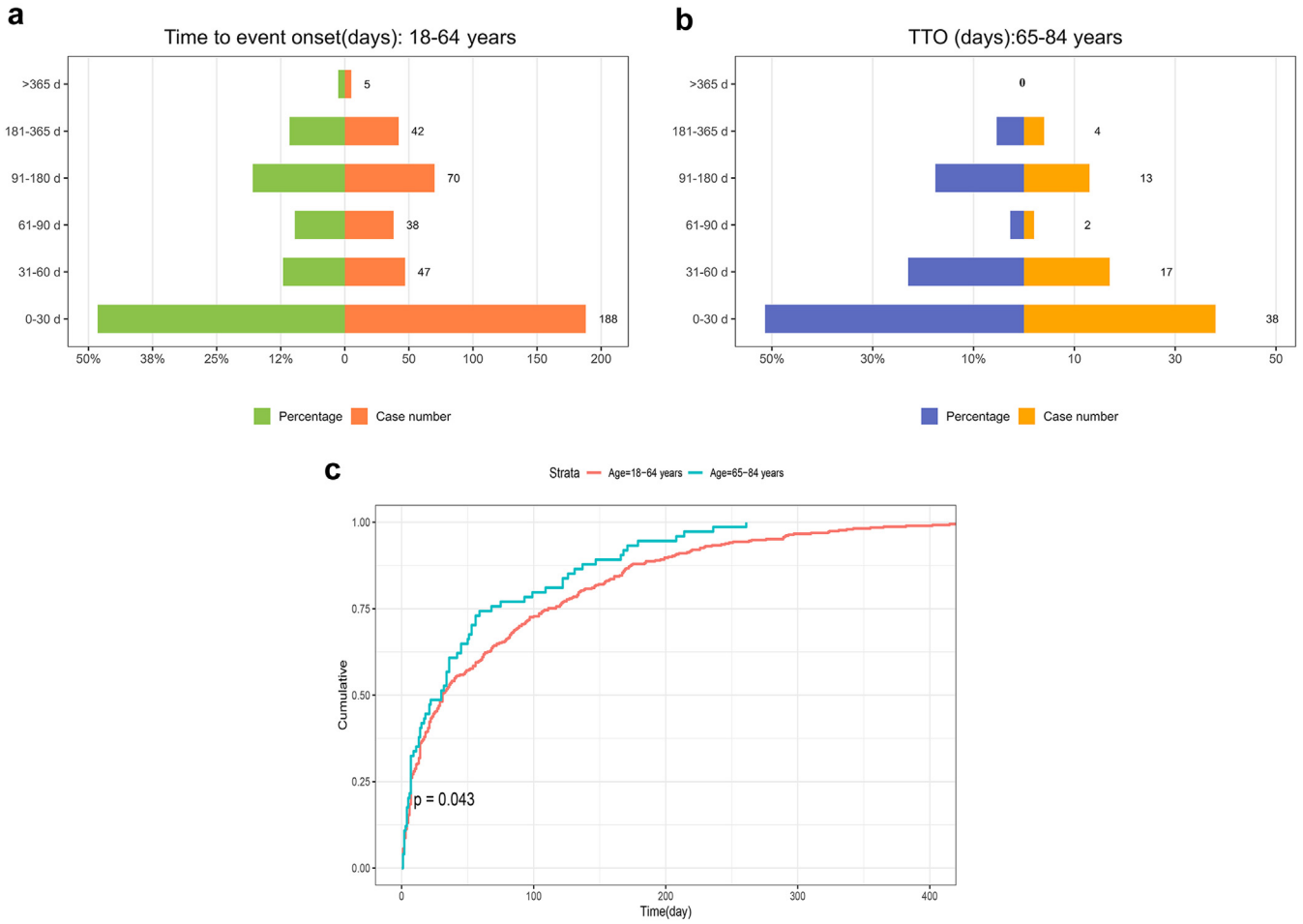

Figure 6. Time-to-onset data and cumulative incidence of adverse events by age subgroups. (a and b) Time-to-onset of Nefecon-related adverse events in patients aged 18 to 64 and 65 to 84 years. (c) Significant difference was observed in the cumulative incidence of adverse events between patients aged 18 to 64 years receiving Nefecon treatment and those aged 65 to 84 years (log-rank test, $P = 0.043$).

tolerability of associated side effects, among other similar inquiries. Clinical prioritization evaluation offers insights into addressing these queries. Among the 23 confirmed positive PT signals, none were associated with mortality or classified as high priority (Table 5). Although acne, hypertension, swelling face, and weight increased were categorized as moderate clinical priorities, investigation into their scoring sources reveals their prevalence and previous disclosure or reporting, indicating overall manageability within the existing safety framework.

We conducted TTO analysis, cumulative incidence analysis of AEs, and subgroup analysis for Nefecon for the first time, thus bridging existing research gaps and furnishing early insights for future precision prevention and treatment across diverse populations. In addition, even more encouraging is that all WSP analysis results indicate an early failure type profile, suggesting that Nefecon exhibits a good safety benefit. We also confirmed the common sense view that has been lacking empirical evidence. According to our results, there was a statistical difference in the cumulative incidence of AEs between patients aged 18 to 64 years and older patients aged 65 to 84 years, and age may be an important factor influencing the onset speed of AEs at the same rate of AEs, suggesting that Nefecon is better tolerated and safer in younger patients. It is also important to note that according to our results, young and middle-aged adults have a higher relative risk of experiencing hypertension and muscle spasms compared to the older adults, particularly concerning hypertension. Hypertension is more prevalent among middle-aged and elderly individuals, with some patients having been on long-term medication even before being diagnosed with IgAN. Therefore, even if hypertension arises during or after Nefecon treatment, it is challenging to conclusively attribute it to Nefecon-induced AEs. In other words, this relative risk may be influenced by preexisting hypertension in older adults or the effects of long-term medication use, rather than

being specific to Nefecon treatment itself. Advanced age is an important factor involved in the adverse renal outcome of IgAN.[49,50] With the median age of the Nefecon treatment group in both the NEFIGAN and NefIgArd studies being less than 45 years, the importance of collecting the safety profile of elderly patients during Nefecon therapy cannot be overstated.

Certainly, this study is not without its intrinsic constraints. First, the FAERS database is a voluntary reporting system, which cannot exclude the possibility of underreporting and delayed reporting of events. Second, though the signals identified through the DPA offer invaluable insights into statistical associations between drugs and AEs, they do not inherently establish causality or precise incidence rates. Lastly, this study focuses primarily on North American populations, with limited representation of individuals of Asian descent due to the absence of racial data. Asians often face a more aggressive disease trajectory and have poorer prognostic outcomes.

CONCLUSION

Our study, drawing on real-world data from the FAERS database, for the very first time unveils novel AEs linked to the utilization of Nefecon in individuals suffering from IgAN. All of these findings provide a comprehensive framework for understanding the potential AEs linked to Nefecon; highlighting the importance of early clinical vigilance, conducting appropriate physical and hematological examinations, educating on rational medication practices, and systematically collecting AE data, particularly in the elderly population, thereby contributing to better risk management.

DISCLOSURE

HZ reports the consultancy for Calliditas, OMEROS, Chinook/Novartis, Ostuka, Roche, Vero, and Alexion/AZ. All the other authors declared no competing interests.

ACKNOWLEDGMENTS

The project was supported by grants from the National Natural Science Foundation of China (82170711, 82070733, 82000680), Beijing Nova Program (20220484147), Beijing Natural Science Foundation (7242144,7224346), Fundamental Research Funds for the Central Universities (Peking University Clinical Scientist Training Program, BMU2024-PYJH021), the National High Level Hospital Clinical Research Funding (Interdisciplinary Research Project of Peking University First Hospital), CAMS Innovation Fund for Medical Sciences (2019-I2M-5-046).

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: All data come from the FAERS database, which is available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

AUTHOR CONTRIBUTIONS

JYW, ZZ, and XZL designed the study, and conducted data analysis and processing. JYW wrote the manuscript. SFS, JCL, YMZ, and HZ revised the manuscript. All the authors read and approved the final draft of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. The flowchart depicting the extraction process of budesonide-related adverse events data from the US Food and Drug Administration Adverse Event Reporting System database from quarter 4, 2021 to quarter 4, 2023.

Table S1. Disproportionate analysis algorithms for signal detection at system organ class level and preferred term level.

Table S2. Overview of Nefecon approved by the US Food and Drug Administration and the European Medicines Agency.

Table S3. Adverse events disclosed in the NEFIGAN and NEFIgArd studies. *Treatment-emergent serious adverse events.

Table S4. Upon utilizing data extracted from the US Food and Drug Administration Adverse Event Reporting System database spanning quarter 4, 2021 to quarter 4, 2023, a total of 355 budesonide-related preferred terms that meet the criteria of the disproportionate analysis algorithms.

Table S5. Summary of all positive signals at preferred term level for gender subgroups. *Indicates signals shared between subgroups.

Table S6. Time-to-onset data and Weibull shape parameter results stratified by gender and age subgroups.

Table S7. Summary of all positive signals at preferred term level for age subgroups. *Indicates signals shared between subgroups.

Table S8. Information on age and preferred terms of dead cases.

STROBE checklist.

REFERENCES

1. Rodrigues JC, Haas M, Reich HN. IgA nephropathy. *Clin J Am Soc Nephrol*. 2017;12:677–686. https://doi.org/10.2215/CJN.07420716
2. Zhang H, Barratt J. Is IgA nephropathy the same disease in different parts of the world? *Semin Immunopathol*. 2021;43:707–715. https://doi.org/10.1007/s00281-021-00884-7
3. Maixnerova D, El Mehdi D, Rizk DV, Zhang H, Tesar V. New treatment strategies for IgA nephropathy: targeting plasma

cells as the main source of pathogenic antibodies. *J Clin Med*. 2022;11:2810. https://doi.org/10.3390/jcm11102810

4. Lai KN, Tang SCW, Schena FP, et al. IgA nephropathy. *Nat Rev Dis Primers*. 2016;2:1–20. https://doi.org/10.1038/nrdp.2016.1
5. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100:S1–S276. https://doi.org/10.1016/j.kint.2021.05.021
6. Tunnicliffe DJ, Reid S, Craig JC, Samuels JA, Molony DA, Strippoli GF. Non-immunosuppressive treatment for IgA nephropathy. *Cochrane Database Syst Rev*. 2024;2:CD003962. https://doi.org/10.1002/14651858.CD003962.pub3
7. Bagchi S, Mani K, Swamy A, et al. Supportive management of IgA nephropathy with renin-angiotensin blockade, the AIIMS primary IgA nephropathy cohort (APPROACH) study. *Kidney Int Rep*. 2021;6:1661–1668. https://doi.org/10.1016/j.ekir.2021.02.018
8. Zhang YM, Lv JC, Wong MG, Zhang H, Perkovic V. Glucocorticoids for IgA nephropathy-pro. *Kidney Int*. 2023;103:666–669. https://doi.org/10.1016/j.kint.2023.01.018
9. Barratt J, Rovin BH, Cattran D, et al. Why target the gut to treat IgA nephropathy? *Kidney Int Rep*. 2020;5:1620–1624. https://doi.org/10.1016/j.ekir.2020.08.009
10. Stamellou E, Seikrit C, Tang SCW, et al. IgA nephropathy. *Nat Rev Dis Primers*. 2023;9:1–21. https://doi.org/10.1038/s41572-023-00476-9
11. Watts P, Smith A. TARGIT technology: coated starch capsules for site-specific drug delivery into the lower gastrointestinal tract. *Expert Opin Drug Deliv*. 2005;2:159–167. https://doi.org/10.1517/17425247.2.1.159
12. Smerud HK, Bárány P, Lindström K, et al. New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria. *Nephrol Dial Transplant*. 2011;26:3237–3242. https://doi.org/10.1093/ndt/gfr052
13. Fellström BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389:2117–2127. https://doi.org/10.1016/S0140-6736(17)30550-0
14. Barratt J, Lafayette R, Kristensen J, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney Int*. 2023;103:391–402. https://doi.org/10.1016/j.kint.2022.09.017
15. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial. *Lancet*. 2023;402:859–870. https://doi.org/10.1016/S0140-6736(23)01554-4
16. Barratt J, Lafayette RA, Rovin BH, Fellström B. Budesonide delayed-release capsules to reduce proteinuria in adults with primary immunoglobulin A nephropathy. *Expert Rev Clin Immunol*. 2023;19:699–710. https://doi.org/10.1080/1744666X.2023.2206119
17. Yates M, Bechman K, Galloway J. The use of real-world data to address questions of patient safety. *Rheumatology (Oxford)*. 2020;59:26–30. https://doi.org/10.1093/rheumatology/kez158
18. Knepper TC, McLeod HL. When will clinical trials finally reflect diversity? *Nature*. 2018;557:157–159. https://doi.org/10.1038/d41586-018-05049-5
19. Beaulieu-Jones BK, Finlayson SG, Yuan W, et al. Examining the use of real-world evidence in the regulatory process. *Clin Pharmacol Ther*. 2020;107:843–852. https://doi.org/10.1002/cpt.1658
20. Food and Drug Administration, HHS. International conference on harmonisation; electronic transmission of postmarket individual case safety reports for drugs and biologics, excluding vaccines; availability of Food and Drug Administration regional implementation specifications for ICH E2B(R3) reporting to the Food and Drug Administration Adverse Event Reporting System. Notice of availability. *Fed Regist*. 2016;81:40890–40891.
21. Shu Y, Ding Y, Liu Y, Zhang Q, He X, Zhang Q. Post-marketing safety concerns with secukinumab: a disproportionality analysis of the FDA Adverse Event Reporting System. *Front Pharmacol*. 2022;13:862508. https://doi.org/10.3389/fphar.2022.862508
22. Research C for de and. FDA Adverse Event Reporting System (FAERS); 2021. *FDA*. Accessed March 3, 2024. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-adverse-event-reporting-system-faers
23. FDA. FAERS quarterly data extract files. Accessed March 9, 2024. https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html
24. Shimada K, Hasegawa S, Nakao S, et al. Adverse reaction profiles of hemorrhagic adverse reactions caused by direct oral anticoagulants analyzed using the Food and Drug Administration Adverse Event Reporting System (FAERS) database and the Japanese Adverse Drug Event Report (JADER) database. *Int J Med Sci*. 2019;16:1295–1303. https://doi.org/10.7150/ijms.34629
25. Noguchi Y, Tachi T, Teramachi H. Detection algorithms and attentive points of safety signal using spontaneous reporting systems as a clinical data source. *Brief Bioinform*. 2021;22:bbab347. https://doi.org/10.1093/bib/bbab347
26. Zhai Y, Ye X, Hu F, et al. Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. *J Immunother Cancer*. 2019;7:286. https://doi.org/10.1186/s40425-019-0754-2
27. Caster DJ, Lafayette RA. The treatment of primary IgA nephropathy: Change, Change, Change. *Am J Kidney Dis*. 2024;83:229–240. https://doi.org/10.1053/j.ajkd.2023.08.007
28. FDA. Drugs@FDA: FDA-approved drugs. Accessed March 3, 2024. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=215935
29. Kinpeygo. European Medicines Agency. Accessed March 3, 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/kinpeygo
30. Gatti M, Antonazzo IC, Diemberger I, De Ponti F, Raschi E. Adverse events with sacubitril/valsartan in the real world: emerging signals to target preventive strategies from the FDA adverse event reporting system. *Eur J Prev Cardiol*. 2021;28:983–989. https://doi.org/10.1177/2047487320915663
31. Deng Z, Liu J, Gong H, Cai X, Xiao H, Gao W. Psychiatric disorders associated with PCSK9 inhibitors: a real-world, pharmacovigilance study. *CNS Neurosci Ther*. 2024;30:e14522. https://doi.org/10.1111/cns.14522

32. EudraVigilance system overview. European Medicines Agency. Accessed May 1, 2024. https://www.ema.europa.eu/en/human-regulatory-overview/research-development/pharmacovigilance-research-development/eudravigilance/eudravigilance-system-overview
33. Signal management. European Medicines Agency. Accessed May 1, 2024. https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/signal-management#designated-medical-events-10341
34. Kinoshita S, Hosomi K, Yokoyama S, Takada M. Time-to-onset analysis of amiodarone-associated thyroid dysfunction. *J Clin Pharm Ther*. 2020;45:65–71. https://doi.org/10.1111/jcpt.13024
35. de Vries ST, Denig P, Ekhart C, Mol PGM, van Puijenbroek EP. Sex differences in adverse drug reactions of metformin: A longitudinal survey study. *Drug Saf*. 2020;43:489–495. https://doi.org/10.1007/s40264-020-00913-8
36. Noguchi Y, Yoshimura T. Detection algorithms for simple two-group comparisons using spontaneous reporting systems. *Drug Saf*. 2024;47:535–543. https://doi.org/10.1007/s40264-024-01404-w
37. European Medicines Agency. Screening for adverse reactions in EudraVigilance. Accessed June 25, 2024. https://www.ema.europa.eu/en/documents/other/screening-adverse-reactions-eudravigilance_en.pdf
38. Ray A. Beyond debacle and debate: developing solutions in drug safety. *Nat Rev Drug Discov*. 2009;8:775–779. https://doi.org/10.1038/nrd2988
39. Silberstein SD, Reshef S, Cohen JM, et al. Adverse events reported with therapies targeting the CGRP pathway during the first 6 months post-launch: a retrospective analysis using the FDA adverse events reporting system. *Adv Ther*. 2023;40:445–459. https://doi.org/10.1007/s12325-022-02346-4
40. Wu X, Lin Z, Toney E, et al. Pharmacokinetics, tissue residue depletion, and withdrawal interval estimations of florfenicol in goats following repeated subcutaneous administrations. *Food Chem Toxicol*. 2023;181:114098. https://doi.org/10.1016/j.fct.2023.114098
41. Liu Y, Chen S, Wen Z, et al. Comparative pharmacokinetics of free doxorubicin and a liposomal formulation in cats following intravenous administration. *Front Vet Sci*. 2024;11:1353775. https://doi.org/10.3389/fvets.2024.1353775
42. Nesbitt H, American Society of Nephrology. Kidney week - abstract details. Accessed March 8, 2024. https://www.asn-online.org/education/kidneyweek/2019/program-abstract.aspx?controlId=3236815
43. Bangsgaard R, Main KM, Boberg-Ans G, et al. Adrenal suppression in infants treated with topical ocular glucocorticoids. *Ophthalmology*. 2018;125:1638–1643. https://doi.org/10.1016/j.ophtha.2018.04.035
44. Afandi B, Toumeh MS, Saadi HF. Cushing's syndrome caused by unsupervised use of ocular glucocorticoids. *Endocr Pract*. 2003;9:526–529. https://doi.org/10.4158/EP.9.6.526
45. Donaldson AM, Choby G, Kim DH, Marks LA, Lal D. Intranasal corticosteroid therapy: systematic review and meta-analysis of reported safety and adverse effects in children. *Otolaryngol Head Neck Surg*. 2020;163:1087–1096. https://doi.org/10.1177/0194599820931454
46. Pofi R, Caratti G, Ray DW, Tomlinson JW. Treating the side effects of exogenous glucocorticoids; can we separate the good from the bad? *Endocr Rev*. 2023;44:975–1011. https://doi.org/10.1210/endrev/bnad016
47. Ramjee L, Vurgun N, Ngai C, Patel M, Tremblay G. Cost-Effectiveness Analysis of Nefecon versus Best Supportive Care for People with Immunoglobulin A Nephropathy (IgAN) in the United States. *Clinicoecon Outcomes Res*. 2023;15:213–226. https://doi.org/10.2147/CEOR.S389456
48. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA nephropathy: a rapidly evolving field. *J Am Soc Nephrol*. 2024;35:103–116. https://doi.org/10.1681/ASN.0000000000000242
49. Tan J, Luo X, Yang J, et al. Clinicopathological characteristics and risk factors in elderly patients with biopsy-proven IgA nephropathy. *Ren Fail*. 2022;44:1027–1037. https://doi.org/10.1080/0886022X.2022.2087527
50. Duan ZY, Cai GY, Chen YZ, et al. Aging promotes progression of IgA nephropathy: a systematic review and meta-analysis. *Am J Nephrol*. 2013;38:241–252. https://doi.org/10.1159/000354646