Chiba Medical J. 100E：7－12, 2024
doi:10.20776/S03035476-100E-1-P7

〔Chiba Medical Society Award Review〕

Paradigm change in treatments for ANCA-associated vasculitis

Shunsuke Furuta

Department of Allergy and Clinical Immunology, Chiba University Hospital, Chiba 260-8677.

（Received October 23, 2023, Accepted October 31, 2023, Published February 10, 2024.）

Abstract

In the 2010s, the standard therapies for induction of remission in anti-neutrophil cytoplasm antibody（ANCA）-associated vasculitis were high-dose glucocorticoids combined with either cyclophosphamide or rituximab. These therapies resulted in high remission rates but were associated with a significant risk of infections. Consequently there was an unmet medical need to reduce the glucocorticoid dose and glucocorticoid-related side effects. Three pivotal trials, LoVAS, PEXIVAS, and ADVOCATE, were undertaken to address this need. The LoVAS trial, conducted in Japan, demonstrated that a reduced-dose glucocorticoid regimen was not inferior to the conventional high-dose glucocorticoid regimen, and resulted in a significant decrease in adverse events, especially serious infections, without compromising efficacy. The PEXIVAS trial in patients with severe glomerulonephritis also showed that a rapid tapering of glucocorticoid dose was as effective and safer than the conventional high-dose glucocorticoid regimen. Lastly, the ADVOCATE trial evaluated avacopan, a C5a receptor inhibitor, and demonstrated its potential to reduce the glucocorticoid doses for induction of remission. In the avacopan group, the dose of glucocorticoid was limited to less than 20 mg/day of prednisolone within four weeks, separate from methylprednisolone pulse therapy. In conclusion, these trials collectively signaled a paradigm shift in the treatment of ANCA-associated vasculitis and provided a clear message that reduced-dose glucocorticoid regimens were as effective as the conventional high-dose glucocorticoid regimens and were associated with a decrease in treatment-related adverse events and improved patient outcomes. Based on the results of these three clinical trials the updated guidelines in the 2020s now recommend these reduced-dose glucocorticoid regimens.

***Key words*: ANCA-associated vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis, rituximab, glucocorticoids**

Address correspondence to Dr. Shunsuke Furuta.
Department of Allergy and Clinical Immunology, Chiba University Hospital, 1-8-1, Inohana, Chuou-ku, Chiba 260-8677, Japan.
Phone: +81-43-226-2198. Fax: +81-43-226-2199.
E-mail: shfuruta@chiba-u.jp

Ⅰ. Introduction

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) is characterized by a small to medium-size vasculitis and the presence of circulating ANCA. Myeloperoxidase (MPO)-ANCA is the predominant serotype in MPA, while proteinase 3 (PR3)-ANCA is usually found in GPA. Based on clinical trials carried out in the 2010's, the standard therapies for induction of remission in ANCA-associated vasculitis were high-dose glucocorticoids combined with either cyclophosphamide or rituximab[1,2]. Similar to other countries, the 2017 Japanese guideline clearly recommended the combination of high-dose glucocorticoids and either cyclophosphamide or rituximab for first-line therapy of ANCA-associated vasculitis[3]. Those therapies proved effective with high remission rates of around 90% in the daily clinical setting[4,5], although the cumulative survival rate at five years remained low at 80%[6]. The most frequent cause of death was infections due to the immunosuppressive therapies, especially high-dose glucocorticoids. In addition to infections, the glucocorticoids were associated with various side effects, such as osteoporosis, peptic ulcers, myopathy, and cataracts. Although those side effects are not related directly to mortality, they significantly decrease the quality of life of patients.

In the 2010s there was an unmet need in the clinical practice of ANCA-associated vasculitis to reduce the dose of glucocorticoids and associated side effects. As shown in Table 1, three clinical trials have been conducted recently to resolve this unmet need[7-9], with the guidelines having been updated based on the results of these trials.

Ⅱ. The LoVAS trial

The author (SF) and his collaborators conducted the LoVAS trial[7], a multi-center, open-label, randomized, noninferiority clinical trial that compared the efficacy and adverse events between a reduced-dose glucocorticoids plus rituximab regimen and the standard high-dose glucocorticoids plus rituximab regimen. A total of 140 Japanese patients with newly diagnosed MPA/GPA without severe glomerulonephritis (estimated glomerular filtration rate [eGFR] <15mL/min) were enrolled. In the reduced-dose glucocorticoid group, prednisolone was started at a dose of 0.5 mg/kg/day and tapered off at 5 months, whereas in the high-dose glucocorticoid group, prednisolone was started at the conventional high-dose of 1.0 mg/kg/day, and then reduced to 10 mg/body/day by 5 months. Forty-nine patients in the reduced-dose group (71.0%) and

Table 1 Summary of the LoVAS, PEXIVAS, and ADVOCATE trials

	LoVAS trial (Furuta et al. JAMA 2021)[7]	**PEXIVAS trial (Walsh et al. NEJM 2020)**[8]	**ADVOCATE trial (Jayne et al. NEJM 2021)**[9]
Subjects	New onset, Japanese (n=140)	New onset/relapsing, Severe nephritis (n=704)	New onset/relapsing (n=340)
ANCA subtypes; MPO: PR3	85%: 15%	60%: 40%	57%: 43%
Cumulative dose of prednisolone at 6 months[a]	Median 1318 mg vs. 4151 mg	1995 mg (+pulse therapy) vs 3920 mg (+pulse therapy)	Mean 1348 mg vs. 3654 mg
Primary endpoint	6 month remission 71% vs. 69%	Death or ESKD 28% vs. 25%	6 month remission 72% vs. 70%
Serious infections	7% vs. 20%	27% vs. 33%	13% vs. 15%

ANCA, anti-neutrophil cytoplasm antibody; MPO, myeloperoxidase; ESKD, end stage kidney disease.

[a]The doses actually used are shown for the LoVAS and ADVOCATE trials. The doses calculated by the protocol are shown for the PEXIVAS trial.

45 in the high-dose group (69.2%) achieved remission at 6 months with the protocolized treatments, the primary endpoint. The difference between the two groups met the criterion for noninferiority (p<0.01 for noninferiority). In addition, the incidence of serious adverse events (SAEs) were less frequent in the reduced-dose group (18.9%) compared to that in the high-dose group (36.9%) (p=0.02). Serious infections were also significantly less frequent in the reduced-dose group (7.2%) than in the high-dose group (20.0%) (p=0.04). In summary, the new reduced-dose glucocorticoid regimen in the LoVAS trial was as effective as the conventional high-dose glucocorticoid regimen and markedly reduced adverse events.

The long-term follow-up results of the LoVAS trial have recently been published[10]. Of the patients who achieved the primary endpoint, relapse-free survival rates at 24 months were not statistically different between the reduced-dose (89.8%) and high-dose (90.5%) groups (p=0.83). However, SAEs were still less frequent in the reduced-dose group (27.5%) than in the high-dose group (46.2%) at 24 months (p=0.02). These results confirmed the long-term efficacy of the reduced-dose glucocorticoid regimen.

A limitation of the LoVAS trial was that the trial only included Japanese participants and it is well-known that there are regional differences in ANCA-associated vasculitis. Indeed, the trial participants was biased towards MPO-ANCA positivity (85.8%), a trend consistent with previously reported features of Japanese patients[11]. Previous studies have also reported that ANCA subtypes are not associated with remission induction rates[12-15], while PR3-ANCA positivity is associated with a higher relapse risk compared to that of MPO-ANCA positivity[16]. However, the reproducibility of the trial results, especially relapse, is still unclear in PR3-ANCA dominant populations such as Europe and North America.

Ⅲ. The PEXIVAS trial

The PEXIVAS trial[8] was an international, open-label, randomized clinical trial, which used a 2-by-2 factorial design to evaluate plasma exchange and a rapid glucocorticoid tapering regimen in newly diagnosed or relapsing MPA/GPA patients with severe glomerulonephritis (eGFR <50 mL/min). After receiving methylprednisolone pulse therapy, prednisolone was started at a dose of 1.0 mg/kg/day in both treatment groups in combination with either cyclophosphamide or rituximab (the choice was made by the local investigator before randomization). The dose of prednisolone was then tapered to 5 mg/body/day by 15 weeks in the rapid-tapering group, while prednisolone was tapered to 5 mg/body/day by 23 weeks in the standard-tapering group. In addition, patients in the plasma exchange group received plasma exchange according to the results of randomization. A total of 704 patients were enrolled in the study. The composite outcome of death or end stage kidney disease (ESKD) was the primary endpoint of the PEXIVAS trial and occurred in 27.9% of the rapid-tapering group and 25.5% of the standard-tapering group. This difference (2.3%; 90%CI, -3.4 to 8.0) between the two groups met the criterion for the noninferiority margin (11%). Although the frequency of SAEs during the overall trial period was similar between the two groups, serious infections at one year were less frequent in the rapid-tapering group (27.2%) than in the standard-tapering group (33.0%) (incidence rate ratio, 0.69; 95% CI, 0.52 to 0.93). In summary, the trial demonstrated that the new rapid glucocorticoid tapering regimen had equal efficacy and better safety profiles compared to the conventional high-dose glucocorticoid regimen in MPA/GPA patients with severe glomerulonephritis.

The PEXIVAS trial also investigated whether plasma exchange influenced the composite endpoint of death and ESKD and showed that the incidence in the plasma exchange group (28.4%) was not superior to that observed in the non-plasma exchange group (31.0%) (p=0.27). However, the same research group published a meta-analysis paper on plasma exchange in ANCA-associated vasculitis[17], that integrated and analysed data from seven trials including 999 patients, mainly from the PEXIVAS trial. This analysis showed that plasma exchange reduced the risk of ESKD at 12

months, leading the research group to conclude that additional plasma exchange should be considered for MPA/GPA patients with severe glomerulonephritis.

Ⅳ. The ADVOCATE trial

The ADVOCATE trial[9] was an international, double-blind, randomized clinical trial that evaluated avacopan, a new C5a receptor inhibitor, for treatment of ANCA-associated vasculitis. A total of 331 newly diagnosed or relapsing MPA/GPA patients were enrolled. The patients received either prednisolone (initial dose of 1 mg/kg/day) or avacopan. Both treatment groups also received either cyclophosphamide or rituximab (chosen by the local investigator before randomization). In the avacopan group, less than 20 mg/day of prednisolone was allowed until 4 weeks, with the cumulative mean dose of prednisolone during the 12-month period of the trial being 1348 mg in the avacopan group and 3654 mg in the prednisolone group. The ADVOCATE trial had two primary endpoints: 1) remission at 6 months was achieved in 72.3% of the avacopan group and 70.1% of the prednisolone group (p<0.01 for noninferiority), and 2) sustained remission at 12 months, occurred in 65.7% of the avacopan group and 54.9% in the prednisolone group (p<0.01 for superiority). For safety profiles, serious infections occurred in 13.3% of the avacopan group and 15.2% of the prednisolone group. In summary, the ADVOCATE trial showed that avacopan reduced the dose of glucocorticoids for induction of remission in MPA/GPA.

Although the original aim of the trial was to establish glucocorticoid-free therapy by using avacopan, the majority of the trial participants (87.3%) actually received glucocorticoids within the allowance of the trial protocol. Therefore, the clinical outcomes of glucocorticoid-free therapy with avacopan remain unclear.

Ⅴ. Conclusion and perspective

The three trials described in this paper had many differences in trial design, participants, and treatment protocols. However, they shared the concept that the dose of glucocorticoids during induction of remission could be reduced compared to that used in the conventional high-dose glucocorticoid regimen. Indeed, based on the results of these three trials the updated guidelines in the 2020s recommend using the reduced-dose glucocorticoid regimen rather than the conventional high-dose glucocorticoid regimen[18,19]. The treatment paradigm for ANCA-associated vasculitis has therefore changed, and the increased use of the new reduced-dose glucocorticoid regimens would be expected to reduce treatment-related adverse events and result in better patient outcomes.

Financial support

The author did not receive financial support relevant to this work. The content is solely the responsibility of the author.

Conflict of interest

The author reports receiving lecture fees from Chugai Pharma (Roche group), Asahi Kasei Pharma, Eisai, Daiichi Sankyo, and Kissei Pharma and a consulting fee from Asahi Kasei Pharma, all of which were unrelated to this work. No other potential conflict of interest relevant to this article is reported.

Ethical approval

Not applicable.

Data availability

Not applicable.

Acknowledgements

The author thanks Prof. Hiroshi Nakajima for critically reading this manuscript.

References

1）Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, Hellmich B, Holle JU, Laudien M, Little MA, Luqmani RA, Mahr A, Merkel PA, Mills J, Mooney J, Segelmark M, Tesar V, Westman K, Vaglio A, Yalçındağ N, Jayne DR, Mukhtyar C.（2016）EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 75, 1583-94.

2）Ntatsaki E, Carruthers D, Chakravarty K, D'Cruz D, Harper L, Jayne D, Luqmani R, Mills J, Mooney J, Venning M, Watts RA; BSR and BHPR Standards, Guidelines and Audit Working Group.（2014）BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. Rheumatology（Oxford）53, 2306-9.

3）Harigai M, Nagasaka K, Amano K, Bando M, Dobashi H, Kawakami T, Kishibe K, Murakawa Y, Usui J, Wada T, Tanaka E, Nango E, Nakayama T, Tsutsumino M, Yamagata K, Homma S, Arimua Y.（2019）2017 Clinical practice guidelines of the Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis for the management of ANCA-associated vasculitis. Mod Rheumatol 29, 20-30.

4）Jayne D.（2009）Treatment of ANCA-associated systemic small-vessel vasculitis. APMIS 127, 3-9.

5）Smith RM, Jones RB, Guerry MJ, Laurino S, Catapano F, Chaudhry A, Smith KG, Jayne DR.（2012）Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 64, 3760-9.

6）Furuta S, Chaudhry AN, Hamano Y, Fujimoto S, Nagafuchi H, Makino H, Matsuo S, Ozaki S, Endo T, Muso E, Ito C, Kusano E, Yamagata M, Ikeda K, Kashiwakuma D, Iwamoto I, Westman K, Jayne D.（2014）Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. J Rheumato 41, 325-33.

7）Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, Umibe T, Kono H, Kurasawa K, Kita Y, Matsumura R, Kaneko Y, Ninagawa K, Hiromura K, Kagami SI, Inaba Y, Hanaoka H, Ikeda K, Nakajima H; LoVAS Collaborators.（2021）Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. JAMA 325, 2178-87.

8）Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, Hawley CM, Khalidi N, Floßmann O, Wald R, Girard LP, Levin A, Gregorini G, Harper L, Clark WF, Pagnoux C, Specks U, Smyth L, Tesar V, Ito-Ihara T, de Zoysa JR, Szczeklik W, Flores-Suárez LF, Carette S, Guillevin L, Pusey CD, Casian AL, Brezina B, Mazzetti A, McAlear CA, Broadhurst E, Reidlinger D, Mehta S, Ives N, Jayne DRW; PEXIVAS Investigators.（2020）Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. N Engl J Med 382, 622-31.

9）Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group.（2021）Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med 384, 599-609.

10）Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, Umibe T, Kono H, Kurasawa K, Kita Y, Matsumura R, Kaneko Y, Ninagawa K, Hiromura K, Kagami SI, Inaba Y, Hanaoka H, Ikeda K, Nakajima H; LoVAS collaborators.（2023）Reduced-dose versus high-dose glucocorticoids added to rituximab on remission induction in ANCA-associated vasculitis: predefined 2-year follow-up study. Ann Rheum Dis ard-2023-224343. doi: 10.1136/ard-2023-224343. Online ahead of print.

11）Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, Hashimoto H, Nunoi H.（2011）Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. Rheumatology（Oxford）50, 1916-20.

12）Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR; European Vasculitis Study Group.（2010）Rituximab versus cyclophosphamide in ANCA-associatedrenalvasculitis. N Engl J Med 363, 211-20.

13）Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group.（2010）Rituximab versus cyclophosphamide for ANCA-associatedvasculitis. N Engl J Med 363, 221-32.

14）De Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, Luqmani R, Pusey CD, Rasmussen N, Sinico RA, Tesar V, Vanhille P, Westman K, Savage CO; EUVAS（European Vasculitis Study Group）.（2009）Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. Ann Intern Med 150, 670-80.

15）Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, Cid MC, Dahlsveen K, de Zoysa J, Espigol-Frigolé G, Lanyon P, Peh CA, Tesar V, Vaglio A, Walsh M, Walsh D, Walters G, Harper L, Jayne D; European Vasculitis Study Group（EUVAS）.（2019）Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. Ann Rheum Dis 78, 399-405.

16）Walsh M, Flossmann O, Berden A, Westman K, Höglund P, Stegeman C, Jayne D; European Vasculitis Study Group.（2012）Risk factors for relapse of anti-neutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 64, 542-8.

17）Walsh M, Collister D, Zeng L, Merkel PA, Pusey CD, Guyatt G, Au Peh C, Szpirt W, Ito-Hara T, Jayne

DRW; Plasma exchange and glucocorticoid dosing for patients with ANCA-associated vasculitis BMJ Rapid Recommendations Group. (2022) The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ 25,376:e064604. doi: 10.1136/bmj-2021-064604.

18) Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, Holle JU, Hollinger N, Karadag O, Kronbichler A, Little MA, Luqmani RA, Mahr A, Merkel PA, Mohammad AJ, Monti S, Mukhtyar CB, Musial J, Price-Kuehne F, Segelmark M, Teng YKO, Terrier B, Tomasson G, Vaglio A, Vassilopoulos D, Verhoeven P, Jayne D. (2023) EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis ard-2022-223764. doi: 10.1136/ard-2022-223764. Online ahead of print.

19) Harigai M, Narita I, Suda T. ANCA-associated vasculitis clinical practice guideline (2023). Tokyo: SHINDAN TO CHIRYO SHA [published in Japanese]