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RESEARCH LETTER

Effects of albuminuria-lowering treatments on inflammation markers: A post hoc analysis from the ROTATE trials

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1 | BACKGROUND

Inflammation plays an important role in the initiation and progression of kidney function decline in individuals with diabetes.[1] In experimental models of diabetes and chronic kidney disease (CKD), interventions with drugs commonly used to treat cardiovascular and kidney complications have shown anti-inflammatory effects, including angiotensin receptor blockers (ARBs),[2–4] sodium-glucose co-transporter-2 (SGLT2) inhibitors,[5–7] dipeptidyl peptidase-4 (DPP-4) inhibitors,[8–10] and Janus kinase-signal transducer and activator of transcription (JAK–STAT) inhibitors.[11,12] In clinical studies, treatment with renin-angiotensin-aldosterone-system inhibitors, SGLT2 inhibitors, DPP-4 inhibitors and JAK–STAT inhibitors has also been shown to exert anti-inflammatory effects.[5,6,11,13–16] The follow-up of most previous studies was more than 6 months. It is therefore not clear if potential anti-inflammatory properties represent a direct anti-inflammatory effect or a secondary effect because of improved glycaemic control or preservation of kidney function. In addition, there are no clinical studies comparing head-to-head the anti-inflammatory properties of these agents. Accordingly, we analysed the data from two randomized crossover clinical studies, ROTATE-1 and ROTATE-2, to compare the anti-inflammatory effects of an ARB, SGLT2 inhibitor, DPP-4 inhibitor and JAK–STAT inhibitor in participants diagnosed with type 1 diabetes and type 2 diabetes.

2 | METHODS

2.1 | Patients and study design

ROTATE-1 and ROTATE-2 were randomized multicentre crossover trials to primarily determine the individual albuminuria-lowering response of the ARB, telmisartan, the SGLT2 inhibitor, empagliflozin, the DPP-4 inhibitor, linagliptin, and the JAK–STAT inhibitor, baricitinib, in participants with type 1 diabetes and type 2 diabetes,

respectively. The study design and primary results were published elsewhere.[17] In short, participants eligible for inclusion were aged 18 years or older, had either a diagnosis of type 1 diabetes or type 2 diabetes, an estimated glomerular filtration rate of more than 45 mL/min/1.73m^2, and a urine albumin-creatinine ratio (UACR) of more than 30 mg/g and 500 mg/g or less. A full list of the inclusion and exclusion criteria can be found in the supplementary of the primary result publication.[17] Participants using an angiotensin-converting

TABLE 1 Baseline characteristics of the total, ROTATE-1 and ROTATE-2 participants.

Characteristic	Total ($N = 63$)	ROTATE-1 ($N = 26$)	ROTATE-2 ($N = 37$)
Age, y	63.9 (10.3)	59.5 (12.0)	67.0 (7.8)
Male sex, *n* (%)	52 (82.5)	19 (73.1)	33 (89.2)
Current smoker, *n* (%)			
Never	20 (31.7)	10 (38.5)	10 (27.0)
Previously	32 (50.8)	13 (50.0)	19 (51.4)
Currently	11 (17.5)	3 (11.5)	8 (21.6)
Race, *n* (%)			
White	52 (82.5)	19 (73.1)	33 (89.2)
Other	11 (17.5)	7 (26.9)	4 (10.8)
History of cardiovascular disease, *n* (%)	21 (33.3)	9 (34.6)	12 (32.4)
History of hypertension, *n* (%)	54 (85.7)	23 (88.5)	31 (83.8)
History of HF, *n* (%)	1 (1.6)	1 (2.7)	0 (0)
BMI, kg/m^2	30.0 (4.2)	29.0 (5.0)	30.7 (3.5)
Systolic BP, mmHg	138.8 (12.0)	138.4 (12.6)	139.0 (11.7)
Diastolic BP, mmHg	78.6 (9.2)	77.5 (10.7)	79.3 (8.1)
HbA1c			
mmol/mol	60.3 (10.5)	60.0 (7.1)	60.5 (12.4)
%	7.7 (3.1)	7.6 (2.8)	7.7 (3.3)
Duration of diabetes, y	24.9 (15.3)	36.5 (13.6)	16.8 (10.6)
eGFR, mL min^{-1} [1.73 m^{-2}]	78.7 (19.0)	79.1 (18.4)	78.3 (19.7)
eGFR < 60, *n* (%)	10 (16.1)	4 (15.4)	6 (16.7)
eGFR ≥ 60, *n* (%)	14 (22.2)	22 (84.6)	30 (83.3)
UACR, mg/g (IQR)	114.7 (65.9, 284.5)	91.9 (64.6, 282.1)	149.1 (72.9, 284.9)
UACR < 300 mg/g, *n* (%)	49 (77.8)	20 (76.9)	29 (78.4)
UACR ≥ 300 mg/g, *n* (%)	14 (22.2)	6 (23.1)	8 (21.6)
Concomitant medication, *n* (%)			
Insulin	43 (68.3)	26 (100.0)	17 (45.9)
Thiazide	20 (31.7)	10 (38.5)	10 (27.0)
Lis diuretics	11 (17.5)	6 (23.1)	5 (13.5)
IL1RA, pg/mL	330.3 (134.3, 992.3)	270.4 (121.5, 735.1)	365.0 (148.4, 1096.6)
IL-6, pg/mL	1.1 (0.3, 5.5)	1.0 (0.3. 5.5)	1.2 (0.4, 4.1)
IL-18, pg/mL	735.1 (330.3, 1339.4)	665.1 (403.4, 1212.0)	812.4 (298.9, 1480.3)
MCP-1, pg/mL	136.2 (115.6, 160.5)	145.6 (118.1, 179.5)	118.1 (90.3, 154.5)
IP-10, pg/mL	403.4 (164.0, 1096.6)	365.0 (164.0, 735.1)	445.9 (221.4, 1339.4)
IFN-γ, pg/mL	6.7 (2.5, 36.6)	7.4 (2.7, 30.0)	6.7 (2.2, 36.6)
VCAM, ng/mL	660.0 (442.4, 1202.6)	597.2 (400.3, 984.6)	660.0 (442.4, 1202.6)
TNFR-1, pg/mL	2981.0 (1808.0, 5431.7)	2697.3 (1998.2, 5431.7)	2981.0 (1636.0, 5431.7)
TNFR-2, pg/mL	9897.1 (4447.1, 18 033.7)	8955.3 (2981.0, 19 930.4)	9897.1 (4914.8, 18 033.7)
KIM-1, pg/mL	134.3 (33.1, 601.8)	99.5 (27.1, 270.4)	164.0 (49.4, 601.8)

Note: All biomarkers are reported as geometric mean with 95% CI.

Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; IFN, interferon; IL, interleukin; IP-10, interferon gamma-induced protein 10; KIM, kidney injury molecule; MCP, monocyte chemoattractant protein; IL1RA, interleukin-1 receptor antagonist; TNFR, tumour necrosis factor receptor; UACR, urine albumin-creatinine ratio; VCAM, vascular cell adhesion protein-1.

enzyme inhibitor, ARB, SGLT2 inhibitor, DPP-4 inhibitor or mineralocorticoid receptor antagonist had to discontinue these drugs for at least 4 weeks before entry into the study.

Eligible participants were randomized to receive 4 weeks of treatment with telmisartan 80 mg/day, empagliflozin 10 mg/day, linagliptin 5 mg/day and baricitinib 2 mg/day in random order with 4-week washout periods in between. As described in the primary result publication, a 4-week treatment period was chosen because previous studies showed that the effects of these drugs were fully present after 4 weeks.[17] The main results of the ROTATE trials also showed that albuminuria concentrations were increased after 4 weeks of discontinuation of the drugs. For these post hoc analyses, we combined the data from both studies. All participants provided informed consent before study initiation. Both trials were conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and were registered with clinicaltrialsregister.eu (2015-005691-26 and 2017-001977-18). Both trials were approved by local ethics committees at each participating site.

2.2 | Biomarker assessment

Blood and urine samples were stored at −80°C during ROTATE-1 and ROTATE-2 at the start and end of each treatment phase for exploratory biomarker research. For this post hoc study, we measured interleukin (IL)-6 and interferon gamma-induced protein 10 (IP-10), tumour necrosis factor receptor (TNFR)-1 and TNFR-2 in plasma, IL-18, interferon gamma (IFN-γ), IL-1 receptor antagonist (IL1RA) and vascular cell adhesion protein-1 (VCAM) in serum, and monocyte chemoattractant protein (MCP)-1 and kidney injury molecule (KIM)-1 in urine samples. All markers were measured using the Mesoscale QuickPlex SQ 120 platform (MesoScale Diagnostics [MSD], Rockville, MD), from December 2021 to February 2022. The mean (SD) coefficients of variation for each assay were IL-6: 3.8% (2.5%); IP-10: 6.2% (3.7%); IL-18: 2.0% (2.1%); IFN-γ: 1.9% (1.5%); VCAM: 1.8% (1.6%); MCP-1: 2.1% (1.8%); IL-1RA: 5.4% (6.9%); TNFR-1: 2.5% (1.9%); TNFR-2: 3.1% (2.6%); and KIM-1: 2.1% (1.9%).

2.3 | Statistical analysis

Continuous variables with a normal distribution or skewed distribution were reported as mean with SD or median with interquartile range (IQR), respectively. Continuous variables having a skewed distribution were logarithmically transformed before analyses to alleviate their skewness. Variables with categorical ordering were reported as number with percentage.

A repeated measures linear mixed effects model was used to estimate the difference in the mean change from baseline of the

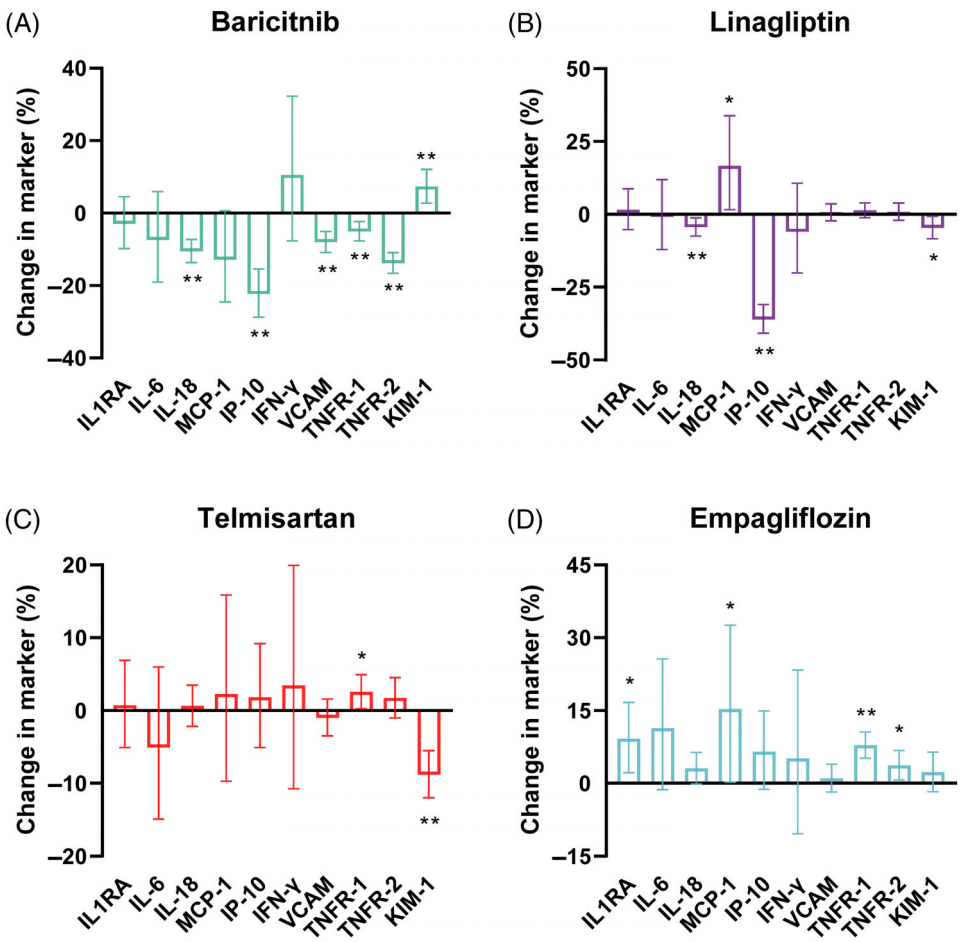

FIGURE 1 Percentage changes in inflammatory markers from baseline to 4 weeks of treatment with A, Baricitinib, B, Linagliptin, C, Telmisartan, and D, Empagliflozin. IFN-γ, interferon gamma; IL, interleukin; IP-10, interferon gamma-induced protein 10; KIM, kidney injury molecule; MCP, monocyte chemoattractant protein; RA, receptor antagonist; TNFR, tumour necrosis factor receptor; VCAM, vascular cell adhesion protein-1. *$p < 0.05$; **$p < 0.01$

inflammation marker. The model included random slopes and intercept for each subject and an unstructured covariance matrix. Correlations between the change in each inflammation marker and change in UACR from baseline were assessed with Pearson correlation. All analyses were performed in R Version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). The *p*-values less than 0.05 were deemed statistically significant.

3 | RESULTS

The baseline characteristics of the ROTATE-1 and ROTATE-2 participants are shown in Table 1. Overall, the concentrations of the inflammation markers were lower in participants with type 1 diabetes compared with those with type 2 diabetes (Table 1).

During the baricitinib treatment period, IL-18, IP-10, VCAM, TNFR-1 and TNFR-2 were statistically significantly decreased (Figure 1A). There were no statistically significant changes in most of these markers after 4 weeks of treatment with linagliptin or telmisartan, with the exception that IP-10 decreased and MCP-1 increased during treatment with linagliptin (Figure 1B,C). After 4 weeks of treatment with empagliflozin, most of the inflammatory markers tended to increase (Figure 1D). There was no difference in the change of the inflammation markers between individuals with type 1 diabetes or type 2 diabetes. After correction for multiple testing, changes from baseline in these inflammatory markers did not correlate with UACR changes (Data S1, Table S1). Comparing the differences in inflammation markers by trial, there was no obvious difference between ROTATE-1 and ROTATE-2, except for the change in IFN-γ (Data S1, Figures S1 and S2).

4 | CONCLUSIONS

Previous studies have established the anti-inflammatory effects of ARBs, DPP-4 inhibitors, SGLT2 inhibitors and baricitinib in individuals with type 1 diabetes or type 2 diabetes. This study extends these findings by comparing the anti-inflammatory properties of these drugs in a head-to-head prospective randomized crossover clinical trial. We show that there was high variability in the change of each inflammatory marker in individuals with type 1 diabetes and type 2 diabetes treated with telmisartan, empagliflozin, linagliptin or baricitinib. Furthermore, we show that 4 weeks of treatment with telmisartan, empagliflozin and linagliptin had, on average, little effect on the biomarker concentrations, while treatment with baricitinib resulted in more pronounced reductions in the inflammatory markers.

The ROTATE studies recruited participants with type 1 diabetes and type 2 diabetes and significant albuminuria. While the underlying pathophysiology of CKD differs between participants with type 1 diabetes and type 2 diabetes, inflammation has been implicated in the progression of kidney disease in both conditions.[1,18] In the ROTATE studies, the concentration of the inflammation markers were higher compared with those reported in the general population.[19–22] At baseline, the concentration of some of the inflammation markers was modestly higher in patients with type 2 diabetes compared with type 1 diabetes. The differences in baseline could be explained by the differences in pathophysiology as type 1 diabetes is primarily characterized as an autoimmune disease, whereas type 2 diabetes is characterized by chronic inflammation. Only the change in IFN-γ differed in response to baricitinib between the type 1 diabetes and type 2 diabetes cohorts. IFN-γ is a cytokine that is considered to be a contributor in the pathophysiology of autoimmune diseases, including type 1 diabetes.[23] However, because of the small sample size, the findings of this study should be carefully interpreted, also because we did not adjust for multiple testing.

As a direct inhibitor of the JAK–STAT pathway, we had expected an anti-inflammatory effect of baricitinib. JAK–STAT is overexpressed in transcriptomic profiles of kidney samples from humans with progressive diabetic kidney disease, and animal studies have shown that JAK inhibition reverses pathophysiological features of diabetic kidney disease.[24,25] In a phase 2 clinical trial, 24 weeks of treatment with baricitinib resulted in a decrease in IP-10, MCP-1, VCAM, TNFR-1 and TNFR-2.[11] In the ROTATE studies, the same inflammation markers were reduced after 4 weeks of treatment with baricitinib, providing independent confirmation of the anti-inflammatory effects of baricitinib in patients with diabetes and CKD. Future trials on long-term clinical outcomes are needed to assess whether these anti-inflammatory effects translate into better kidney outcomes.

Previous studies in patients with type 2 diabetes and CKD who were followed for more than 1 year reported that SGLT2 inhibition causes a modest reduction in plasma inflammation markers.[5,6] Whether these beneficial effects are because of a direct anti-inflammatory effect, or result from improved glycaemic control or kidney function, is unknown. In the ROTATE studies, empagliflozin did not reduce any inflammatory marker and even tended to increase some. We have no explanation for this finding, but it is possible that the follow-up was too short. In a prior study in patients with type 2 diabetes and moderate albuminuria, dapagliflozin also did not reduce TNF-alpha.[26] We note, however, that in contrast to previous studies, empagliflozin did not reduce albuminuria in the ROTATE studies, suggesting that the drug was not efficacious in terms of its kidney protective profile.[27] We also note that the ROTATE studies did not involve a placebo group and the sample size was small, which makes it difficult to draw definitive conclusions. Taken together, the results of the ROTATE studies suggest that the anti-inflammatory effect, as observed in studies with SGLT2 inhibitors and prolonged long-term follow-up, may be a secondary effect of improved glycaemic control or organ function and not a direct anti-inflammatory effect per se.[5,28,29]

A few studies have reported that ARBs and DPP-4 inhibitors reduce inflammation markers in individuals with type 1 diabetes or type 2 diabetes.[2–4,8–10] There were no clear reductions in any of the measured markers during treatment with these drugs in our study, although the decrease in IL-18 and IP-10 observed after 4 weeks of treatment with linagliptin was observed in a prior study with DPP-4 inhibitors.[10,30] The contrasting findings may be attributable to the short treatment period in ROTATE or because we measured the

biomarkers in the systemic circulation, which is not always a proper reflection of the inflammatory marker concentration within tissues or organs.[31] Unfortunately, we were unable to assess changes of the inflammatory markers in urine because these data were not available.

In conclusion, baricitinib reduces markers of inflammation in individuals with type 1 diabetes and type 2 diabetes. Four weeks of treatment with other drugs used in the management of individuals with type 2 diabetes and CKD did not reduce inflammation markers.

AUTHOR CONTRIBUTIONS

TS and HJLH wrote the first draft. NJ performed the statistical analyses. HJLH, FP, and PR designed the study. VRC, AK, and GDL were involved in data collection and interpretation. FP, PR, VRC, AK and GDL revised the draft manuscript. All authors approved the submission for publication.

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CONFLICT OF INTEREST

TS, VRC and NJ have nothing to disclose. GDL has served on advisory boards of Boehringer Ingelheim, Eli Lilly Alliance, Sanofi, Novo Nordisk, AstraZeneca and Vifor Pharma, and received research grants from AstraZeneca, Sanofi, Novo Nordisk and Vifor Pharma. AK has received lecture and/or consultancy fees from Bayer, Boehringer Ingelheim, Merck Sharpe and Dohme, Mundipharma and Novo Nordisk, and research grants from Boehringer Ingelheim, Novo Nordisk and ZonMw. FP has served as a consultant, on advisory boards or as educator for AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Sanofi, Mundipharma, MSD, Novartis and Amgen, and has received research grants to institution from Novo Nordisk, Boehringer Ingelheim, Amgen and AstraZeneca. PR has received consultancy and/or speaking fees (to his institution) from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Novo Nordisk and Sanofi Aventis, and research grants from AstraZeneca and Novo Nordisk. HJLH has served as a consultant for AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, Dimerix, Eli-Lilly, Gilead, Goldfinch, Janssen, Merck, Novo Nordisk and Travere Pharmaceuticals; and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Deidentified participant data will be made available on reasonable request 2 years after the date of publication. Requests should be directed to the senior author (Hiddo JL Heerspink). Requestors will be required to send a protocol, statistical analysis plan and sign a data access agreement to ensure the appropriate use of the study data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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