THE BURDEN ASSOCIATED WITH IMMUNOGLOBULIN A NEPHROPATHY (IgAN)

PUK31

George AT[1], Zaour N[2], Nic Lochlainn E[2]

[1]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [2]Novartis Pharma AG, Basel, Switzerland

BACKGROUND

- IgAN or Berger's disease is an autoimmune condition and the most prevalent form of chronic glomerulonephritis (GN), characterised by the presence of predominant IgA1 deposits in the glomerular mesangium.[1]
- The incidence of IgAN is estimated to be 2.5 per 100,000 population per year worldwide[2], with the peak incidence observed in young adults aged 20-30 years.[3]
- Currently, renal biopsy is considered as the gold standard for the diagnosis of IgAN.[4]
- The clinical course of IgAN varies from person to person. It can exist undiagnosed in many individuals. When diagnosed, some might experience very few problems, whereas others gradually progress to end-stage renal disease (ESRD).[5]
- This highlights the need to consolidate existing evidence to better understand the clinical, economic and humanistic burden associated with the condition, through a targeted literature review.

OBJECTIVE

- To gather and narratively synthesise evidence on the clinical, economic and humanistic burden associated with IgAN.

METHODS

- EMBASE and MEDLINE databases were searched for relevant English-language studies from 2000 to 2017, which were selected based on pre-defined inclusion criteria (**Table 1**), using a 2-step screening process, (i) abstract screening and (ii) fulltext screening (**Figure 1**).

Table 1. Criteria for including studies in the review

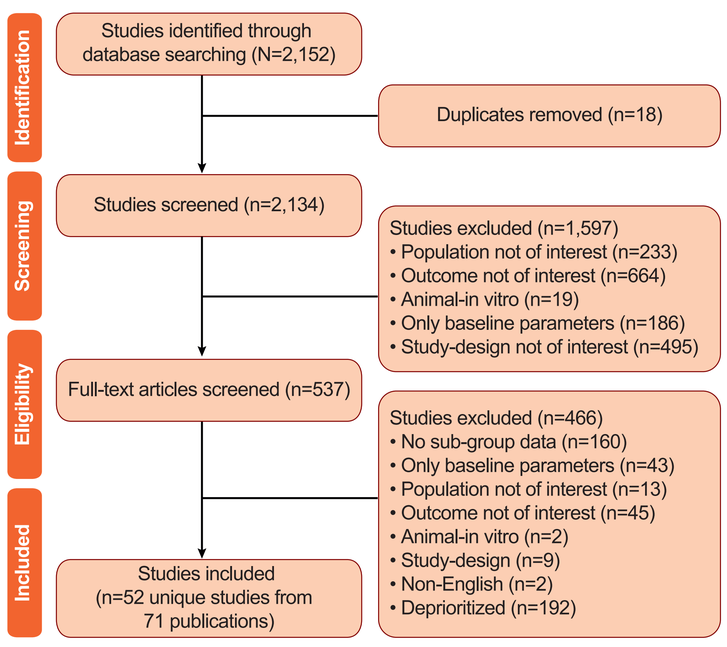
Population	Patients diagnosed with IgAN/Berger's Disease, ≥18 years of age
Interventions/ comparators	NA
Outcomes	**Clinical burden:** Comorbidities, proteinuria, eGFR, haematuria, serum creatinine, mortality, ESRD, dialysis and kidney transplant
	Economic burden: All direct/indirect costs, productivity loss, absenteeism, presenteeism, out-of-pocket costs, co-payment information, resource utilisation, hospitalisation, length of stay and readmission
	Humanistic burden: PROs, QoL/HRQoL, patient preferences, impact on daily living, QALY, DALY and caregiver burden
Study designs	Studies with >5 patients, studies providing parameters at diagnosis and at follow-up and observational studies (retrospective, prospective, longitudinal, cross-sectional, real-world studies, registry etc.) Editorials, letters, RCTs, narrative reviews and case reports were excluded
Analysis	Descriptive statistics; data presented as numbers and/or percentages

Abbreviations: DALY, disability-adjusted life year; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HRQoL, health-related quality of life; IgAN, immunoglobulin A nephropathy; NA, not applicable; PRO, patient-reported outcome; QALY, quality-adjusted life-year; QoL, quality of life; RCT, randomised controlled trial

RESULTS

- Of the 2,152 records obtained, a total of 52 unique studies from 71 publications were included for the current review (**Figure 1**).

Figure 1. Study selection flowchart



NOTE: At the abstract and full-text screening stage, studiess providing only baseline parameters were excluded. During the full-text screening stage, due to the large number of included studies and because this was not a systematic literature review, studies were deprioritised if they had only a specific parameter of interest, already covered in multiple included studies

- The included studies were highly heterogeneous with respect to the patient and study characteristics.

Study characteristics

- Study sample size and setting: The number of IgAN patients in the included studies varied from 19[6] to 11,963.[7] Most of the studies were conducted at a single-centre setting (30 studies) vs. multi-centre setting (15 studies). Seven studies did not report details on the study setting.
- Geographical distribution: Most of the included studies were conducted in Asia (32 studies), followed by Europe (11 studies) and North America (4 studies). The location was not available in 5 studies.

Patient characteristics

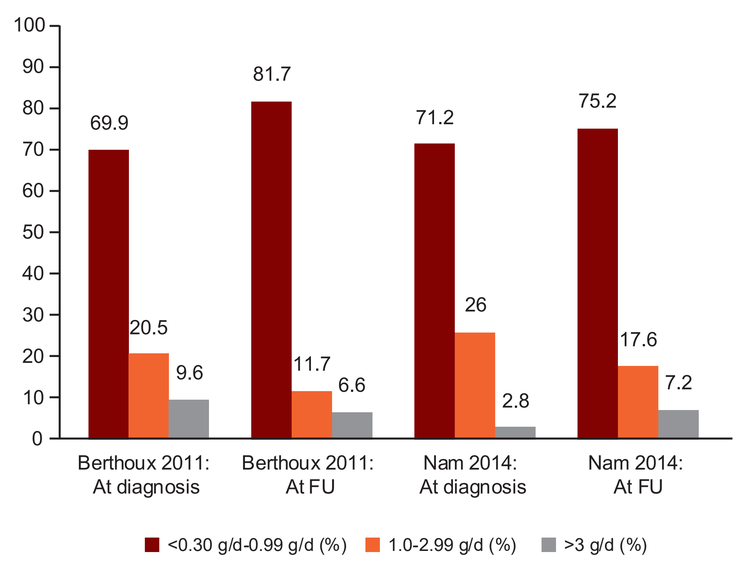
- Age and gender: The mean age of the patients in the included studies ranged from 25.2[8] to 50.3[9] years, with a predominance of male patients observed in more than 60% of the studies.
- Comorbid conditions: The most frequently reported comorbid condition in IgAN patients was hypertension, ranging from 12.7%[10] to 79.1%.[6]

Clinical burden

IgAN patients presented with varying symptoms

- Proteinuria: The mean and median proteinuria values at diagnosis ranged from 0.75 g/day to 3.04 g/day[13] and from 0.3 g/day[14] to 2.5 g/day[15], respectively.
  - The proportion of patients presenting with proteinuria of ≥1 g/day ranged from 30.1%[16] to 80.0%.[17]
  - The change in the different ranges of proteinuria from diagnosis to follow-up was reported in 2 studies.[14,16] Both studies reported a decrease in the proportion of IgAN patients with proteinuria ≥1 g/day (30.1% vs. 18.3%; 28.8% vs. 24.8%)[14,16] at a mean follow-up of 11.3 and 5.4 years, respectively (**Figure 2**).

Figure 2. Proportion of patients with different proteinuria ranges at diagnosis and at follow-up

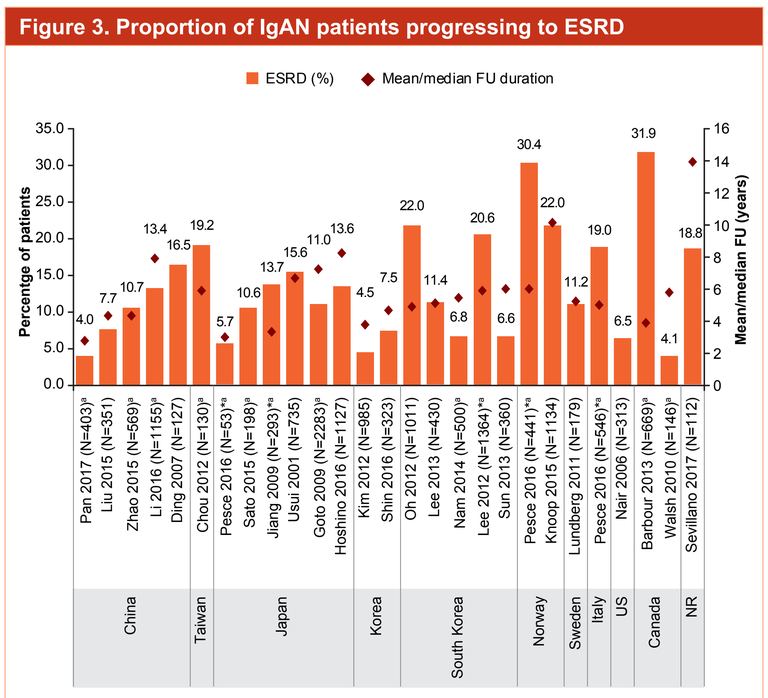


Abbreviations: d, day; FU, follow-up.

IgAN patients in Berthoux 2011 were either on long-term angiotensin I converting enzyme inhibitors and/or angiotensin II receptor blockers and/or steroids. IgAN patients in Nam 2014 were on reninangiotensin system and/or steroids

- Haematuria: The proportion of IgAN patients presenting with haematuria ranged from 13%[11] to 100%.[12]
- Serum creatinine: The mean and median serum creatinine levels at presentation varied from 0.7 mg/dL[18] to 2.08 mg/dL[9] and from 1 mg/dL[19] to 1.1 mg/dL[20], respectively.
  - Increase in the mean serum creatinine levels ranged from 0.18 mg/dL[11] to 0.71 mg/dL[21] at a median of 1 to 2.8 years of follow-up. Moreover, the proportion of IgAN patients who had doubled their serum creatinine levels ranged from 0.85% at a mean follow-up of 4.3 years[22] to 24.6% at a mean follow-up of 4.9 years.[23]
- Estimated glomerular filtration rates (eGFR): The mean and median eGFR levels at presentation ranged from 8.4 mL/min per 1.73 m^2 [6] to 104 mL/min per 1.73 m^2 [11] and from 47 mL/min per 1.73 m^2 [24] to 84.1 mL/min per 1.73 m^2 [25], respectively.
  - Within 5 years of follow-up, a ≥50% decline in eGFR was observed in 0.6% (Swedish patients)[26] to 26.9% (Pacific Asian patients)[27] of IgAN patients.
  - Evidence suggests that in the Pacific Asian population, the presence of proteinuria, albuminuria, tubular atrophy, increase in mean atrial pressure and IgG deposits were significant risk factors for eGFR decline (p<0.05 in all).
- ESRD: The proportion of IgAN patients progressing to ESRD varied from 4%[28] to 31.9%[27] at different years of follow-up, ranging from 2.8 years[28] to 14 years[29], with variations observed across geographies (**Figure 3**).

Figure 3. Proportion of IgAN patients progressing to ESRD



*Time-to-complications reported instead of FU duration; [a]Median follow-up

Abbreviations: ESRD, end-stage renal disease; FU, follow-up; IgAN, immunoglobulin A nephropathy; N, number of included patients; NR, not reported

- Various demographic, histological and clinical features that were significantly associated with IgAN patients advancing to ESRD are shown in **Table 2.**

Table 2. Factors associated with progression to ESRD

Study Name	Analysis type	Variable	HR (95% CI)	p value
Pesce 2016*[30]	Univariate logistic regression	Age	1.02 (1.01-1.03)	<0.001
Goto 2009[31]	Multivariable analysis	Male gender	1.7 (1.25-2.38)	0.001
Barbour 2013[27]	Multivariate Cox proportional analysis	Pacific Asian population	1.56 (1.10-2.22)	0.01
Chou 2012[32]	Multivariable analysis	Hypertension	6.92 (1.83-26.22)	0.004
Goto 2009[31]	Multivariable analysis	Histological grade III or IV	1.7 (1.12-2.56)	0.012
Knoop 2015[15]	Cox proportional hazard model	Interstitial fibrosis (focal mild)	3.8 (1.7-8.3)	0.001
		Interstitial fibrosis (focal moderate)	11.1 (4.6-26.8)	<0.001
		Interstitial fibrosis (focal extensive)	74.2 (19.5-282)	<0.001
		Tubular atrophy (mild)	3.3 (1.7-6.6)	0.001
		Tubular atrophy (moderate)	9.2 (4.4-19.3)	<0.001
		Tubular atrophy (extensive)	17.5 (7.2-42.3)	<0.001
Lee 2012[12]	Multivariate analysis	Segmental sclerosis >20%	1.7 (1.2-2.4)	0.005
		eGFR 60-90 mL/min per 1.73 m^2)	2.39 (1.12-5.14)	<0.025
		eGFR 30-60 mL/min per 1.73 m^2)	7.33 (3.49-15.36)	<0.001
		eGFR 15-30 mL/min per 1.73 m^2)	12.9 (6.5-29.6)	<0.001
		eGFR <15 mL/min per 1.73 m^2)	41.7 (17.3-100.1)	<0.001
Goto 2009[31]	Multivariable analysis	Proteinuria 30-99 mg/dL	3.4 (1.3-9.1)	<0.01
		Proteinuria 100-299 mg/dL	8.1 (3.2-20.5)	<0.001
		Proteinuria >300 mg/dL	12.4 (4.9-31.3)	<0.001

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; OR, odds ratio

- Dialysis: The proportion of IgAN patients undergoing dialysis ranged from 4.0%[33] to 19.2%[32] and those undergoing transplantation ranged from 7.8%[34] to 27.1%[9] at ~5 years of follow-up.
- Mortality: Mortality rates among the IgAN patients ranged from 0.7%[35] in China to 19.3%[9] in Scotland at a follow-up period of 4.3 years and 6.3 years respectively. The most commonly reported cause of death among IgAN patients was cardiovascular disease, followed by malignancy, renal disease and infections.

Economic and humanistic burden

- None of the included studies had information on economic or humanistic burden among IgAN patients.

LIMITATION

- Heterogeneity in the patient characteristics, sample size, study design, study objectives and the definitions used to report the study endpoints limits the ability to compare data.

CONCLUSION

- IgAN patients presented with varying symptoms, with a sizable proportion progressing to ESRD irrespective of the treatments they were receiving.
- Existing evidence suggests that there is a high clinical burden associated with IgAN in the diagnosed population and as their condition deteriorates a substantial proportion of these patients progress to ESRD, requiring them to undergo dialysis/transplantation.
- The inability of the current interventions to delay or arrest the progression of this condition and prevent ESRD highlights the unmet need in this population.
- There is a need to undertake research on the humanistic and economic burden to address this identified evidence gap and quantify the impact of the high clinical burden of IgAN on patient and caregivers' quality of life and costs to healthcare systems.

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