Table 16 The frequency of classification of clinical diagnoses in IgA nephropathy in native kidneys in J-RBR 2009 and 2010

Clinical diagnosis	2009		2010		Total	
	n	%	*n*	%	*n*	%
Chronic nephritic syndrome	886	88.5	1,064	90.5	1,950	89.6
Recurrent or persistent hematuria	49	4.9	40	3.4	89	4.1
Nephrotic syndrome	30	3.0	36	3.1	66	3.0
Rapidly progressive nephritic syndrome	14	1.4	20	1.7	34	1.6
Acute nephritic syndrome	8	0.8	9	0.8	17	0.8
Renal disorder with collagen disease or vasculitis	4	0.4	1	0.1	5	0.2
Acute renal failure	2	0.2	2	0.2	4	0.2
Drug-induced nephropathy	2	0.2	1	0.1	3	0.1
Renal disorder with metabolic disease	1	0.1	0	–	1	0.0
Hypertensive nephropathy	0	–	1	0.1	1	0.0
Others	5	0.5	2	0.2	7	0.3
Total	1,001	100.0	1,176	100.0	2,177	100.0

Table 17 The frequency of pathological diagnoses as classified by histopathology in IgAN in native kidneys in J-RBR 2009 and 2010

Pathological diagnosis by histopathology	2009		2010		Total	
	n	%	*n*	%	*n*	%
Mesangial proliferative glomerulonephritis	937	93.6	1,111	94.5	2,048	94.1
Endocapillary proliferative glomerulonephritis	12	1.2	2	0.2	14	0.6
Minor glomerular abnormalities	12	1.2	15	1.3	27	1.2
Focal segmental glomerulosclerosis	9	0.9	6	0.5	15	0.7
Crescentic and necrotizing glomerulonephritis	8	0.8	10	0.9	18	0.8
Nephrosclerosis	6	0.6	4	0.3	10	0.5
Membranous nephropathy	4	0.4	2	0.2	6	0.3
Membranoproliferative glomerulonephritis (types I and III)	4	0.4	5	0.4	9	0.4
Sclerosing glomerulonephritis	3	0.3	2	0.2	5	0.2
Chronic interstitial nephritis	1	0.1	2	0.2	3	0.1
Acute interstitial nephritis	0	–	1	0.1	1	0.0
Others	5	0.5	16	1.4	21	1.0
Total	1,001	100.0	1,176	100.0	2,177	100.0

research studies (J-RBR201001 and J-KDR201001) being performed by members of the JSN who had already participated in the registry and who registered cases under the precise regulations presented on the website of the JSN in 2011.

With regard to estimating the number of yearly native renal biopsies in Japan, the Research Group on Progressive Renal Disease from the Ministry of Health, Labor and Welfare of Japan recently reported by a questionnaire method that it was between 18,000 and 21,000 in 2010. The J-RBR may cover nearly one fourth to one fifth of the number of yearly native renal biopsies in Japan in 2010. Since 128,057,352 people resided in Japan in 2010, the estimated rate of renal biopsy was 140.6 to 164.0 per million population. This rate was higher than that in Romania [24], Spain [25], the Czech Republic [10], Denmark [26], and Scotland [27], was similar to that in France [28], and was lower than that in USA, Finland [29], and Australia [30].

There are some limitations in the J-RBR and J-KDR. The J-RBR records three diagnoses for each case, viz., the clinical diagnosis, diagnosis based on the pathogenesis, and the diagnosis based on a histopathological examination, so there may be still some inconsistency in the case records. The terms hypertensive nephropathy, hypertensive nephrosclerosis, nephrosclerosis, and diabetic nephropathy may need to be defined more precisely to improve the accuracy of the report by the J-RBR. The incidence of renal biopsy

Table 18 Distribution of CKD stages and clinical parameters in total in IgA nephropathy in J-RBR: Combined data of 2009 and 2010

	CKD stage					Total	*P* value*
	G1	G2	G3a/b	G4	G5		
Total	663	814	551	111	30	2,169	–
n (%)	30.6	37.5	25.4	5.1	1.4	100.0	–
Age (years), average	23.5 ± 10.9	40.3 ± 13.5	50.9 ± 13.0	55.7 ± 16.2	46.3 ± 20.4	38.7 ± 17.1	<0.0001
Median	22 (17–29)	38 (30–50)	52 (42–61)	59 (44–68)	46 (29–62)	37 (25–52)	<0.0001
Body mass index	21.0 ± 4.0	22.9 ± 3.8	23.6 ± 3.7	23.0 ± 4.5	23.4 ± 5.9	22.5 ± 4.0	<0.0001
Estimated GFR (mL/min/1.73 m^2)	108.2 (96.9–128.0)	75.2 (67.8–82.7)	49.1 (42.0–54.6)	23.6 (20.9–27.6)	8.5 (6.1–12.0)	74.6 (53.8–95.0)	<0.0001
Proteinuria (g/day)	0.30 (0.10–0.81)	0.50 (0.21–1.00)	0.92 (0.40–2.00)	1.60 (0.71–2.84)	2.81 (1.17–4.58)	0.59 (0.22–1.29)	<0.0001
Proteinuria (g/gCr)	0.39 (0.14–0.91)	0.63 (0.28–1.23)	1.03 (0.51–2.01)	1.69 (0.77–4.21)	2.91 (1.30–4.58)	0.70 (0.27–1.47)	<0.0001
Sediment RBC ≥5/hpf (%)	82.4	81.3	74.6	82.0	86.7	80.0	0.0075
Serum creatinine (mg/dL)	0.60 (0.53–0.70)	0.79 (0.70–0.91)	1.16 (1.00–1.36)	2.10 (1.86–2.47)	5.34 (4.06–7.66)	0.81 (0.65–1.07)	<0.0001
Serum albumin (g/dL)	4.15 ± 0.46	4.02 ± 0.49	3.79 ± 0.59	3.45 ± 0.63	3.22 ± 0.59	3.96 ± 0.56	<0.0001
Serum total cholesterol (mg/dL)	184.6 ± 37.4	204.3 ± 46.2	209.9 ± 51.1	211.6 ± 52.3	221.0 ± 58.6	200.2 ± 46.8	<0.0001
Systolic BP (mmHg)	113.9 ± 14.0	123.3 ± 16.2	130.3 ± 17.5	137.6 ± 22.5	147.5 ± 27.9	123.2 ± 18.1	<0.0001
Diastolic BP (mmHg)	67.6 ± 11.4	75.1 ± 12.3	78.9 ± 12.5	81.0 ± 15.6	87.8 ± 18.0	74.2 ± 13.3	<0.0001
Anti-hypertensive agents (%)	13.8	33.3	59.6	75.8	71.4	37.0	<0.0001
Diabetes mellitus (%)	1.5	3.1	7.7	21.1	0.0	4.6	<0.0001

Data are presented as the mean ± SD or the medians (interquartile ranges)

CKD chronic kidney disease, *GFR* glomerular filtration rate, *RBC* red blood cell count, *BP* blood pressure

* ANOVA, Kruskal–Wallis or χ^2-test as appropriate. There are eight (0.4 %) missing values of CKD stage because of inappropriate data for serum creatinine

Table 19 The frequency of classification of clinical diagnoses in other 680 cases than J-RBR in J-KDR 2009 and 2010

Classification	Other cases 2009 (n = 680)		Other cases 2010 (n = 575)		Total (n = 1,255)	
	n	%	n	%	n	%
Chronic nephritic syndrome	165	24.3	72	12.5	237	18.9
Hypertensive nephropathy	142	20.9	43	7.5	185	14.7
Renal disorder with metabolic disease	106	15.6	177	30.8	283	22.5
Nephrotic syndrome	86	12.6	118	20.5	204	16.3
Renal disorder with collagen disease or vasculitis	24	3.5	7	1.2	31	2.5
Rapidly progressive nephritic syndrome	21	3.1	18	3.1	39	3.1
Inherited renal disease	18	2.6	3	0.5	21	1.7
Acute renal failure	9	1.3	10	1.7	19	1.5
Recurrent or persistent hematuria	8	1.2	0	–	8	0.6
Acute nephritic syndrome	5	0.7	4	0.7	9	0.7
Drug-induced nephropathy	5	0.7	0	–	5	0.4
Renal transplantation	2	0.3	9	1.6	11	0.9
Polycystic kidney disease	–	–	82	14.3	82	6.5
Others	89	13.1	32	5.6	121	9.6
Total	680	100.0	575	100.0	1,255	100.0

and the incidence of biopsy-proven renal diseases such as IgAN and primary glomerular disease (except IgAN) could be surveyed in major renal centers in Japan in terms of the epidemiological aspects to work out appropriate countermeasures. In this aspect, the incidence of pediatric IgAN was reported to be 4.5 cases/year per 100,000 children under 15 years of age from 1983 to 1999 in Yonago City, Japan [31], although center variations in the country in terms of the incidence, indications and diagnosis of adult native renal biopsy have been reported [27].

Finally, a committee report of J-KDR including J-RBR in 2009, 2010 and their total was conducted. The J-RBR exhibited the majority of the registry system to elucidate yearly demographic data of renal biopsies in Japan, and J-KDR was utilized to promote advanced clinical research in the field of nephrology in our country.

Acknowledgments The authors greatly acknowledge the help and assistance of many colleagues in centers and affiliate hospitals with collection of data for the J-RBR/J-KDR. We also sincerely thank Ms. M. Irie of the UNIN-INDICE and Ms. Y. Saito of the JSN for supporting the registration system and Ms. K. Fukuda of the JSN for submitting the manuscript. This study was supported by the committee grant from the Japanese Society of Nephrology and by a grant-in-aid from the Research Group on Progressive Renal Disease from the Ministry of Health, Labor and Welfare, Japan.

Conflict of interest T. Saito was supported by Novartis Pharma Co. and Kyowa-Kirin Co. Other authors declare no competing interests.

Appendix

The following facilities and investigators participated in the project for the J-RBR and J-KDR:

Hokkaido District

- Asahikawa Medical University Hospital (Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine), Naoyuki Hasebe, Naoki Nakagawa, Junko Chinda
- National Hospital Organization Hokkaido Medical Center (Department of Nephrology), Tetsuya Kawata, Tsuyoshi Yamamura
- Hokkaido University Graduate School of Medicine (Department of Medicine II), Saori Nishio, Sekiya Shibazaki, Yasunobu Ishikawa, Daigo Nakazawa
- Hokkaido University Graduate School of Medicine (Department of Pediatrics), Satoshi Sasaki, Yasuyuki Sato, Takeshi Yamazaki, Takayuki Okamoto
- KKR Sapporo Medical Center (Department of Pathology), Akira Suzuki

Tohoku District

- Iwate Prefectural Central Hospital (Department of Nephrology), Jun Soma, Izaya Nakaya, Mayumi Yahata
- Fukushima Medical University School of Medicine (Department of Nephrology, Hypertension, Diabetology, Endocrinology, and Metabolism), Tsuyoshi Watanabe, Koichi Asahi, Hiroaki Satoh
- Sendai Shakaihoken Hospital (Department of Nephrology), Toshinobu Sato, Asako Fujimori, Hisako Sugai, Mitsuhiro Sato
- Tohoku University Hospital and affiliated hospitals (Internal Medicine), Keisuke Nakayama, Takashi Nakamichi
- Yamagata University School of Medicine (Department of Cardiology, Pulmonology, and Nephrology), Tsuneo Konta, Kazunobu Ichikawa, Ami Ikeda, Kazuko Suzuki
- Yamagata University School of Medicine (Department of Pediatrics), Akira Matsunaga

Kanto District

- National Hospital Organization Chiba-East National Hospital (Clinical Research Center), Hiroshi Kitamura, Takashi Kenmochi, Motonobu Nishimura, Hideaki Kurayama (Department of Urology), Koichi Kamura
- Dokkyo Medical University Koshigaya Hospital (Department of Nephrology), Tetsuro Takeda
- Dokkyo Medical University School of Medicine (Department of Cardiology and Nephrology), Toshihiko Ishimitsu
- Gunma University Graduate School of Medicine (Department of Science and Clinical Medicine), Yoshihisa Nojima, Keijyu Hiromura
- Jichi Medical University (Division of Nephrology), Eiji Kusano
- The Jikei University School of Medicine (Division of Kidney and Hypertension), Tatsuo Hosoya, Tetsuya Kawamura, Yasunori Utsunomiya, Yoichi Miyazaki
- The Jikei University School of Medicine, Katsushika Medical Center (Division of Kidney and Hypertension), Masato Ikeda, Keita Hirano, Akihiro Shimizu
- The Jikei University School of Medicine, Daisan Hospital (Division of Kidney and Hypertension), Kazushige Hanaoka, Kentaro Koike, Haruko Suetsugu, Mai Tanaka
- The Jikei University Kashiwa Hospital (Division of Kidney and Hypertension), Makoto Ogura, Akihiko Hamaguchi, Yukio Maruyama, Seiji Kobayashi
- Juntendo University Faculty of Medicine (Division of Nephrology, Department of Internal Medicine), Yasuhiko Tomino, Isao Ohsawa, Chieko Hamada, Satoshi Horikoshi
- Kawaguchi Municipal Medical Center (Division of Nephrology), Takeo Ishii
- Kyorin University School of Medicine (Department of Urology), Kikuo Nutahara
- Mito Saiseikai General Hospital (Division of Nephrology), Itaru Ebihara, Chihiro Satho
- Nippon Medical School (Division of Nephrology, Department of Internal Medicine), Yasuhiko Iino, Tomohiro Kaneko, Akiko Mii, Akio Hirama
- Nihon University School of Medicine (Division of Nephrology, Hypertension and Endocrinology), Koichi Matsumoto
- Saitama Medical University, Faculty of Medicine (Department of Nephrology), Hirokazu Okada, Hiromichi Suzuki, Tsutomu Inoue
- Saitama Medical University, Saitama Medical Center (Department of Nephrology and Hypertension), Tetsuya Mitarai, Juko Asakura, Sinpei Okazaki, Hajime Hasegawa
- Showa University School of Medicine (Division of Nephrology), Aki Kuroki
- Showa University Fujigaoka Hospital (Division of Nephrology), Yoshihiko Inoue
- St. Marianna University School of Medicine (Division of Nephrology and Hypertension, Department of Internal Medicine), Kenjiro Kimura, Takashi Yasuda, Sayuri Shirai
- Tokai University School of Medicine (Division of Nephrology, Endocrinology and Metabolism), Masayuki Endoh, Hisae Tanaka
- Teikyo University School of Medicine (Department of Internal Medicine), Shunya Uchida
- Teikyo University School of Medicine (Department of Urology), Shigeo Horie, Satoru Muto
- Tokyo Medical University Ibaraki Medical Center (Department of Nephrology), Masaki Kobayashi, Kouichi Hirayama, Homare Shimohata
- Tokyo Metropolitan Children's Medical Center (Department of Nephrology), Hiroshi Hataya
- Tokyo Women's Medical University (Department of Pediatric Nephrology), Motoshi Hattori, Kiyonobu Ishizuka, Noriko Sugawara
- Tokyo Women's Medical University (The Forth Department of Medicine), Kosaku Nitta, Keiko Uchida, Takahito Moriyama
- University of Tokyo Hospital (Department of Hemodialysis & Apheresis), Norio Hanafusa
- University of Tokyo (Department of Nephrology and Endocrinology), Toshiro Fujita, Masaomi Nangaku, Takehiko Wada
- University of Tsukuba, Faculty of Medicine (Department of Nephrology), Kunihiro Yamagata, Joichi Usui, Tetsuya Kawamura
- Yokohama City University Graduate School of Medicine and School of Medicine (Department of Medical Science and Cardiorenal Medicine), Satoshi Umemura, Masato Oosawa
- Yokohama City University Medical Center, Nobuhito Hirawa, Keisuke Yatsu, Yuichiro Yamamoto, Sanae Saka

Koushinetsu District

- Niigata University Graduate School of Medical and Dental Sciences (Division of Clinical Nephrology and Rheumatology), Ichiei Narita, Shin Goto, Yumi Itoh, Naofumi Imai
- Shinshu University School of Medicine (Division of Nephrology), Yuji Kamijo, Wataru Tsukada, Koji Hashimoto
- University of Yamanashi Hospital (Third Department of Internal Medicine), Fumihiko Furuya, Daiichiro Akiyama, Kazuya Takahashi, Ayako Okamura

Hokuriku District

- National Hospital Organization Kanazawa Medical Center (Department of Nephrology and Rheumatology), Mitsuhiro Yoshimura, Takuyuki Ise
- Kanazawa Medical University School of Medicine (Division of Nephrology), Hitoshi Yokoyama, Hiroshi Okuyama, Keiji Fujimoto, Junko Imura
- Kanazawa Medical University (Division of Diabetes & Endocrinology), Daisuke Koya, Yuka Kurosima, Miho Ohba
- Kanazawa University Hospital (Division of Nephrology), Takashi Wada, Kiyoki Kitagawa, Kengo Furuichi
- Katou Hospital, Yasuhiro Katou, Hiroyuki Yamauchi, Yasunori Iwata, Kazutoshi Yamada
- Moriyama Koshino Clinic, Yoshitaka Koshino
- Pubulic Central Hospital of Matto-Ishikawa, Kazuya Takasawa, Chikako Takaeda
- Sugita Genpaku Memorial Obama Municipal Hospital, Haruyoshi Yoshida, Takayasu Horiguchi
- Toyama Prefectural Central Hospital (Department of Internal Medicine), Junya Yamahana, Masahiko Kawabata
- University of Fukui, Faculty of Medical Sciences (Division of Nephrology, Department of General Medicine), Masayuki Iwano, Hideki Kimura, Naoki Takahashi, Kenji Kasuno
- University of Toyama (Second Department of Internal Medicine), Fumihiro Tomoda

Tokai District

- Aichi Children's Health and Medical Center (Department of Pediatric Nephrology), Osamu Uemura, Takuhito Nagai, Satoshi Yamakawa
- Aichi Medical University School of Medicine (Division of Nephrology and Rheumatology), Naoto Miura, Hirokazu Imai
- Fujinomiya City General Hospital, Masanori Sakakima, Kazuto Kitajima, Taichi Sato, Yutaro Kawakatsu
- Fujita Health University School of Medicine (Department of Nephrology), Yukio Yuzawa, Satoshi Sugiyama
- Hamamatsu University School of Medicine, University Hospital (Internal Medicine1, Division of Nephrology), Yoshihide Fujigaki, Masafumi Ono, Takamasa Iwakura
- Japanese Red Cross Nagoya Daini Hospital (Kidney Center), Kunio Morozumi, Asami Takeda, Yasuhiro Otsuka
- Nagoya City University Graduate School of Medical Sciences (Department of Cardio-Renal Medicine and Hypertension), Genjiro Kimura, Michio Fukuda, Toshiyuki Miura, Atsuhiro Yoshida
- Nagoya Kyoritsu Hospital (Department of Internal Medicine), Hirotake Kasuga
- Nagoya University Graduate School of Medicine (Department of Nephrology), Seiichi Matsuo, Shoichi Maruyama, Waichi Sato, Yoshinari Yasuda
- Shizuoka General Hospital (Department of Nephrology), Noriko Mori, Satoshi Tanaka

Kinki District

- Hyogo Prefectural Nisihinomiya Hospital (Department of Pathology), Kazumasa Oka
- Ikeda City Hospital (Division of Nephrology), Nobuyuki Kajiwara
- Kitano Hospital, The Tazukekofukai Medical Research Institute (Division of Nephrology and Dialysis), Eri Muso, Kazuo Tosikoshi, Tomomi Endo, Yukako Iwasaki
- Kobe University Graduate School of Medicine (Division of Nephrology and Kidney Center), Shinichi Nishi, Shunske Goto
- National Hospital Organization Kyoto Medical Center (Division of Nephrology), Koichi Seta, Kensei Yahata
- Kyoto Prefectural University School of Medicine (Division of Nephrology, Department of Medicine), Yasukiyo Mori, Keiichi Tamagaki
- Kyoto University Graduate School of Medicine (Department of Nephrology), Motoko Yanagita, Tatsuo Tsukamoto, Noriyuki Iehara, Takeshi Matsubara
- Kyoto University Graduate School of Medicine (Department of Medicine and Clinical Science), Masashi Mukoyama, Hideki Yokoi, Tomoko Kawanishi, Akira Ishii
- Mie University Graduate School of Medicine Hospital (Department of Nephrology and Hemodialysis Center), Shinsuke Nomura, Mika Fujimoto, Eiji Ishikawa, Tomohiro Murata
- Nara Medical University (First Department of Internal Medicine), Yoshihiko Saito, Kenichi Samejima
- National Cerebral and Cardiovascular Center (Division of Hypertension and Nephrology), Satoko Nakamura
- Osaka City University Graduate School of Medicine (Department of Nephrology), Eiji Ishimura, Ikue Kobayashi, Mitsuru Ichii, Yoshiteru Ohno
- Osaka City General Hospital (Division of Nephrology and Hypertension), Masahito Imanishi, Takashi Morikawa, Chizuko Kitabayashi, Yoshio Konishi
- Osaka General Medical Center (Department of Kidney Disease and Hypertension), Yoshiharu Tsubakihara, Tatsuya Shoji
- Osaka Medical Center and Research Institute for Maternal and Child Health (Department of Pediatric Nephrology and Metabolism), Kenichi Satomura
- Osaka Red Cross Hospital (Department of Nephrology), Akira Sugawara, Masao Koshikawa, Yoshihisa Ogawa, Tomoko Kawanishi

- Osaka University Graduate School of Medicine (Department of Geriatric Medicine and Nephrology), Yoshitaka Isaka, Yasuyuki Nagasawa, Ryohei Yamamoto
- Saiseikai Shiga Hospital (Division of Nephrology), Toshiki Nishio
- Shiga University of Medical Science (Department of Medicine), Shinichi Araki
- Shirasagi Hospital (Kidney Center), Shigeichi Shoji, Kenjiro Yamakawa, Senji Okuno
- Toyonaka Municipal Hospital (Division of Nephrology), Megumu Fukunaga
- Wakayama Medical University (Department of Pediatrics), Norishige Yoshikawa, Koichi Nakanishi, Yuko Shima
- Wakayama Medical University (Division of Nephrology, Department of Internal Medicine), Takashi Shigematsu, Masaki Ohya
- Yokkaichi Social Insurance Hospital (Division of Nephrology and Blood Purification), Yasuhide Mizutani, Hitoshi Kodera, Masato Miyake

Chugoku District

- Kawasaki Medical School (Department of Nephrology and Hypertension), Naoki Kashihara,Tamaki Sasaki, Sohachi Fujimoto
- Kurashiki Central Hospital (Division of Nephrology), Kenichiro Asano, Masaru Kinomura
- Hiroshima University Hospital (Department of Nephrology), Takao Masaki, Sigehiro Doi, Yukio Yokoyama, Ayumu Nakashima
- Mizushima Kyodo Hospital (Department of Internal Medicine), Nobuyoshi Sugiyama, Yuichirou Inaba, Kan Yamasaki, Kouji Ozeki
- Okayama Saiseikai General Hospital (Department of Nephrology), Makoto Hiramatsu, Keisuke Maruyama, Noriya Momoki
- Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (Department of Medicine and Clinical Science), Hiroshi Morinaga, Tatsuyuki Inoue, Keiichi Takiue
- Saiseikai Yamaguchi General Hospital (Department of Internal Medicine), Tsuyoshi Imai
- Shimane University Faculty of Medicine (Division of Nephrology), Takafumi Ito
- Tottori University Hospital (Division of Pediatrics and Perinatology), Shinichi Okada, Yasuo Kawaba, Koichi Kitamoto

Shikoku District

- Kagawa University, Faculty of Medicine (Department of CardioRenal and Cerebrovascular Medicine & Departmnet of Clinical Pathology), Masakazu Kohno, Kumiko Moriwaki, Taiga Hara, Yoshio Kushida
- Kochi University, Kochi Medical School (Department of Endocrinology, Metabolism and Nephrology), Yoshio Terada, Toru Kagawa, Taro Horino, Yoshiko Shimamura
- The University of Tokushima Graduate School of Medicine (Department of Pediatrics, Institute of Health Bioscience), Shoji Kagami, Maki Urushihara, Shuji Kondo
- The University of Tokushima, Graduate School of Medicine (Department of Nephrology), Toshio Doi, Hideharu Abe, Kojiro Nagai

Kyushu District

- Fukuoka University School of Medicine (Division of Nephrology & Rheumatology, Departments of Internal Medicine), Takao Saito, Yoshie Sasatomi, Satoru Ogahara, Satoshi Hisano
- Japanese Red Cross Fukuoka Hospital (Department of Pediatrics), Ken Hatae, Maiko Hinokiyama, Hiroyo Maruyama
- Japanese Red Cross Fukuoka Hospital (Nephrology and Dialysis Center), Hideki Hirakata, Koji Mitsuiki
- Kumamoto University Graduate School of Medical Sciences (Department of Nephrology), Kenichiro Kitamura, Yushi Nakayama
- Jinseikai Clinic Hikarinomori, Yukimasa Kohda
- Kurume University School of Medicine (Division of Nephrology, Department Medicine), Seiya Okuda, Daisuke Wakasugi, Kiyomi Koike
- Kyushu University Graduate School of Medical Sciences (Department of Medicine and Clinical Science), Kazuhiko Tsuruya, Shunsuke Yamada, Akihiro Tsuchimoto
- Kyushu University Graduate School of Medical Sciences (Department of Environmental Medicine), Yutaka Kiyohara, Toshiharu Ninomiya, Masaharu Nagata
- Miyazaki Prefectural Miyazaki Hospital (Division of Nephrology), Naoko Yokota-Ikeda, Shigehiro Uezono, Keiko Kodama
- Nagasaki University Hospital (Department of Pathology), Takashi Taguchi
- Nagasaki University Hospital (Second Department of Internal Medicine), Tomoya Nishino, Hideyuki Arai, Yoko Obata, Tadashi Uramatsu
- National Fukuoka Higashi Medical Center (Kidney Unit), Ritsuko Katafuchi
- Oitaken Kouseiren Tsurumi Hospital (Division of Nephrology), Ryokichi Yasumori
- Saga University, Faculty of Medicine (Department of Cardiovascular and Renal Medicine), Toru Sanai
- St. Mary's Hospital, Harumichi Higashi
- University of Miyazaki Hospital (First Department of Internal Medicine), Shouichi Fujimoto, Yuji Sato, Masao Kikuchi

- University of Occupational and Environmental Health (Second Department of Internal Medicine), Masahito Tamura, Tetsu Miyamoto
- Ryukyu University Graduate School of Medicine (Department of Cardiology, Nephrology and Neurology), Yusuke Ohya, Kentaro Kohagura, Kunitoshi Iseki, Yusuke Ohya

References

1. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan. Clin Exp Nephrol. 2011;15:493–503.
2. Churg J, Bernstein J, Glassock RJ, editors. Renal disease, classification and atlas of glomerular disease. 2nd ed. Tokyo: Igaku-Shoin; 1995.
3. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
4. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. Am J Kidney Dis. 1997;29:526–32.
5. Moriyama T, Suzuki K, Sugiura H, Itabashi M, Tsukada M, Takei T, et al. Frequency of renal disease in Japan: an analysis of 2,404 renal biopsies at a single center. Nephron Clin Pract. 2010;115:c227–36.
6. Nationwide and long-term survey of primary glomerulonephritis in Japan as observed in 1,850 biopsied cases. Research Group on Progressive Chronic Renal Disease. Nephron. 1999;82:205–13.
7. Chang JH, Kim DK, Kim HW, Park SY, Yoo TH, Kim BS, et al. Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. Nephrol Dial Transplant. 2009;24:2406–10.
8. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004;66:920–3.
9. Gesualdo L, Di Palma AM, Morrone LF, Strippoli GF, Schena FP. The Italian experience of the national registry of renal biopsies. Kidney Int. 2004;66:890–4.
10. Rychlik I, Jancova E, Tesar V, Kolsky A, Lacha J, Stejskal J, et al. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994–2000. Nephrol Dial Transplant. 2004;19:3040–9.
11. Goto M, Kawamura T, Wakai K, Ando M, Endoh M, Tomino Y. Risk stratification for progression of IgA nephropathy using a decision tree induction algorithm. Nephrol Dial Transplant. 2009;24:1242–7.
12. Goto M, Wakai K, Kawamura T, Ando M, Endoh M, Tomino Y. A scoring system to predict renal outcome in IgA nephropathy: a nationwide 10-year prospective cohort study. Nephrol Dial Transplant. 2009;24:3068–74.
13. Kim JK, Kim JH, Lee SC, Kang EW, Chang TI, Moon SJ, et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol. 2012;7:427–36.
14. McQuarrie EP, Mackinnon B, Stewart GA, Geddes CC. Membranous nephropathy remains the commonest primary cause of nephrotic syndrome in a northern European Caucasian population. Nephrol Dial Transplant. 2010;25:1009–10 (author reply 1010–1).
15. Yokoyama H, Taguchi T, Sugiyama H, Sato H. Membranous nephropathy in Japan: Analysis of the Japan Renal Biopsy Registry (J-RBR). Clin Exp Nephrol. 2012;16:557–63.
16. Shiiki H, Saito T, Nishitani Y, Mitarai T, Yorioka N, Yoshimura A, et al. Prognosis and risk factors for idiopathic membranous nephropathy with nephrotic syndrome in Japan. Kidney Int. 2004;65:1400–7.
17. Polanco N, Gutierrez E, Covarsi A, Ariza F, Carreno A, Vigil A, et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. J Am Soc Nephrol. 2010;21:697–704.
18. Polanco N, Gutierrez E, Rivera F, Castellanos I, Baltar J, Lorenzo D, et al. Spontaneous remission of nephrotic syndrome in membranous nephropathy with chronic renal impairment. Nephrol Dial Transplant. 2012;27:231–4.
19. Omokawa A, Komatsuda A, Nara M, Fujiwara T, Sato R, Togashi M, et al. Renal biopsy in patients aged 80 years and older: a single-center experience in Japan. Clin Nephrol. 2012;77:461–7.
20. Yokoyama H, Sugiyama H, Sato H, Taguchi T, Nagata M, Matsuo S, et al. Renal disease in the elderly and the very elderly Japanese: analysis of the Japan Renal Biopsy Registry (J-RBR). Clin Exp Nephrol. 2012 (in press).
21. Koyama A, Yamagata K, Makino H, Arimura Y, Wada T, Nitta K, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. Clin Exp Nephrol. 2009;13:633–50.
22. Yamagata K, Usui J, Saito C, Yamaguchi N, Hirayama K, Mase K, et al. ANCA-associated systemic vasculitis in Japan: clinical features and prognostic changes. Clin Exp Nephrol. 2012;16:580–8.
23. Matsuo S, Yamagata K, Makino H, Arimura Y, Muso E, Nitta K, et al. The guideline for rapidly progressive glomerulonephritis. Jpn J Nephrol (in Japanese). 2011;53:509–55.
24. Covic A, Schiller A, Volovat C, Gluhovschi G, Gusbeth-Tatomir P, Petrica L, et al. Epidemiology of renal disease in Romania: a 10 year review of two regional renal biopsy databases. Nephrol Dial Transplant. 2006;21:419–24.
25. Rivera F, Lopez-Gomez JM, Perez-Garcia R. Frequency of renal pathology in Spain 1994–1999. Nephrol Dial Transplant. 2002;17:1594–602.
26. Heaf J, Lokkegaard H, Larsen S. The epidemiology and prognosis of glomerulonephritis in Denmark 1985–1997. Nephrol Dial Transplant. 1999;14:1889–97.
27. McQuarrie EP, Mackinnon B, Young B, Yeoman L, Stewart G, Fleming S, et al. Centre variation in incidence, indication and diagnosis of adult native renal biopsy in Scotland. Nephrol Dial Transplant. 2009;24:1524–8.
28. Simon P, Ramee MP, Boulahrouz R, Stanescu C, Charasse C, Ang KS, et al. Epidemiologic data of primary glomerular diseases in western France. Kidney Int. 2004;66:905–8.
29. Wirta O, Mustonen J, Helin H, Pasternack A. Incidence of biopsy-proven glomerulonephritis. Nephrol Dial Transplant. 2008;23:193–200.
30. Briganti EM, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, et al. The incidence of biopsy-proven glomerulonephritis in Australia. Nephrol Dial Transplant. 2001;16:1364–7.
31. Utsunomiya Y, Koda T, Kado T, Okada S, Hayashi A, Kanzaki S, et al. Incidence of pediatric IgA nephropathy. Pediatr Nephrol. 2003;18:511–5.

NDT Advance Access published March 3, 2014

Nephrol Dial Transplant (2014) 0: 1–8
doi: 10.1093/ndt/gfu020

ndt
Nephrology Dialysis Transplantation

Original Article

A multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with immunoglobulin A nephropathy

Tetsuya Kawamura[1], Mitsuhiro Yoshimura[2], Yoichi Miyazaki[1], Hidekazu Okamoto[1], Kenjiro Kimura[3], Keita Hirano[1], Masato Matsushima[4], Yasunori Utsunomiya[1], Makoto Ogura[1], Takashi Yokoo[1], Hideo Okonogi[1], Takeo Ishii[1], Akihiko Hamaguchi[1], Hiroyuki Ueda[1], Akira Furusu[5], Satoshi Horikoshi[6], Yusuke Suzuki[6], Takanori Shibata[7], Takashi Yasuda[3], Sayuri Shirai[3], Toshiyuki Imasawa[8], Koichi Kanozawa[9], Akira Wada[10], Izumi Yamaji[11], Naoto Miura[12], Hirokazu Imai[12], Kenji Kasai[13], Jun Soma[14], Shouichi Fujimoto[15], Seiichi Matsuo[16], and Yasuhiko Tomino[6] The Special IgA Nephropathy Study Group

[1]Division of Kidney and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan, [2]Department of Internal Medicine, Kanazawa Medical Centre, Kanazawa, Japan, [3]Division of Kidney and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan, [4]Division of Clinical Epidemiology, Research Center for Medical Science, Jikei University School of Medicine, Tokyo, Japan, [5]Second Department of Internal Medicine, Nagasaki University Hospital of Medicine and Dentistry, Nagasaki, Japan, [6]Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan, [7]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan, [8]Department of Internal Medicine, Chiba-East Hospital, Chiba, Japan, [9]Division of Kidney and Hypertension, Department of Internal Medicine, Saitama University Medical Centre, Saitama, Japan, [10]Department of Internal Medicine, National Hospital Organization, Osaka National Hospital, Osaka, Japan, [11]Department of Internal Medicine, Teine Keijinkai Hospital, Sapporo, Japan, [12]Division of Nephrology and Rheumatology, Department of Internal Medicine, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan, [13]Department of Internal Medicine, Fuji City Central Hospital, Fuji, Japan, [14]Department of Internal Medicine, Iwate Prefectural Central Hospital, Morioka, Japan, [15]Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan and [16]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, University of Nagoya, Nagoya, Japan

Correspondence and offprint requests to: Tetsuya Kawamura; E-mail: kawatetu@coral.ocn.ne.jp

ABSTRACT

Background. The study aim was, for the first time, to conduct a multicenter randomized controlled trial to evaluate the effect of tonsillectomy in patients with IgA nephropathy (IgAN).

Methods. Patients with biopsy-proven IgAN, proteinuria and low serum creatinine were randomly allocated to receive tonsillectomy combined with steroid pulses (Group A; $n = 33$) or steroid pulses alone (Group B; $n = 39$). The primary end points were urinary protein excretion and the disappearance of proteinuria and/or hematuria.

Results. During 12 months from baseline, the percentage decrease in urinary protein excretion was significantly larger in Group A than that in Group B ($P < 0.05$). However, the frequency of the disappearance of proteinuria, hematuria, or both (clinical remission) at 12 months was not statistically different between the groups. Logistic regression analyses revealed the assigned treatment was a significant, independent

factor contributing to the disappearance of proteinuria (odds ratio 2.98, 95% CI 1.01–8.83, P = 0.049), but did not identify an independent factor in achieving the disappearance of hematuria or clinical remission.

Conclusions. The results indicate tonsillectomy combined with steroid pulse therapy has no beneficial effect over steroid pulses alone to attenuate hematuria and to increase the incidence of clinical remission. Although the antiproteinuric effect was significantly greater in combined therapy, the difference was marginal, and its impact on the renal functional outcome remains to be clarified.

Keywords: clinical remission, estimated glomerular filtration rate, hematuria, proteinuria

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis worldwide, with primary IgAN characterized by the deposition of IgA antibodies in the glomerulus. The renal outcome of IgAN varies among individual patients [1–4]. Although ~20% of patients remain stable in their renal function [1], 30–40% develop end-stage renal disease (ESRD) within 20 years from its onset [1–4]. The most important determinant of renal outcome in IgAN is the severity and duration of proteinuria, and a decreased severity in proteinuria is distinctly associated with a better renal outcome [1–10].

A number of studies have shown that corticosteroid therapy is effective for progressive IgAN [11–15]. A randomized controlled trial and its 10-year follow-up examined whether steroid pulse therapy is more effective than conventional therapy for long-term preservation of renal function [14, 15]. The risk of a doubling in serum creatinine after 10 years was found to be significantly lower in the group receiving steroid pulses than in the one receiving supportive therapy alone. However, steroid pulse therapy is associated with several problems. For instance, only a small fraction of the treated patients achieved remission of proteinuria after 1 year [15], and severe proteinuria relapsed in a sizable fraction of the patients after the cessation of treatment [15].

Several studies have examined the therapeutic efficacy of tonsillectomy in IgAN. A retrospective study by Rasche *et al.* [16] reported that tonsillectomy had no impact on renal outcome 10 years after biopsy. By contrast, in a retrospective study of 329 IgAN patients, Hotta *et al.* [17] found that tonsillectomy was an independent predictor of the remission of urine abnormalities and a lack of progression in renal injury. Xie *et al.* [18] followed-up 118 patients for an average of 20 years, and found that renal survival was better in the group with prior tonsillectomy than in the one without tonsillectomy at 240 months. More recently, in a non-randomized prospective study, Komatsu *et al.* [19] found that tonsillectomy combined with steroid pulse treatment had a significant impact on the disappearance of both proteinuria and hematuria, when compared with steroid pulse treatment alone. A recent meta-analysis has also reported that tonsillectomy combined with either conventional steroid or steroid pulse treatment resulted in higher remission rates with favorable long-term efficacy [20]. Thus, tonsillectomy combined with steroid pulses has become one of the most widely used therapy protocols in the treatment of active IgAN, and is now being performed in ~50% of the institutions in Japan [21]. However, none of the previous analyses were randomized controlled studies, and there is growing concern that the evidence to date is insufficient for recommending tonsillectomy to IgAN patients [22, 23]. Importantly, the recent Kidney Disease: Improving Global Outcomes clinical guideline for glomerulonephritis suggests that tonsillectomy not be performed for IgAN, because no randomized controlled trial of tonsillectomy has been performed [24].

Here, we report the results of a multicenter, randomized, controlled trial of tonsillectomy combined with steroid pulse therapy in patients with IgAN conducted by the Special IgAN Study Group of the Progressive Glomerular Diseases Study Committee organized by the Ministry of Health, Labour and Welfare of Japan.

MATERIALS AND METHODS

Patients

This multicenter study was conducted between 1 April 2005 and 31 March 2010 in 18 university or community hospitals located in major cities across Japan. The participating institutions routinely performed tonsillectomy combined with steroid pulses to treat IgAN. The study was approved by the local ethics committees and was regulated by an independent data safety and monitoring board.

The inclusion criteria were established primarily according to the previous trial by Pozzi *et al.* [14, 15], and were biopsy-proven IgAN, an age ranging from 10 to 69 years, urinary protein excretion ranging from 1.0 to 3.5 g/day, serum creatinine of ≤1.5 mg/dL, a histological grade diagnosed as a relatively good prognosis, a relatively poor prognosis, or a poor prognosis in the classification proposed in 2004 [25], and systolic and diastolic blood pressures of <140 and <90 mmHg, respectively, regardless of the use or non-use of antihypertensive drugs. Exclusion criteria were nephrotic syndrome, serum creatinine of >1.5 mg/dL, recent treatment with corticosteroids and/or immunosuppressive agents, and contraindications for general anesthesia and/or tonsillectomy as assessed by otolaryngologists. Informed consent was obtained from individual patients following the confirmation of eligibility.

We estimated the frequency of the disappearance of proteinuria at 12 months after the initiation of the treatment would be 40% in patients treated with tonsillectomy plus steroid pulses [21, 26] and 10% in those with steroid pulses alone [14, 15]. Based on the power of 80% for detecting a significant difference (P < 0.05, two-sided), 38 patients were required for each study group. To compensate for non-evaluable patients, we planned to enroll 40 patients per group.

Randomization and masking

The profiles of patients with informed consent were sent to the registration center located at Jikei University School of Medicine. Randomization was done by a technical assistant in

the registration center using a computer-based allocation program with a minimization method, which was developed by an outside company (East Asia Trading Corporation, Hyogo) independent of this study. Immediately after the input of patient information, including the date of enrollment, gender, histological grade, the severity of proteinuria (<2.0 g/day or ≥2.0 g/day), serum creatinine (male, <1.2 mg/dL or ≥1.2 mg/dL; female, <0.9 mg/dL or ≥0.9 mg/dL) and the use or non-use of renin-angiotensin system (RAS) inhibitors, the participants were randomly assigned to receiving tonsillectomy combined with steroid pulses (Group A) or steroid pulses alone (Group B). Since the allocation was based on the presence or absence of tonsillectomy, neither the patients nor the physicians were blinded to the group assignment. Although those assessing the outcomes were not blinded, they assessed the data regarding the pre-defined outcomes using pre-specified statistical analyses.

Study protocol

After the random allocation to Group A or Group B, the center sent the enrollment certificate with the results of randomization to the participating institutions. The patients assigned to Group A underwent tonsillectomy and subsequently received 0.5 g/day of methylprednisolone intravenously for 3 consecutive days at 1–3 weeks later and then at 2 and 4 months later. The patients were also given oral prednisolone at a dose of 0.5 mg/kg every other day for 6 months. The patients assigned to Group B received only the steroid pulse therapy, and were also given oral prednisolone in a manner identical to that in Group A. The protocol of steroid pulse therapy was essentially the same as the one in the trial by Pozzi *et al.* [14, 15], with the exception that a half dose of intravenous methylprednisolone was provided in the current study. The entire trial period (treatment + follow-up) was 12 months. If needed, the patients in both groups were given antihypertensive drugs to control blood pressure to <125/75 mmHg during the trial period. RAS inhibitors were the primary antihypertensive drugs recommended during the study.

Data collection

During the trial, the patients were examined every other month for blood pressure, urinary protein excretion, serum creatinine and urinary sediment with red blood cells. Other data including the incidence of adverse effects and the prescription of additional drugs were also obtained. Urinary protein was measured primarily by the Pyrogaroll Red method. Urinary protein at baseline was represented by a mean value from three consecutive data points prior to the treatment (i.e. tonsillectomy in Group A, first steroid pulses in Group B). The disappearance of proteinuria was defined as urinary protein excretion of <0.3 g/g creatinine in a 24-h urine collection or in urine samples at visits as described previously [15, 27], although the distinct value for disappearance of proteinuria had not been specified at pre-registration. Urinary creatinine concentration was not available in three patients (one patient, Group A; two, Group B). In these patients, the disappearance of proteinuria was defined as levels of <0.3 g/day. Disappearance of hematuria was defined as a number of red blood cells in urinary sediments of <5 per high power field. Clinical remission was defined as the disappearance of both proteinuria and hematuria. eGFR was computed using the following equation [28] developed as a modification of the modified MDRD equation [29]: eGFR (mL/min/1.73 m^2) = 194 × (serum creatinine in mg/dL)$^{-1.094}$ × (age in years)$^{-0.287}$ (×0.739 if female).

Outcome definitions

The primary end points were the percentage decrease in urinary protein excretion from baseline and the frequency of the disappearance of proteinuria and/or hematuria 12 months after the initial treatment. The secondary end points were a change in eGFR from baseline, the frequencies of a 100% increase in serum creatinine from baseline, a 50% decrease in eGFR from baseline, indications for renal replacement therapy and adverse effects.

Statistical analysis

Data were subjected to intention-to-treat analysis. All patients, physicians and those assessing the outcomes were not blinded to group assignment. Stata version 11 for Windows (StataCorp LP, College station, TX, USA) was used for the analysis. The percent reduction of proteinuria from baseline was compared between Groups A and B by analyzing the values from six fixed time points (2, 4, 6, 8, 10 and 12 months after randomization) using a mixed effects model. We included as fixed effects group allocation, time, baseline eGFR, mean arterial pressure and the use of RAS inhibitors at baseline. Time was coded as months after the randomization and was given the values of 0, 2, 4, 6, 8, 10 and 12. The patients were included as a random effect. For comparing the parameters between the two groups, the unpaired *t*-test and nonparametric Wilcoxon rank-sum test were used for normally and non-normally distributed variables, respectively. The difference in frequency between the two groups was evaluated using Pearson's chi-square test. Logistic regression analysis was used to evaluate the impact of tonsillectomy, eGFR, mean arterial pressure, urinary protein excretion and the use of RAS inhibitors at baseline on the disappearance of proteinuria, hematuria or both after adjusting for the other covariates. The results were presented as odds ratios with 95% confidence intervals and P-values; $P < 0.05$ was considered statistically significance in all analyses.

RESULTS

Characteristics of the study subjects

Eighty eligible patients were enrolled and randomly allocated to receive tonsillectomy with steroid pulses (Group A) or steroid pulses alone (Group B) (Figure 1). In Group A, three and four patients failed to meet the inclusion criteria and withdrew consent, respectively. In Group B, one patient withdrew consent. One patient in Group A did not undergo tonsillectomy after randomization but was analyzed within this group according to the policy of intention-to-treat analysis. Likewise, two patients in Group B who underwent tonsillectomy after

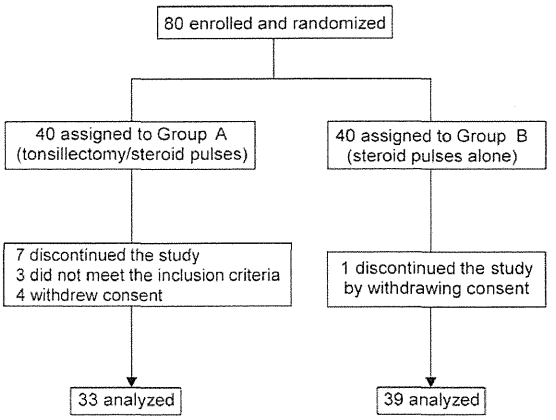

FIGURE 1: Trial profile.

Table 1. Baseline patient characteristics

	Group A Tonsillectomy/steroid pulse therapy ($n = 33$)	Group B Steroid pulse therapy alone ($n = 39$)
Age (years)	36 (13)	40 (13)
Gender		
Male	17* (52)	18* (46)
Female	16* (48)	21* (54)
eGFR (mL/min/1.73 m^2)	75 (24)	69 (22)
Proteinuria (g/day)	1.6 (0.5)	1.6 (0.6)
Proteinuria (g/g creatinine)	1.7 (1.0)	1.7 (1.0)
Systolic blood pressure (mmHg)	117 (12)	121 (10)
Diastolic blood pressure (mmHg)	69 (9)	73 (8)
Mean arterial pressure (mmHg)	85 (9)	89 (8)
Patients receiving RASi (%)	16* (48)	18* (46)
Histological grade		
Good prognosis	0*	0*
Relatively good prognosis	2* (6)	3* (8)
Relatively poor prognosis	20* (61)	23* (59)
Poor prognosis	11* (33)	13* (33)

Data are mean (SD) or *number of patients (%). Histological grade was assessed by the classification proposed by the Special IgAN Study Group in 2004 [30].
eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitors.

randomization were analyzed as part of Group B. We therefore analyzed 33 and 39 patients in Groups A and B, respectively. The two groups did not differ in age, gender distribution, estimated glomerular eGFR, urinary protein excretion, blood pressure, the proportion of patients given RAS inhibitors or histological grades (Table 1).

Impact of steroid pulses and tonsillectomy on proteinuria

Figure 2 shows the percent changes in urinary protein excretion from baseline during the trial period. As revealed by a mixed effect model employing six fixed effects (group allocation, eGFR, mean arterial pressure, the use of RAS inhibitors at baseline, time and the interaction of group and time; Supplementary Table S1), the percentage decrease in urinary protein excretion during the 12 months from baseline was significantly larger in Group A than that in Group B (coefficient estimate −1.316, 95% CI −2.617 to −0.015, P = 0.047).

The percentage of patients with the disappearance of proteinuria (<0.3 g/gCr) was significantly higher in Group A than in Group B after 10 months (P = 0.029; Figure 3). However, at 12 months, the difference was not statistically significant (Group A, 63%; Group B, 39%; P = 0.052).

Impact of steroid pulses and tonsillectomy on hematuria

The severity of microscopic hematuria gradually decreased following the initiation of therapy in both groups (Figure 4). However, the proportion of patients with the disappearance of hematuria was not different between the two groups at any time point (e.g. at 12 months, Group A, 68%; Group B, 64%, P = 0.672).

Impact of steroid pulses and tonsillectomy on clinical remission

The disappearance of both proteinuria and hematuria (i.e. clinical remission) did not occur at a higher rate in Group A than in Group B at any time point (P = 0.160 at 10 months, P = 0.103 at 12 months; Figure 5).

Impact of steroid pulse and tonsillectomy on renal functions

eGFR remained stable throughout the trial period and was comparable between the two groups at 12 months (Group A, 75 mL/min/1.73 m^2; Group B, 69 mL/min/1.73 m^2; Figure 6). No patient in either group showed a 100% increase in serum creatinine from baseline or a 50% decrease in eGFR from baseline, or had indications for renal replacement therapy. No adverse effect related to tonsillectomy or general anesthesia was reported. One patient in Group A and three in Group B developed diabetes during the trial period, with one of these Group B patients requiring insulin therapy during the

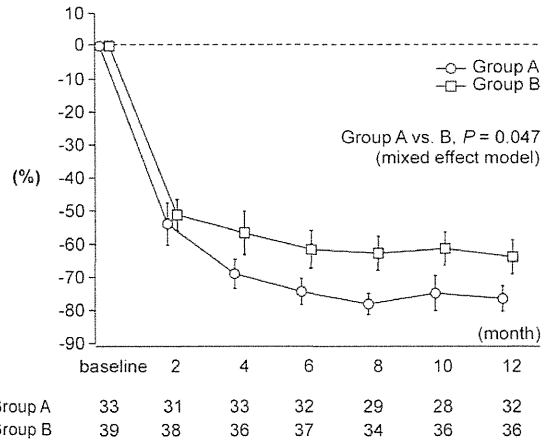

FIGURE 2: Urinary protein excretion during the trial period. Mean values and standard errors are presented. The rate of decrease in urinary protein excretion was significantly higher in Group A than in Group B using a mixed effect model. The numbers of patients analyzed at each time point are shown below the figure for each group.

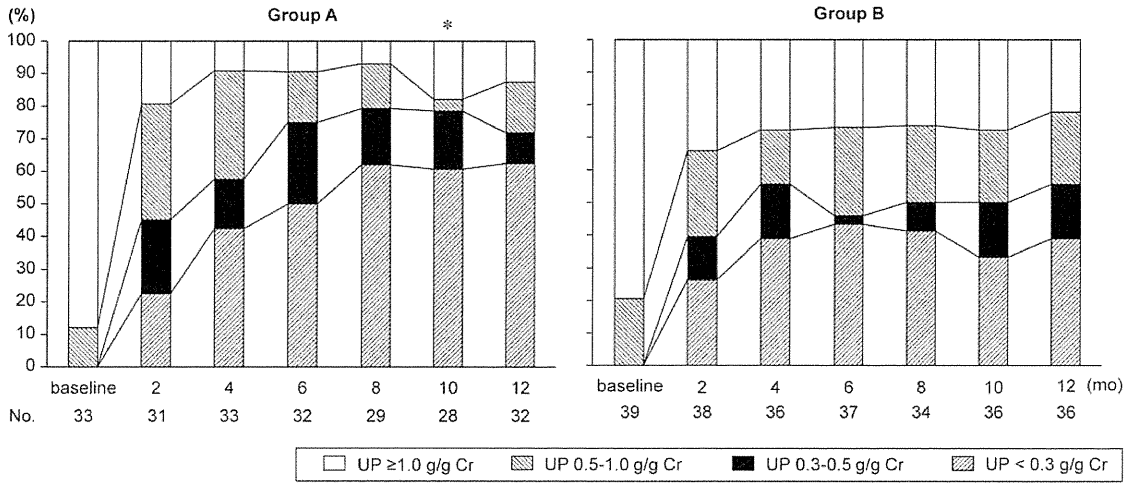

FIGURE 3: Patient distribution of the severity of proteinuria during the trial period. The severity of proteinuria was divided into the four grades shown below the figure according to the level of urinary protein (UP) in g/g creatinine (Cr). The patient distribution in the four grades is shown as a percentage. *The rate of the disappearance of proteinuria (UP level of <0.3 g/g Cr) was significantly higher in Group A than in Group B (Pearson's chi-square test).

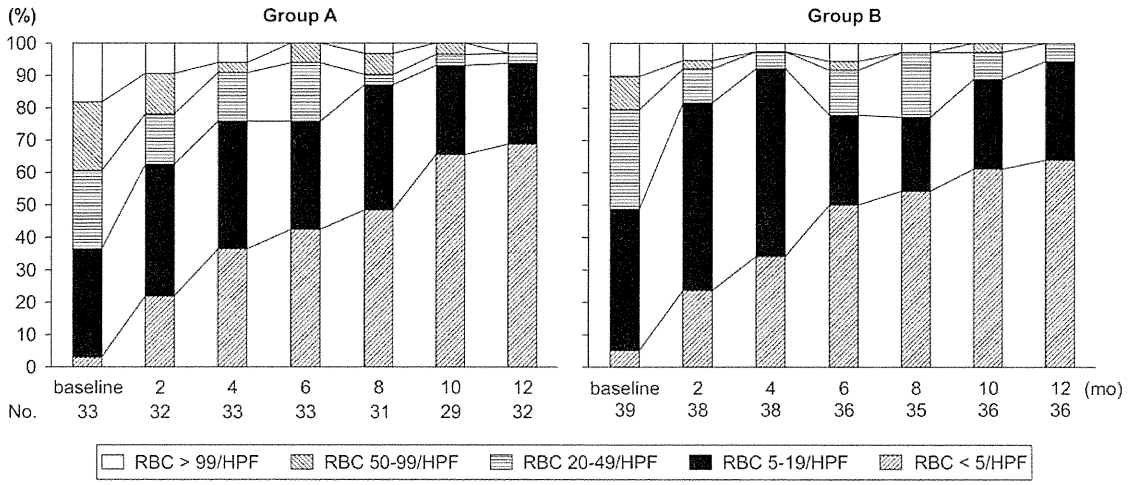

FIGURE 4: Patient distribution of the severity of hematuria during the trial period. The severity of hematuria was divided into the five grades according to the number of red blood cells per high power field (HPF). The patient distribution in the five grades is shown as a percentage. The rate of the disappearance of hematuria, defined as the number of red blood cells <5/HPF, was not different between both groups at any time point (Pearson's chi-square test).

treatment with corticosteroid. At the end of the study, blood sugar levels of all four patients were restored to the normal range without any medications. No patient had a new onset of hypertension.

Logistic regression analysis

Logistic regression analysis was performed to evaluate the impact of multiple covariates on the disappearance of proteinuria or hematuria and the occurrence of clinical remission. Independent variables included the allocated treatment, eGFR, mean blood pressure, urinary protein excretion and the use of RAS inhibitors at baseline (Table 2). Only the allocated treatment had a significant and independent impact on the disappearance of proteinuria (hazard ratio, 2.98; 95% confidence interval, 1.01–8.83; P = 0.049). No independent factors were identified as achieving the disappearance of hematuria or clinical remission.

Use of RASi during the trial

RAS inhibitors were started after the initiation of treatment in three patients in Group A (losartan 50 mg, telmisartan 40 mg or valsartan 80 mg) and four patients in Group B (aliskiren 150 mg, losartan 50 mg, olmesartan 10 mg or valsartan 80 mg). The disappearance of proteinuria was achieved in two

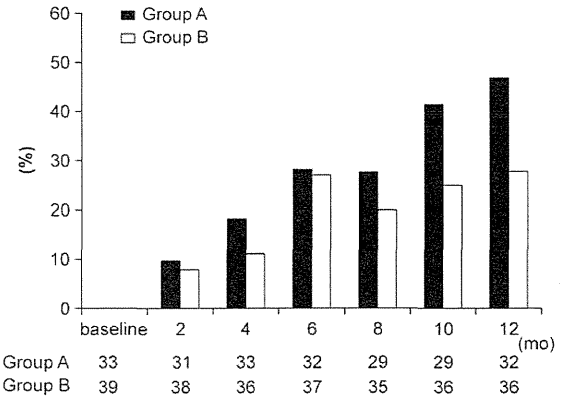

FIGURE 5: Frequency of clinical remission during the trial period. The frequency of patients with clinical remission (i.e. the disappearance of both proteinuria and hematuria) is shown for each time point. The frequency was not significantly higher in Group A than Group B at any time point (Pearson's chi-square test).

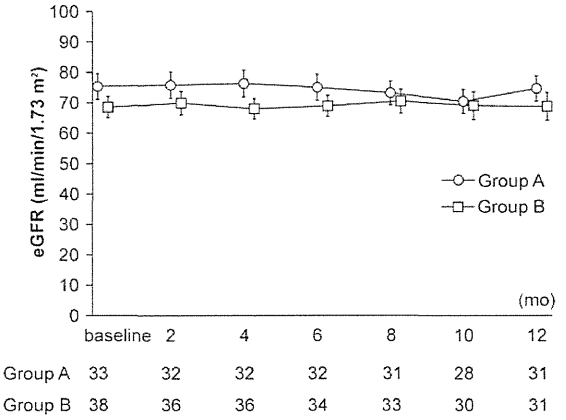

FIGURE 6: Renal function during the trial period. Mean values and standard errors of the estimated glomerular filtration rate (eGFR) are shown. The value of eGFR remained stable in both groups.

of these patients from each group after 12 months. No patient started other antihypertensive drugs during the period.

DISCUSSION

For the first time, we performed a multicenter randomized controlled trial of tonsillectomy combined with steroid pulse therapy in patients with IgA nephropathy. The findings of the present study indicated that the decrease in urinary protein excretion during follow-up was significantly greater, albeit marginally, in patients receiving tonsillectomy combined with steroid pulse therapy than in those receiving steroid pulse therapy alone, as shown by a mixed effect model and logistic regression analysis. However, 12 months after the initial treatment, the frequency of the disappearance of microscopic hematuria and clinical remission was comparable between the two groups. Thus, we conclude that tonsillectomy has no

Table 2. Logistic regression analysis of the impact of tonsillectomy, renal function, blood pressure and urinary protein excretion at baseline and after disappearance of proteinuria, hematuria or both at study completion

	Odds ratio	95% CI	P-value
Disappearance of proteinuria			
Assigned treatment	2.98	1.01–8.83	0.049
eGFR (baseline)	0.99	0.97–1.02	0.560
Mean blood pressure (baseline)	1.04	0.97–1.11	0.297
Proteinuria (baseline)	0.61	0.33–1.13	0.115
RASi (baseline)	0.51	0.16–1.68	0.270
Disappearance of hematuria			
Assigned treatment	1.23	0.43–3.55	0.697
eGFR (baseline)	0.99	0.97–1.01	0.304
Mean blood pressure (baseline)	0.97	0.91–1.04	0.450
Proteinuria (baseline)	0.91	0.54–1.54	0.737
RASi (baseline)	0.95	0.29–3.13	0.930
Clinical remission			
Assigned treatment	2.24	0.77–6.51	0.140
eGFR (baseline)	0.99	0.97–1.02	0.554
Mean blood pressure (baseline)	1.01	0.94–1.08	0.858
Proteinuria (baseline)	0.75	0.41–1.38	0.348
RASi (baseline)	0.63	0.19–2.06	0.445

Logistic regression analysis was used to determine the association of assigned treatment, eGFR, mean blood pressure or urinary protein excretion at baseline with the disappearance of proteinuria, hematuria or both (clinical remission) after 12 months of treatment with tonsillectomy plus steroid pulse therapy or steroid pulse therapy alone after adjusting for the other covariates.
CI, confidence interval; eGFR, estimated glomerular filtration rate; RASi, renin-angiotensin system inhibitors.

impact on the disappearance of hematuria, but can have a beneficial effect on the decrease in proteinuria of IgAN patients, at least for those clinically comparable to the present patients. However, whether this subtle antiproteinuric effect by tonsillectomy indeed leads to better renal outcome remains to be elucidated.

Our patients had urinary protein excretion ranging from 1.0 to 3.5 g/day, and most patients showed moderate to severe histological damage (i.e. relatively poor prognosis or poor prognosis; Table 1), indicating that the present study excluded patients with mild IgAN. In view of the possible effectiveness of steroid pulses alone, as revealed in the present and previous studies [14, 15], a question remains as to whether the advantage of tonsillectomy seen in the present study is relevant to patients with milder IgAN than those in the present patients. Moreover, based on the randomized controlled trial by Pozzi *et al.* [15] demonstrating an ~10% incidence in the disappearance of proteinuria following steroid pulses, it can be speculated that only a few patients with advanced IgAN, such as those with serum creatinine of >1.5 mg/dL, can achieve the disappearance of proteinuria following steroid pulses alone. In this regard, tonsillectomy combined with steroid pulse therapy can be more effective in patients with advanced IgAN, as suggested by a previous report [30], which found that renal outcome was better with tonsillectomy plus steroid pulses in IgAN patients, particularly in patients with serum creatinine of 1.5–2.0 mg/dL. Further studies are necessary to clarify the profiles of IgAN patients suited for treatment with tonsillectomy plus steroid pulses.

This study had several limitations. First, the follow-up period was too short to be able to assess several long-term

outcomes, i.e. renal function, incidence of relapse/recurrence of proteinuria, frequency of patients who need additional therapies, etc. Indeed, none of the patients were found to reach the end points. In this regard, the secondary end points established in this trial appeared inadequate in view of a short follow-up period. The primary end points used in this study (e.g. the disappearance of proteinuria and/or hematuria after 12 months) were surrogate markers, since the real hard end points should have represented long-term renal survival, such as the progression of renal disease or the development of ESRD. Nevertheless, many previous studies indicate that a marked reduction of proteinuria as an early response to the initial treatment ensures stable renal function after the cessation of treatment [14, 15, 17, 31, 32]. In addition to those studies that examined the relationship between the level of proteinuria after 12 months and the final renal outcome, Hirano *et al.* recently reported that, in the IgAN patients receiving 6 months of steroid therapy (Pozzi's protocol), the achievement of proteinuria <0.4 g/day after 12 months could be a therapeutic indicator for a favorable renal outcome [27]. Therefore, a superior antiproteinuric effect of tonsillectomy plus steroid pulses compared with steroid pulses alone could lead to better preservation of renal function in the long-term. Since it is crucially important whether tonsillectomy can protect IgAN patients from the progressive deterioration of renal function or the relapse/recurrence of proteinuria during a long-term follow-up, we are now in the process of a study to follow-up the present patients for 3 years.

Second, the incidence of the disappearance of proteinuria and/or hematuria after 12 months was not significantly different between the two groups. In our study, the disappearance of proteinuria with steroid pulses alone was more frequent than that extrapolated from the results of the previous reports [14, 15, 26]. This unexpectedly high incidence may have resulted in the failure to find statistical difference between the two groups. More patients should be included for a more definitive conclusion. Third, the pattern in the decrease of urinary protein excretion could not be analyzed using repeated ANOVA, because the data available at some time points were insufficient for analysis. Fourth, a few of the enrolled patients had to be excluded from the analysis, which may have reduced the effectiveness of randomization. Nevertheless, all the parameters at baseline were comparable between the two groups. This notion is supported by the results of the logistic regression analysis. Fifth, RAS inhibitors were administered only in nearly half of the patients in both groups at baseline. Therefore, some patients could show proteinuria <1 g/day at baseline, if all the patients were given RAS inhibitors prior to the trial. The mixed effect model revealed that a significantly greater antiproteinuric effect of tonsillectomy plus steroid pulses was independent from the use of RAS inhibitors at baseline. Nevertheless, the differential use of RAS inhibitors by different investigators could have potentially biased the results. Moreover, the impact of RAS inhibitors on patients who started RAS inhibitors during the trial was not clear. Finally, the study lacks sufficient information for the removed tonsil, such as, the frequency of presence of tonsils with infection as assessed by the presence of crypt abscesses or bacterial colonies in tonsillar tissues by macroscopic or microscopic inspection. It has been reported that the efficacy of tonsillectomy is difficult to predict on the basis of the appearance of tonsils or clinical episodes of recurrent tonsillitis [33]; thus, the relationship between the condition of removed tonsils and the outcome of proteinuria remains elusive.

In conclusion, tonsillectomy combined with steroid pulses had no additional benefit over steroid pulses alone in the disappearance of hematuria or the achievement of clinical remission. Although the antiproteinuric effect was significantly larger in the treatment with tonsillectomy plus steroid pulses than in steroid pulses alone, the difference was very subtle. Whether this marginal antiproteinuric effect improves renal outcome remains to be clarified.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

ACKNOWLEDGEMENTS

The study is registered with UMIN Clinical Trial Registry (registration number, C000000384), and was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research (Research on Intractable Disease) from the Ministry of Health, Labour and Welfare of Japan. We thank the study participants and the clinicians for their day-to-day clinical care. We thank Dr Homma for his valuable advice during manuscript preparation.

CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

REFERENCES

1. Koyama A, Igarashi M, Kobayashi M. Natural history and risk factors for immunoglobulin A nephropathy in Japan. Research Group on Progressive Renal Diseases. Am J Kidney Dis 1997; 29: 526–532
2. D'Amico G. Natural history of idiopathic IgA nephropathy: Role of clinical and histological prognostic factors. Am J Kidney Dis 2000; 36: 227–237
3. Nicholls KM, Fairley KF, Dowling JP *et al.* The clinical course of mesangial IgA associated nephropathy in adults. Q J Med 1984; 53: 227–250
4. Beukhof JR, Kardaun O, Schaafsma W *et al.* Toward individual prognosis of IgA nephropathy. Kindey Int 1986; 29: 549–556
5. Alamartine E, Sabatier JC, Guerin C *et al.* Prognostic factors in mesangial IgA glomerulonephritis: An extensive study with univariate and multivariate analysis. Am J Kidney Dis 1991; 18: 12–19.
6. Donadio JV, Bergstralh EJ, Offord KP *et al.* Clinical and histopathological associations with impaired renal function in IgA nephropathy. Mayo Nephrology Collaborative Group. Clin Nephrol 1994; 41: 65–71.
7. Bartosik LP, Lajoie G, Sugar L *et al.* Predicting progression in IgA nephropathy. Am J Kidney Dis 2001; 38: 728–735.
8. Syrjänen J, Mustonen J, Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 2000; 15: 34–42.

9. Li PK, Ho KK, Szeto CC *et al.* Prognostic indicators of IgA nephropathy in the Chinese—clinical and pathological perspectives. Nephrol Dial Transplant 2002; 17: 64–69
10. Daniel L, Saingra Y, Giorgi R *et al.* Tubular lesions determine prognosis of IgA nephropathy. Am J Kidney Dis 2000; 35: 13–20
11. Kobayashi Y, Hiki Y, Kokubo T *et al.* Steroid therapy during the early stage of progressive IgA nephropathy. A 10-year follow-up study. Nephron 1996; 72: 237–242
12. Julian B, Barker C. Alternate-day prednisone therapy in IgA nephropathy: preliminary analysis of a prospective, randomized, controlled trial. Contrib Nephrol 1993; 104: 198–206
13. Lai KN, Lai FM, Ho CP *et al.* Corticosteroid therapy in IgA nephropathy with nephrotic syndrome: a long-term controlled trial. Clin Nephrol 1986; 26: 174–180
14. Pozzi C, Bolasco PG, Fogazzi GB *et al.* Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet 1999; 353: 883–887
15. Pozzi C, Andrulli S, Del Vecchio L *et al.* Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol 2004; 15: 157–163
16. Rasche FM, Schwarz A, Keller F. Tonsillectomy does not prevent a progressive course in IgA nephropathy. Clin Nephrol 1999; 51: 147–152
17. Hotta O, Miyazaki M, Furuta T *et al.* Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis 2001; 38: 736–743
18. Xie Y, Nishi S, Ueno M *et al.* The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int 2003; 63: 1861–1867
19. Komatsu H, Fujimoto S, Hara S *et al.* Effect of tonsillectomy plus steroid pulse therapy on clinical remission of IgA nephropathy: a controlled study. Clin J Am Soc Nephrol 2008; 3: 1301–1307
20. Wang Y, Chen J, Wang Y *et al.* A meta-analysis of the clinical remission rate and long-term efficacy of tonsillectomy in patients with IgA nephropathy. Nephrol Dial Transplant 2011; 26: 1923–1931
21. Miura N, Imai H, Kikuchi S *et al.* Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy. Clin Exp Nephrol 2009; 13: 460–466
22. Appel GB, Waldman M. The IgA nephropathy treatment dilemma. Kidney Int 2006; 69: 1939–1944
23. Locatelli F, Vecchio LD, Pozzi C. IgA glomerulonephritis: beyond angiotensin-converting enzyme inhibitors. Nat Clin Pract Nephrol 2006; 2: 24–31
24. KDIGO Clinical Practice Guideline for Glomerulonephritis. Chapter 10: Immunoglobulin A nephropathy. Kidney Int Suppl 2012; 2: 209–217
25. Tomino Y, Sakai H. Clinical guidelines for immunoglobulin A (IgA) nephropathy in Japan, second version. Clin Exp Nephrol 2003; 7: 93–97
26. Hotta O. Use of corticosteroids, other immunosuppressive therapies, and tonsillectomy in the treatment of IgA nephropathy. Semin Nephrol 2004; 24: 244–255
27. Hirano K, Kawamura T, Tsuboi N *et al.* The predictive value of attenuated proteinuria at 1 year after steroid therapy for renal survival in patients with IgA nephropathy. Clin Exp Nephrol 2012; 17: 555–562
28. Matsuo S, Imai E, Horio M *et al.* Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982–992
29. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461–470
30. Sato M, Hotta O, Tomioka S *et al.* Cohort study of advanced IgA nephropathy: efficacy and limitations of corticosteroids with tonsillectomy. Nephron Clin Pract 2003; 93: c137–c145
31. Reich HN, Troyanov S, Scholey JW *et al.* Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. J Am Soc Nephrol 2007; 18: 3177–3183
32. Tatematsu M, Yasuda Y, Morita Y *et al.* Complete remission within 2 years predicts a good prognosis after methylprednisolone pulse therapy in patients with IgA nephropathy. Clin Exp Nephrol 2012; 16: 883–891
33. Matutani S, Honma R, Adachi M *et al.* Clinical observation of palatine tonsils with IgA nephropathy. Acta Otolaryngol Suppl 2004; 555: 58–61

Received for publication: 25.10.2013; Accepted in revised form: 17.1.2014

Clin Exp Nephrol (2013) 17:555–562
DOI 10.1007/s10157-012-0744-x

ORIGINAL ARTICLE

The predictive value of attenuated proteinuria at 1 year after steroid therapy for renal survival in patients with IgA nephropathy

Keita Hirano · Tetsuya Kawamura · Nobuo Tsuboi · Hideo Okonogi · Yoichi Miyazaki · Masato Ikeda · Masato Matsushima · Kazushige Hanaoka · Makoto Ogura · Yasunori Utsunomiya · Tatsuo Hosoya

Received: 5 September 2012 / Accepted: 13 November 2012 / Published online: 6 December 2012

Abstract
Background The relationship between the urinary protein excretion (UPE) initially achieved after steroid therapy and the long-term renal outcome of IgA nephropathy (IgAN) has not been clarified. We investigated the threshold UPE at 1 year after steroid therapy which predicts a favorable renal survival.
Methods We enrolled 141 IgAN patients who received 6 months of steroid therapy. The endpoint was defined as a 50 % increase in serum creatinine from baseline. The spline model was used to define the threshold UPE predicting renal survival.
Results Thirteen patients (9.2 %) reached the endpoint at a median follow-up of 3.8 years. When evaluating the relative hazard ratio (HR) of the UPE at 1 year for the endpoint, we found an inflection point at 0.40 g/day on the spline curve. The multivariate Cox model revealed that, in addition to the *Disappeared* category of UPE (range <0.30 g/day), the *Mild* category (range 0.30–0.39 g/day) was associated with more reduced risk of the endpoint [HR 0.02, 95 % confidence intervals (CI) 0.00–0.29] relative to the *Severe* category (range ≥1.00 g/day), whereas the *Moderate* category (range 0.40–0.99 g/day) was not. The estimated glomerular filtration rate <60 ml/min/1.73 m^2 was also an independent predictor of the endpoint. When renal survival was adjusted with pathological parameters in the Cox model, UPE <0.40 g/day was still an independent favorable predictor (HR 0.08, 95 % CI 0.01–0.45).
Conclusions In IgAN patients receiving 6 months of steroid therapy, the achievement of proteinuria <0.4 g/day at 1 year could be a therapeutic indicator for a favorable renal outcome.

Keywords Corticosteroid therapy · Proteinuria · Threshold · Clinical remission · Endocapillary hypercellularity · Tonsillectomy

Introduction

IgA nephropathy (IgAN), a major component of chronic glomerulonephritis, causes end-stage renal disease in up to 50 % of affected patients [1]. Although proteinuria has been considered one of the most important predictors of renal outcome [2–6], few studies have clarified what degree of proteinuria at an early phase after initial treatment predicts renal survival. Donadio et al. [7] showed a lower amount of proteinuria at 1 year after the introduction of treatment to be associated with a better renal survival. However, they did not define the proteinuria level predicting a favorable renal outcome.

Among the many clinical trials demonstrating the efficacy of steroid therapy for IgAN [8–10], a randomized controlled trial by Pozzi et al. [11, 12] clearly demonstrated that 6 months of steroid therapy significantly reduced the

Electronic supplementary material The online version of this article (doi:10.1007/s10157-012-0744-x) contains supplementary material, which is available to authorized users.

K. Hirano · T. Kawamura (✉) · N. Tsuboi · H. Okonogi · Y. Miyazaki · M. Ikeda · K. Hanaoka · M. Ogura · Y. Utsunomiya · T. Hosoya
Division of Kidney and Hypertension, Department of Internal Medicine, Jikei University School of Medicine,
3-25-8 Nishi-Shinbashi, Minato-Ku, Tokyo 105-8461, Japan
e-mail: kawatetu@coral.ocn.ne.jp

M. Matsushima
Division of Clinical Epidemiology, Research Center for Medical Science, Jikei University School of Medicine,
3-25-8 Nishi-Shinbashi, Minato-Ku, Tokyo 105-8461, Japan

risk of a 100 % increase in serum creatinine from the baseline compared to conventional therapy during a 5- or 10-year follow-up. They demonstrated that the steroid therapy induced the lowest level of proteinuria at 1 year of follow-up.

We herein aimed to define the target level of proteinuria at 1 year after initiating steroid therapy to establish a prognostic threshold for a favorable renal survival of IgAN patients.

Subjects and methods

Patients and study design

We collected the medical records from 169 patients with IgAN who received 6 months of steroid therapy between 2004 and 2010 in four affiliated hospitals of Jikei University School of Medicine, employing a historical cohort design. Four patients followed for <1 year after the introduction of steroid therapy were excluded. Another 24 patients who were recruited into a prospective randomized controlled trial were also excluded. Finally, the data obtained from 141 patients were analyzed to elucidate the renal outcome. The patients were followed up until April 2012 or the last day of serum creatinine measurement before April 2012. The cohort study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of Jikei University School of Medicine.

Definitions

The endpoint was defined as a 50 % increase in serum creatinine from baseline. Disappeared proteinuria or hematuria was defined as a urinary protein excretion (UPE) <0.3 g/day or having urinary sediment of red blood cells (U-RBC) <5/high power field (hpf). Clinical remission was defined as the disappearance of both proteinuria and hematuria. The estimated glomerular filtration rate (eGFR) was calculated by the Japanese eGFR equation based on age, sex and serum creatinine [13]. Uncontrolled hypertension was defined as arterial blood pressure (BP) ≥130/80 mmHg [14]. Smoking status was defined according to a report by Yamamoto et al. [15].

Treatment

The 6-month steroid therapy was previously reported by Pozzi et al. [11, 12], and was modified for Japanese patients as follows: the patients received 0.5 g of methylprednisolone intravenously for three consecutive days at the beginning of the steroid course and again 2 and 4 months later; they were also given oral prednisolone at a dose of 0.5 mg/kg every other day for 6 months. Some patients received a tonsillectomy for chronic tonsillitis complicated with IgAN just before the 6 months of steroid therapy. The patients were administered angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (RAAS inhibitors) and antiplatelet agents as needed.

Histology

To examine the impact of pathological changes on renal survival, renal biopsy data were obtained if a biopsy was performed within 1 year before corticosteroid therapy. All renal biopsy specimens were processed routinely for light microscopy. Sections were stained with hematoxylin and eosin and periodic acid–Schiff, together with silver methenamine and Masson's trichrome. Pathological variables were evaluated according to the Oxford classification [16]. "Histological grade (HG)" recently reported from the Special Study Group on Progressive Glomerular Disease in Japan was also adopted in this study [17]. Briefly, four histological grades, HG 1, HG 2, HG 3 and HG 4, were established corresponding to <25, 25–49, 50–74 and ≥75 % of glomeruli exhibiting cellular or fibrocellular crescents, global sclerosis, segmental sclerosis or fibrous crescents.

Statistical analyses

Normally distributed variables were expressed as the mean ± standard deviation (SD) and compared using the *t* test or one-way ANOVA. Nonparametric variables were expressed as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test, Kruskal–Wallis test, Spearman correlation or Friedman test. Categorical variables were expressed in percentages and compared using the chi-squared test.

To identify a threshold UPE at 1 year that predicts a favorable outcome, we first specified the median UPE for each decile. Second, using the highest decile as the referred category, the relative hazard ratios (HRs) adjusted by the baseline eGFR were plotted according to the specified median values of each decile. Third, quadratic splines were fitted to the relative HR with knots. The spline model is considered to be a smooth function that is sensitive to changes in the relationship between a predictor variable and an outcome across the range of the predictor [18]. The UPE was log-transformed for the spline analyses. The result of the threshold analysis was additionally ascertained by a receiver operating curve (ROC) analysis.

Renal survival was analyzed using the Kaplan–Meier method. In addition, it was analyzed in multivariate Cox regression models to explore the independent prognostic value of predictors. The variables with p value <0.1 in the

univariate analysis were selected as predictors for the multivariate model. The start point of follow-up was 1 year after steroid therapy in Cox–hazard models. Different relevant multivariate models were tested, obeying the standard statistical rules. The results were expressed as HR with 95 % confidence intervals (CI).

Values of $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed with IBM SPSS Statistics ver. 19.0 software (Chicago, IL, USA).

Results

Baseline characteristics and outcome

The clinical and pathological characteristics at baseline and the outcomes are presented in Table 1. The median initial proteinuria was 1.00 g/day, and the mean eGFR was 72.8 ml/min/1.73 m^2. During a median follow-up of 3.8 years (IQR 2.5–5.3), 13 patients (9.2 %) reached the endpoint. One hundred and eighteen patients (83.7 %), who underwent a renal biopsy within 1 year before the steroid therapy, had clinical backgrounds similar to the overall patients.

Changes in proteinuria during follow-up, and clinical remission rate at 1 year after steroid therapy

As shown in Fig. 1, the median values for UPE were significantly decreased at 6 months, 1 year and the last follow-up. The lowest level of UPE was seen at 1 year, with a 78.2 % (IQR 50.0–88.5 %) reduction of the UPE from baseline. At the 1 year follow-up, 49 patients (34.8 %) had reached clinical remission.

Table 1 Baseline characteristics and outcomes of the 141 patients analyzed in the study

Variables	Overall ($N = 141$)	Patients who received RBx within 1 year before treatment ($N = 118$)
Baseline features		
Age (years)	34 (26–43)	35 (27–43)
Female	72 (51.1)	58 (49.1)
Current smokers	34 (24.1)	27 (22.9)
BP ≥130/80 mmHg	43 (30.5)	40 (33.9)
UPE (g/day)	1.00 (0.65–1.70)	0.94 (0.63–1.67)
U-RBC		
≥30/hpf	77 (54.6)	66 (55.9)
5–29/hpf	58 (41.1)	46 (39.0)
<5/hpf	6 (4.3)	6 (5.1)
eGFR (ml/min/1.73 m^2)	72.8 ± 28.0	71.6 ± 28.7
eGFR <60 ml/min/1.73 m^2	51 (36.2)	45 (38.1)
Concurrent treatments		
Tonsillectomy	68 (48.2)	48 (40.7)
RAAS inhibitors	62 (44.0)	52 (44.1)
Oxford classification		
M1	–	38 (32.2)
E1	–	74 (62.7)
S1	–	96 (81.4)
T0/T1/T2	–	93/20/5 (78.8/16.9/4.2)
Ext, present	–	108 (91.5)
HG[a]		
HG1/HG2/HG3 + 4	–	32/56/30 (27.1/47.5/25.4)
Follow-up		
Period (years)	3.8 (2.5–5.3)	3.8 (2.3–5.3)
Outcome	13 (9.2)	10 (8.5)

Values are presented as numbers (%), medians (IQR) or mean ± SD

RBx renal biopsy, *BP* blood pressure, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *eGFR* estimated glomerular filtration rate, *RAAS* renin–angiotensin–aldosterone system, *M* mesangial hypercellularity, *E* endocapillary hypercellularity, *S* segmental sclerosis, *T* tubulointerstitial atrophy/fibrosis, *Ext* extracapillary lesion, *HG* histological grade

[a] According to Ref. [17]

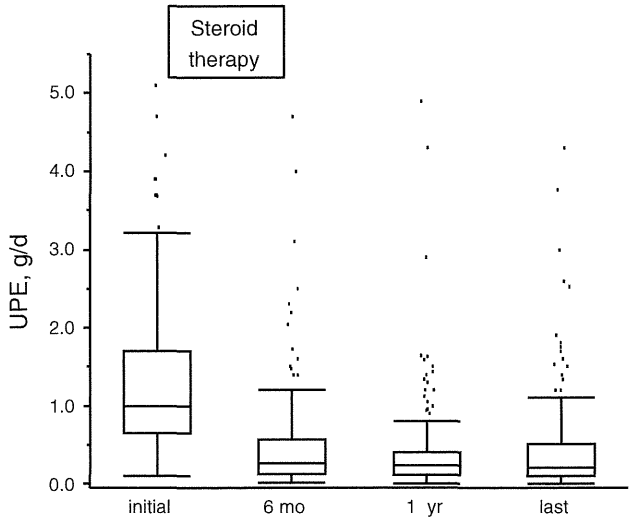

Fig. 1 Changes in proteinuria at baseline, 6 months, 1 year and at the last follow-up. The *lines* in the middle and those delimiting the *boxes* indicate the median, 25th and 75th percentile values, respectively. The *whiskers* at the ends of the boxes are lines that show the distance from the end of the box to the largest and smallest observed values that are <1.5 box-length from either end. *Dots* indicate outliers

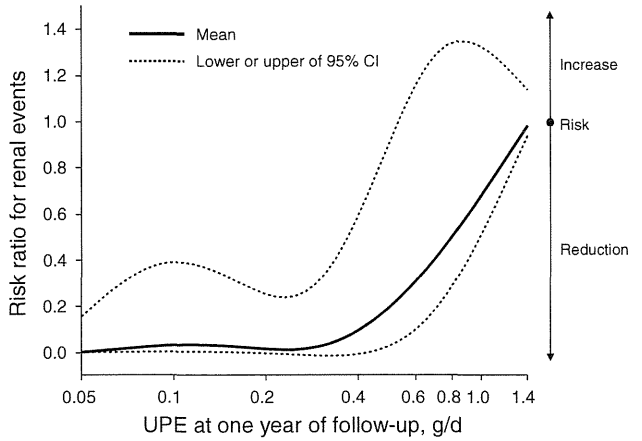

Fig. 2 Risk ratio for the endpoint associated with the UPE at the 1-year follow-up. Plots of the risk ratios and 95 % confidence intervals adjusted for the baseline eGFR for the endpoint using the level of proteinuria at the 1-year follow-up examination as the continuous variable are shown (reference: the highest decile, the median of which was 1.44 g/day). The degree of proteinuria was log transformed

Threshold proteinuria after steroid therapy predicting the renal outcome

We further explored what degree of UPE at 1 year after steroid therapy was associated with renal survival. The spline model of UPE at 1 year was used to predict the relative HR of the endpoint (Fig. 2). The spline curve showed that the relative HRs were equivalent in the range of UPE under 0.4 g/day, but increased as the UPE increased beyond this value, indicating an inflection at approximately 0.40 g/day. Furthermore, the ROC of UPE at 1 year indicated that the optimal cutoff for predicting an unfavorable outcome was 0.40 g/day; the area under the curve and p value were 0.78 and <0.001, respectively.

Categorization of UPE at 1 year after steroid therapy

"Disappeared proteinuria" was previously defined as UPE <0.3 g/day [19] and UPE >1.0 g/day was generally associated with following deterioration of renal function [4–6]. Based on the results from our threshold analysis (0.4 g/day) and the above two values, we divided the UPE at 1 year of follow-up into four categories; *Disappeared* category (<0.30 g/day), *Mild* category (0.30–0.39 g/day), *Moderate* category (0.40–0.99 g/day) and *Severe* category (≥1.00 g/day). The clinical parameters were not significantly different among the four categories, except for the baseline proteinuria (Table 2).

Renal survival according to the UPE category at 1 year by Kaplan–Meier analysis and multivariate Cox model

The results of the univariate time-dependent analyses by the Kaplan–Meier method are shown in Fig. 3. Patients in the *Disappeared* and *Mild*categories showed significantly better renal survival compared to the *Moderate* or *Severe* categories (log-rank, $p < 0.05$ for both strata), whereas there was no such difference between the *Moderate* and *Severe* categories (log-rank, $p > 0.2$).

The clinical predictors for the endpoint in the Cox–hazard model are presented in Table 3. Relative to the *Severe* category in the multivariate model, the *Disappeared* and *Mild* categories were favorable predictors, with risk reduction of approximately 90 and 70 %, respectively, whereas the *Moderate* category was not associated with renal survival. In contrast, eGFR <60 ml/min/1.73 m^2 at baseline was an unfavorable predictor. Clinical remission, as well as a U-RBC <5/hpf at 1 year after steroid therapy, was not associated with renal survival in the univariate model.

Significance of UPE <0.4 g/day as a predictor when the renal survival was adjusted for pathological parameters

The predictive value of UPE <0.4 g/day at 1 year for the outcome when adjusted for pathological parameters in the Oxford classification and "HG" from Japan was examined by the univariate and multivariate models and the data are summarized in Table 4. The univariate analysis revealed that the existence of endocapillary hypercellularity (E1) was significantly associated with a preferable renal survival

Table 2 Baseline characteristics according to the category of proteinuria at 1 year of follow-up

Variables	Category of UPE at 1 year of follow-up (g/day)				*p* value
	Disappeared (<0.3)	*Mild* (0.30–0.39)	*Moderate* (0.40–0.99)	*Severe* (≥1.00)	
Number of patients	80	23	22	16	
Age (years)	35 (26–44)	30 (25–42)	32 (26–36)	35 (26–42)	>0.2
Female	39 (48.8)	11 (47.8)	12 (54.5)	9 (56.3)	>0.2
Current smokers	18 (22.5)	5 (21.7)	6 (27.3)	5 (31.3)	>0.2
BP >130/80 mmHg	25 (31.3)	9 (39.1)	5 (22.7)	4 (25.0)	>0.2
UPE (g/day)	0.82 (0.57–1.28)	0.80 (0.64–2.17)	1.58 (0.97–2.28)	1.90 (1.25–2.80)	<0.001[#]
U-RBC >30/hpf	48 (60.0)	12 (52.2)	8 (36.4)	9 (56.3)	>0.2
eGFR (ml/min/1.73 m^2)	75.1 ± 27.1	73.7 ± 29.1	68.2 ± 29.5	66.3 ± 29.1	>0.2
eGFR <60	25 (31.3)	10 (43.5)	10 (45.5)	6 (37.5)	>0.2
Tonsillectomy	40 (50.0)	10 (43.5)	12 (54.5)	6 (37.5)	>0.2
RAAS inhibitors	35 (43.8)	9 (39.1)	11 (50.0)	7 (43.8)	>0.2

Values are presented as numbers (%), medians (IQR) or mean ± SD

BP blood pressure, *UPE* urinary protein excretion, *U-RBC* urinary sediments of red blood cells, *eGFR* estimated glomerular filtration rate.
[#] $p < 0.05$

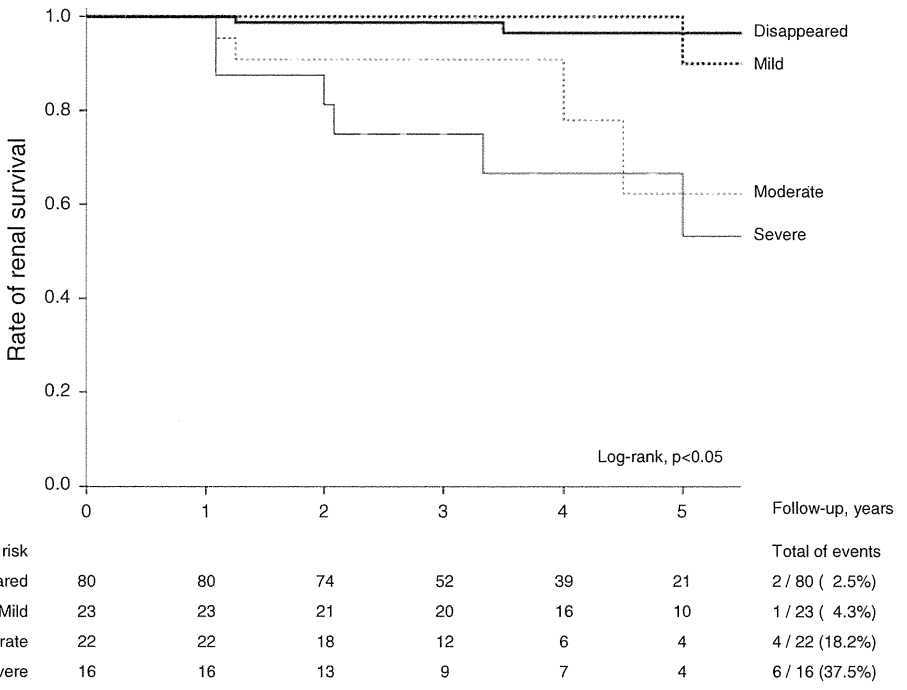

Fig. 3 Renal survival determined by the Kaplan–Meier method, stratified by the category of UPE at 1 year after 6 months of steroid therapy. These unadjusted curves demonstrate that, in addition to the *Disappeared* category, the *Mild* category showed significantly better renal survival compared to that in the *Moderate* or *Severe* categories (log-rank, $p < 0.05$ for both strata)

relative to the absence of endocapillary hypercellularity (E0). T1 or T2 tubular atrophy/interstitial fibrosis was significantly associated with impaired renal survival relative to T0. In addition, HG 2 was significantly associated with favorable renal outcome relative to HG 3 plus HG 4. Although HG 1 was not significantly associated with favorable outcome, no event was observed in 32 patients of HG 1.

The multivariate model A and model B in Table 4 examined the predictive power of UPE <0.4 g/day at 1 year for renal survival after adjusting for pathological predictors in the Oxford classification and HG, respectively. A UPE <0.4 g/day at 1 year was selected as an independent predictor in both model A and model B.

Adverse effects

Serious adverse events were not observed during the study period. Although three patients developed type 2 diabetes during the 6 months of treatment, they showed normal levels of glycosylated HbA1 at 1 year with diet therapy alone. Seven patients developed infections during the