International Physicians Delphi Survey:
Managing Patients With IgA Nephropathy

Jürgen Floege1, Jonathan Barratt2, Rosanna Coppo3, Richard Lafayette4, Jai Radhakrishnan5, Heather N. Reich6, Brad H. Rovin7, David T. Selweski8, Marina Vivarelli9, Christopher Pham10 and Vladimír Tesař11

1Division of Nephrology and Immunology, Rheinisch-Westfälische Technische Hochschule Aachen, Aachen, Germany; 2Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; 3Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy; 4Department of Nephrology, Stanford University, Stanford, California, USA; 5Division of Nephrology, Columbia University Medical Center, New York, New York, USA; 6Division of Nephrology, Department of Medicine, University Health Network and University of Toronto, Toronto, Ontario, Canada; 7Division of Nephrology, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA; 8Division of Pediatric Nephrology, Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina, USA; 9Division of Nephrology and Dialysis, Department of Pediatric Subspecialties, Bambino Gesù Pediatric Hospital Istituto di Ricerca e Cura a Carattere Scientifico, Rome, Italy; 10ApotheCom, San Francisco, California, USA; and 11Department of Nephrology, Charles University and General University Hospital, Prague, Czech Republic

Correspondence: Jürgen Floege, Division of Nephrology and Immunology, Rheinisch-Westfälische Technische Hochschule Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. E-mail: jfloege@ukaachen.de

Received 13 April 2022; accepted 16 May 2022; published online 26 May 2022

Kidney Int Rep (2022) 7, 2076–2080; https://doi.org/10.1016/j.ekir.2022.05.022

KEYWORDS: corticosteroids; Delphi; guidelines; IgA nephropathy; IgAN; proteinuria

© 2022 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

INTRODUCTION

IgA nephropathy (IgAN) typically is a slowly progressing disease, with 10% to 60% of patients developing chronic kidney failure within 10 years.1 Practice guidelines (e.g., Kidney Disease: Improving Global Outcomes [KDIGO]) are available, but it is unknown how uniformly nephrologists in different countries agree with and may follow these guidelines. The Delphi Focal Segmental Glomerulosclerosis and IgA Nephropathy Experts: Physicians (DEFINE: Physicians) study sought to capture nephrologist opinions on IgAN pathophysiology, diagnosis, treatment, and monitoring. In this 2-round Delphi survey, agreement with 20 statements about IgAN was scored by adult and pediatric nephrologists from 7 countries using a 1 to 9 Likert scale (9 = strongly agree). Moderate versus high consensus was defined as 75% to 89% versus ≥90% of participants scoring 7 to 9, respectively. Methods and participant characteristics are detailed in the Supplementary Materials.

In round 1, most statements (19 [95%]) met the criteria for high consensus, including those regarding pathophysiology, diagnosis, and treatment of early stage and rapidly progressive IgAN (Table 1). Participants agreed that proteinuria is a key determinant of prognosis and treatment strategy. High levels of agreement were also observed for statements regarding the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers as part of supportive therapy in patients with persistent proteinuria (96%, 98%; number [#27 and #30, respectively; Table 1), corticosteroid use in pediatric patients (98%; #31; Table 1), and treatment of rapidly progressive or severe disease with corticosteroids and cyclophosphamide in appropriate patients (97%, 94%; #29 and #32, respectively; Table 1).

The only statement not meeting criteria for high consensus in round 1 was statement #28, which described short-term use of corticosteroids in adult patients with high levels of proteinuria despite optimized supportive therapy with a renin-angiotensin-aldosterone system inhibitor (Table 2). With 89% of participants agreeing, this statement met criteria for moderate consensus. The percentage of adult nephrologists agreeing with this statement was significantly lower than the percentage of pediatric nephrologists agreeing with statement #31, which addresses corticosteroid use in pediatric patients (89% vs. 98%; P = 0.044). For round 2, statement #28 was split into 2 statements (#28A and #28B; Table 2). The first statement, regarding corticosteroid use in patients with high proteinuria despite optimal supportive care (#28A), was rated separately from the statement that...
corticosteroids should not be used long term (#28B). Levels of agreement with the revised statements in round 2 were very similar to round 1 results (88%, 89%; #28A and #28B, respectively) and remained at a moderate consensus level.

Further analyses explored differences in agreement levels among participants practicing in different geographic locations (Supplementary Tables S1 and S2). When comparing responses from North American versus European participants, most statements had similar levels of agreement, but in round 1, statement #28 on corticosteroid use in adults had a >10% difference (Supplementary Table S1; 95% of North American nephrologists vs. 82% of European nephrologists agreed; P = 0.011). Further analyses by country can be found in Supplementary Table S2. In addition, there were no significant differences between academic and nonacademic nephrologists in how both
groups rated statements, except for statement #28. This statement had 83% agreement among academic nephrologists and 93% agreement among nonacademic nephrologists (Supplementary Table S3; P = 0.045). In round 2, the difference in agreement between academic and nonacademic nephrologists for both statements #28A and #28B was no longer statistically significant (P = 0.460 and 0.486, respectively). It is possible that academic nephrologists may assess the long-term risk-benefit profile of corticosteroids more conservatively than their nonacademic colleagues.

The DEFINE: Physicians Delphi survey on IgAN identified high consensus overall after just 1 round of the survey. This finding suggests that nephrologists in North America and Europe have similar opinions on IgAN management and that these opinions are largely consistent with the KDIGO guideline. The statement with the lowest level of agreement (although still moderate) was statement #28, which described corticosteroid use in adults. Corticosteroids for managing IgAN is a controversial topic, considering recent results from studies including the STOP-IGAN and TESTING trials.\(^2\)\(^-\)\(^5\) Results from these trials reveal that although there is some evidence for corticosteroid efficacy in particular in Asian patients, they come with significant risks for adverse events.

The high level of agreement found for the pathophysiology and treatment goal statements (Table 1; #1–4, #19, and #35) reveals that nephrologists see proteinuria as an important prognostic marker and that reducing proteinuria as much as possible is vital to preserving kidney function. Most nephrologists agreed that proteinuria itself is also a driver of disease progression by causing or contributing to kidney damage (Table 1; #3).\(^6\)

Most statements in this survey aligned with the 2021 KDIGO guideline for glomerular diseases.\(^7\) However, some slight differences exist in specific laboratory values for initiating the use of renin-angiotensin-aldosterone system inhibitors in adult patients. The KDIGO guideline suggests starting renin-angiotensin-aldosterone system inhibitors if proteinuria is >0.5 g/d, but statement #27 for this survey did not mention a specific proteinuria value. In pediatric patients, the 2021 KDIGO guideline has no statement that directly parallels statement #31 in our survey, which describes initiating corticosteroids in children if proteinuria remains >0.5 g/d despite supportive therapy. Last, the 2021 KDIGO guideline does not provide specific information on monitoring or follow-up frequency,\(^7\) whereas statements #33, #34, and #37 from this study do address this topic (Table 1).

The high levels of agreement found in this study may be driven by the fact that treatment options for IgAN are limited, with no alternatives to consider. However, the treatment landscape of IgAN may change, as many studies are currently investigating potential therapies for this disease.\(^8\) For instance, a delayed-release budesonide formulation was recently approved by the Food and Drug Administration for IgAN treatment.\(^9\)

Limitations of this study include that it was conducted in English and did not involve nephrologists from Asia or South America. Furthermore, there was a limited number of female participants and pediatric nephrologists in this survey (Supplementary Tables S4 and S5). Statements were written by the research team and steering committee (Supplementary Table S6) and were thus predetermined before the survey was administered. To ensure high completion and retention rates, this survey investigated a limited number of statements. Statements on experimental therapies or therapies with little evidence available may have resulted in lower consensus. Furthermore, some statements in this survey combined several points or topics, which may have affected agreement if a participant disagreed with one part but not all of the statement. Another limitation is attrition bias; participants who did not return in round 2 potentially had different perspectives than those who responded in round 2 (Supplementary Tables S7 and S8).

In summary, the lowest levels of agreement were observed on corticosteroid use in adult patients who receive optimized supportive therapy but still have...
elevated proteinuria. Although overall agreement was high regarding this topic, some nephrologists, particularly in Europe, disagreed with the use of corticosteroids in this setting. This suggests that further research on the risk-benefit profile of corticosteroids and new therapies in IgAN are needed. Overall, the DEFINE: Physicians study found high levels of consensus regarding the pathophysiology, diagnosis, management, and monitoring of IgAN among nephrologists from North America and Europe and that, in general, their opinions align with the latest KDIGO guideline for statements evaluated herein.

DISCLOSURE

JF is employed by Rheinish-Westfälische Technische Hochschule University of Aachen; has consultancy agreements with Amgen, Bayer, Calliditas, Novo Nordisk, Omeros, Traver Therapeutics, Inc., Vifor, and Visterra; has received honoraria from Amgen, Astellas, Bayer, Calliditas, Novo Nordisk, Omeros, Traver Therapeutics, Inc., Vifor, and Visterra; is a scientific advisor for Calliditas, Omeros, and Traver Therapeutics, Inc.; and is on the speakers bureau for Amgen and Vifor. JB has received research grants from Argenx, Calliditas, Chinoon Therapeutics, Galapagos, GSK, Novartis, Traver Therapeutics, Inc., and Vera Therapeutics; and serves as a medical/scientific advisor to Alnylam Pharmaceuticals, Argenx, Astellas, Biocryst, Calliditas, Chinoon Therapeutics, Dimerix, Galapagos, GlaxoSmithKline, Novartis, Omeros, Traver Therapeutics, Inc., UCB, Vera Therapeutics, and Visterra. RC has consultancy agreements with Amgen, Argenx, Calliditas, Novartis, Ostuka, Reata, Recordati, and Traver Therapeutics, Inc., and has an agreement with UpToDate. RL has received research funding from Calliditas, Chinoon, National Institutes of Health, Novartis, Traver Therapeutics, Inc., Pfizer, Vera, Omeros, and Visterra; and is an advisor for Alexion, Calliditas, Chemoentryx, Chinoon, Novartis Omeros, Pfizer, Reatta, Traver Therapeutics, Inc., and Visterra. JR has received research grants from Traver Therapeutics, Inc.; is on a steering committee for Traver Therapeutics, Inc.; and has consulting/advisory board roles with Angion Biomedica and Traver Therapeutics, Inc. HNR has received consulting fees from Calliditas, Chinoon, Novartis, and Traver Therapeutics, Inc.; has received honoraria from Novartis; is an advisor for Novartis and Traver Therapeutics, Inc.; has served as national coordinating investigator for trials by Calliditas and Chinoon; has served as an investigator for GN clinical trials by Alnylam, Calliditas, Chemoentryx, Omeros, and Pfizer; and is director of the Glomerulonephritis Fellowship funded by the Louise Fast Foundation. BR has received consulting fees from Calliditas, Novartis, Omeros, and Traver Therapeutics, Inc. DTS has consultancy agreements with BioPorto and Traver Therapeutics, Inc. MV is on advisory boards for Apellis, Novartis, Roche, and Traver Therapeutics, Inc.; receives consulting fees from Alexion; and has participated in studies sponsored by Bayer, Novartis, Chemocentrix, and Chinook. This does not influence the content of the present study. CP is employed by ApotheCom, which received funding support from Traver Therapeutics, Inc. for the DEFINE: Physicians study. VT has served as principal investigator and steering committee member for clinical studies in focal segmental glomerulosclerosis supported by Traver Therapeutics, Inc., and has consultancy agreements with AstraZeneca, Boehringer Ingelheim, Calliditas, Novartis, Omeros, and Traver Therapeutics, Inc.

ACKNOWLEDGMENTS

Logistical support of the Delphi process was provided by ApotheCom (San Francisco, CA) and Psmya International Inc. (Berwyn, PA) with funding from Traver Therapeutics, Inc. (San Diego, CA). Statistical analyses were performed by Monia Ezzalfani, PhD, of Creativ-Ceutical (Luxembourg). Writing and editorial support for this manuscript was provided by Steffen Biechele, PhD, and Alya Raphael, PhD, of ApotheCom (San Francisco, CA) and funded by Traver Therapeutics, Inc. (San Diego, CA). Some contents of this paper were previously presented as an abstract at the American Society of Nephrology Kidney Week 2021 (Vivarelli M, Floge J, Barratt J, Copp R, Lafayette RA, Radhakrishnan J, Rovin BH, Selewski DT, Tesar V, Tonelli M, Reich HN. An international Delphi survey on IgA nephropathy: results from the DEFINE Physicians study [abstract PO1641]. J Am Soc Nephrol. 32;2021:511). The DEFINE: Physicians study was funded by Traver Therapeutics, Inc. (San Diego, CA). The steering committee and research team (except Marcello Tonelli) received compensation as part of a research agreement with Traver Therapeutics, Inc. (San Diego, CA) for the guidance of the Delphi process, including the study design, conception of the study, statement development/revision, and interpretation of research findings. The authors did not receive compensation for their work on this manuscript. Traver Therapeutics, Inc. (San Diego, CA) was involved in proposing study designs for the steering committee to select, was informed of the analysis and interpretation of data, reviewed versions of the manuscript before submission, and participated in the decision to submit the article for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Participant disposition.
Table S1. Analysis of select statements in rounds 1 and 2 by geographic region.
Table S2. Analysis of select statements by country.
Table S3. Analysis of select statements by practice setting.
Table S4. Characteristics used for participant screening.
Table S5. Additional participant characteristics.
Table S6. Steering committee and research team membership.
Table S7. Participant countries and specialties: round 1 and round 2.
Table S8. Comparison of characteristics between participants and nonparticipants in round 2.

REFERENCES
1. Barbour S, Feehally J. An update on the treatment of IgA nephropathy. *Curr Opin Nephrol Hypertens*. 2017;26:319–326. https://doi.org/10.1097/MNH.0000000000000336
2. Rauen T, Wied S, Fitzner C, et al. After ten years of follow-up, no difference between supportive care plus immunosuppression and supportive care alone in IgA nephropathy. *Kidney Int*. 2020;98:1044–1052. https://doi.org/10.1016/j.kint.2020.04.046
3. Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. 2015;373:2225–2236. https://doi.org/10.1056/NEJMoa1415463
4. Lv J, Zhang H, Wong MG, et al. Effect of oral methylprednisolone on clinical outcomes in patients with IgA nephropathy: the TESTING randomized clinical trial. *JAMA*. 2017;318:432–442. https://doi.org/10.1001/jama.2017.9362
5. V. Perkovic, J. Lv, M.G. Wong, et al., The TESTING study: steroids vs. placebo in high risk IgA nephropathy. Presented at Kidney Week 2021; November 5, 2021. *Virtual*. Abstract FR-OR61.
6. Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. *Nat Rev Nephrol*. 2015;11:76–87. https://doi.org/10.1038/nrneph.2014.216
7. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group workgroup. 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
8. Gutiérrez E, Carvaca-Fontán F, Luzardo L, et al. A personalized update on IgA nephropathy: a new vision and new future challenges. *Nephron*. 2020;144:555–571. https://doi.org/10.1159/000509997
9. FDA approves first drug to decrease urine protein in IgA nephropathy, a rare kidney disease. US Food and Drug Administration. Updated December 17, 2021. Accessed January 20, 2022. https://www.fda.gov/drugs/fda-approves-first-drug-decrease-urine-protein-iga-nephropathy-rare-kidney-disease