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Obinutuzumab in Patients With Active Lupus Nephritis: A Meta-Analysis

To the Editor:

Lupus nephritis (LN) is the most predominant severe organ-threatening complication of systemic lupus erythematosus and remains a significant cause of morbidity and mortality despite progress in therapeutic strategies. Treatment aims to preserve renal function and prevent the need for kidney replacement therapy while reducing therapeutic effects.[1,2] Although immunosuppressive medications are frequently used to treat active LN, these are associated with significant toxicity and variable response rates also. From the last few years, obinutuzumab, a type II anti-CD20 monoclonal antibody, has become an appropriate therapeutic choice because of its improved B-cell depletion properties and potential for better clinical results.[3] According to a recent clinical trial, obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, greatly increases the complete renal response rate for patients receiving conventional treatment alone.[4] The safety profile of obinutuzumab must be taken into account in addition to its effectiveness. It emphasizes the need of weighing the benefits and disadvantages of its use. By combining data from randomized controlled trials (RCTs), our meta-analysis aims to evaluate the safety and efficacy of obinutuzumab in patients

Table 1. Baseline characteristics of included trials.

Study	Patients included			Age (yrs)		Female		Serum creatinine level		Estimated glomerular filtration rate		Urinary protein-to-creatinine ratio	
	Obinutuzumab		Placebo	Obinutuzumab	Placebo	Obinutuzumab		Obinutuzumab	Placebo	Obinutuzumab	Placebo	Obinutuzumab	Placebo
	N		N	Mean (SD)	Mean (SD)	n (%)		Mean	Mean	Mean	Mean	Mean	
REGENCY 2025	135		136	33.0 (10.5)	32.7 (10.0)	114 (84.4)		0.79	0.74	107	109	2.13	
NOBILITY 2021	64		61	33.1 (9.8)	31.9 (10.1)	55 (87)		0.87	0.8	102	102.1	3.3	

The authors have no conflicts of interest to declare.
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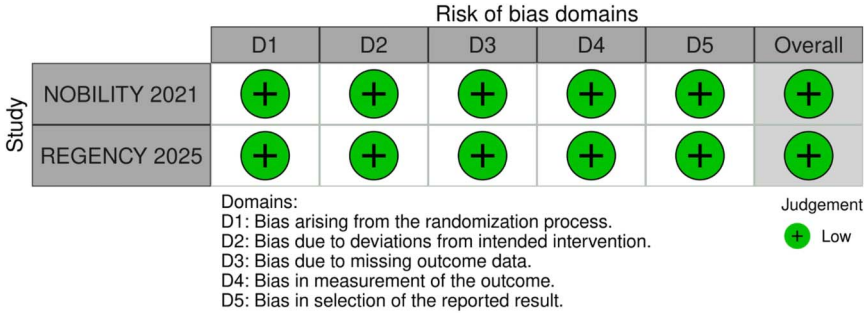

FIGURE 1. Risk of bias analysis of included trials.

with active lupus nephritis and comprehend its function in causing renal remission, lowering disease activity, and minimizing adverse events.

This meta-analysis was conducted as per the guidelines set by the Preferred Reporting for Systematic Review and Meta-Analysis.[5] A search of extensive databases, including Pubmed, Embase, Cochrane (Central), was conducted from their inception until March 2, 2025. The aim was to identify randomized controlled trials comparing obinutuzumab with placebo, both in combination with standard therapy (mycophenolate mofetil + prednisone) in patients diagnosed with active lupus nephritis. To manage duplicates, screen, and eliminate repeated studies from our literature search, we used Rayyan AI software. Two reviewers independently screened the abstract and titles to filter out irrelevant articles, and a third reviewer settled any conflicts. The complete search methodology and results are given in **Supplemental Digital Content 1** (see **Table S1**, http://links.lww.com/AJT/A224). Inclusion criteria required studies to (1) RCTs evaluating obinutuzumab plus standard therapy versus placebo plus standard therapy, (2) included adults aged 18–75 years with biopsy confirming active lupus nephritis (class III or IV, with or without Class V disease), (3) assessed at least 1 outcome related to complete kidney response, defined by a urinary protein-to-creatinine ratio <0.5, an eGFR of at least 85% of baseline, and absence of treatment failure, rescue therapy, death or early withdrawal. Exclusion criteria included nonrandomized studies, single-arm trials, case reports, observational studies, and abstracts. The quality of study was assessed using the Cochrane Risk of Bias Tool (RoB 2.0).[6] Statistical analyses were performed using Revman 5.4, using mean difference (MD) and 95% confidence intervals (CI). We analyzed dichotomous outcomes, using both risk ratios (RR) and odds ratios (OR) with 95% CI to provide a comprehensive assessment of treatment effects.

Two RCTs meeting the predefined inclusion criteria were included in qualitative and quantitative analyses.[3,4] These RCTs reported data from 396 patients with active proliferative lupus nephritis (obinutuzumab =198 patients, placebo = 198 patients). Multiple countries participated in the studies including United States, Canada, Israel, Latin American, European, and Asian countries. The mean age of patients was 32.02 ($\pm$10.29) years (Table 1). The 2 RCTs evaluated using the ROB 2 tool showed low risk of bias (Figure 1).

The pooled analysis showed that treatment with obinutuzumab resulted in a significantly higher rate of complete renal response (Figure 2A) compared with placebo [RR = 1.43, 95% CI (1.10–1.87), P = 0.82]. The incidence of any adverse events (Figure 2B) was higher in the obinutuzumab group than in placebo, but the difference was not statistically significant [RR = 1.07, 95% CI (1.00–1.14), P = 0.43]. Serious adverse events (Figure 2C) occurred in a similar proportion of patients across both groups, with no statistically significant differences observed [RR = 1.28, 95% CI (0.60–2.75), P = 0.03]. The mortality rates (Figure 2D) were comparable between the 2 groups, with no meaningful difference between obinutuzumab and placebo [RR = 0.67, 95% CI (0.11–4.07), P = 0.19]. The incidence of gastroenteritis (Figure 2E) was higher in the obinutuzumab group than in placebo, although the difference was not statistically significant [RR = 0.73, 95% CI (0.24–2.17), P = 0.31].

This meta-analysis considered the effectiveness and safety of obinutuzumab in active patients with proliferative lupus nephritis. The combination of 2 randomized controlled trials involving 396 patients showed that obinutuzumab significantly raised the complete renal response rate over placebo. Adverse events were more common in the group that received obinutuzumab, but there were no statistically significant differences in serious adverse events or mortality rates between groups.

The result of a considerably higher rate of complete renal response in the obinutuzumab arm [RR = 1.43, 95% CI (1.10–1.87)] is consistent with earlier literature emphasizing the effectiveness of anti-CD20 monoclonal antibodies in lupus nephritis.[3] The REGENCY trial also found obinutuzumab to enhance renal outcomes when used with conventional therapy.[4] Another research conducted by Furie et al (2022) also showed increased renal remission rates with obinutuzumab than with placebo.[2] A systematic review by Davidson et al[7] (2021) also confirms the use of B-cell depletion in the therapy of lupus nephritis with improved renal outcomes using targeted biologic drugs. These findings indicate that obinutuzumab could offer an effective treatment alternative for patients with lupus nephritis that do not respond well to traditional immunosuppressive treatment.[8]

In terms of safety, even though adverse effects were more frequent in the obinutuzumab group, the difference was not statistically significant. This concurs with previous research that although obinutuzumab adds the risk of infection and infusion reactions, it does not result in an elevated risk of life-threatening adverse events.[2,4] The serious adverse events were

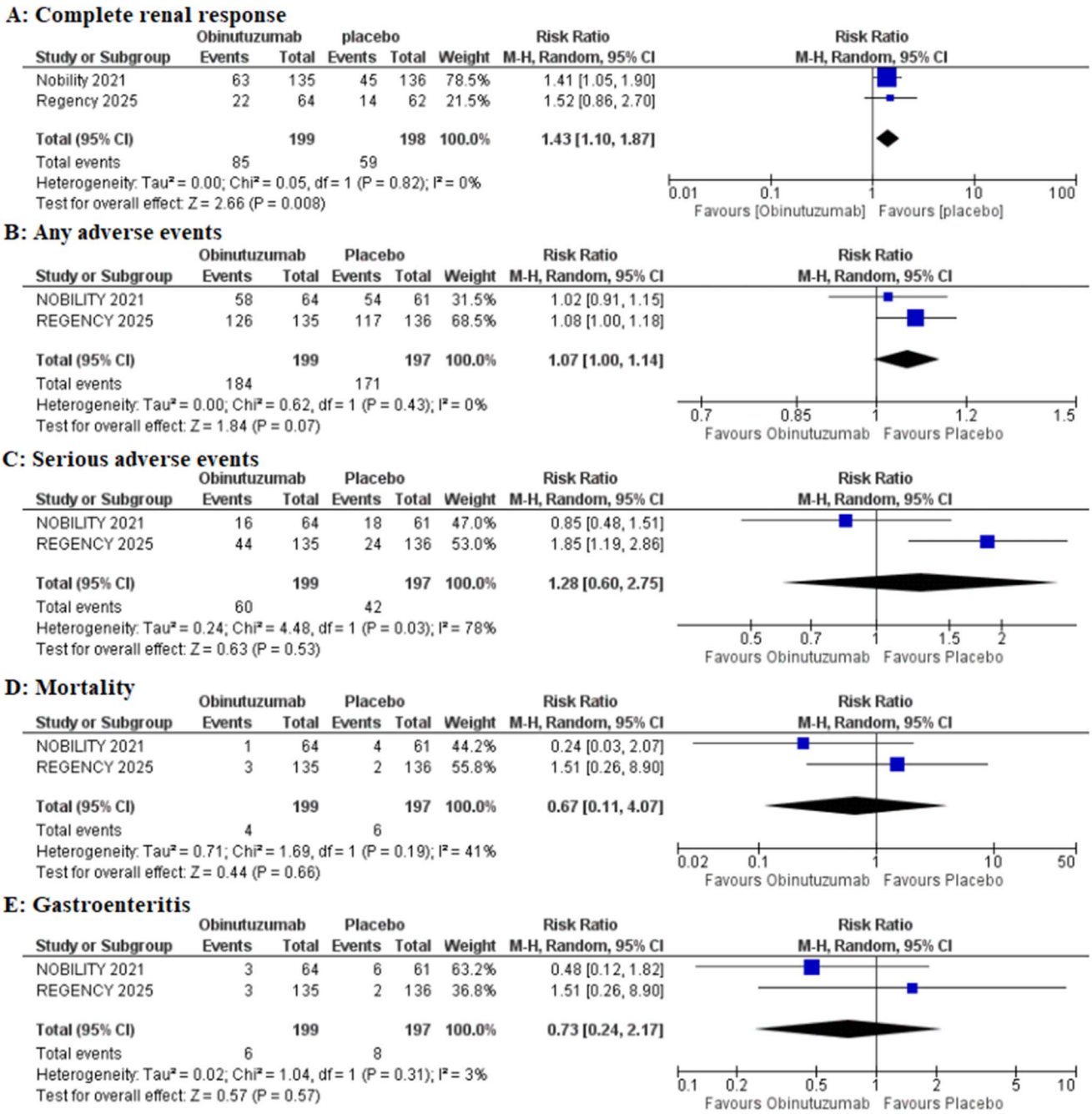

FIGURE 2. Forest plots for labeled outcomes, A: Complete renal response, B: Any adverse events, C: Serious adverse events, D: Mortality, E: Gastroenteritis.

not significantly different either, indicating that the drug is relatively safe if combined with standard treatment.

The 2 groups had similar mortality, which is reassuring and consistent with prior results that obinutuzumab does not add to excess mortality in patients with lupus nephritis.[2] Although gastroenteritis incidence was marginally lower in the obinutuzumab group, the result was not statistically significant. This indicates that although certain gastrointestinal side effects will be present, they are not a significant clinical issue.

There are some limitations that should be noted. First, only a small number of included RCTs were used, and this can limit the generalizability of the results. Second, differences in baseline disease severity and concomitant therapies may have had an impact on the results. Finally, follow-up periods within the included trials may not have been long enough to detect long-term safety and efficacy outcomes. Confirmation of these findings will require future large-scale, long-term trials.

This meta-analysis indicates that obinutuzumab substantially enhances complete renal response rates in active lupus nephritis without a notable rise in serious adverse events or death. These data provide evidence to support the possible use of obinutuzumab as an effective therapeutic agent in lupus nephritis. Further research is warranted to establish its long-term benefits and safety profile.

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