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Eosinophils as a predictive marker of treatment-related adverse events in mRCC patients treated with first-line immune-checkpoint inhibitor combination therapy

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Immune checkpoint inhibitors (ICIs) are a key component of first-line treatment for metastatic renal cell carcinoma (mRCC). However, predicting treatment-related adverse events (TRAEs) remains challenging. This study investigated the utility of eosinophil-related biomarkers as predictors of Common Terminology Criteria for Adverse Events grade ≥ 3 TRAEs in mRCC patients undergoing ICI combination therapy. In this retrospective analysis across 21 hospitals in Japan, we examined 180 patients treated with ICI/ICI therapy and 216 patients treated with ICI/tyrosine kinase inhibitor (TKI) therapy. Grade ≥ 3 TRAEs occurred in 39.4% and 31.9% of patients in the ICI/ICI and ICI/TKI groups, respectively. An elevated eosinophil proportion of ≥ 2.0% (odds ratio [OR]: 2.36; 95% CI [confidence interval] 1.23–4.54, p = 0.01) and a low neutrophil/eosinophil ratio (NER) of ≤ 40.0 (OR: 2.78, 95% CI 1.39–5.53, p = 0.004) were significant predictors of severe TRAEs in the ICI/ICI group. However, no significant associations were found in the ICI/TKI group. These findings may help identify patients who suffer from grade ≥ 3 TRAEs and help determine individualized treatment strategies in patients with mRCC.

Keywords Renal cell carcinoma, Immune checkpoint inhibitor, ICI, Eosinophil, Immune-related adverse event, Treatment-related adverse event

Abbreviations

ICI	Immune checkpoint inhibitor
TKI	Tyrosine kinase inhibitor
mRCC	Metastatic renal cell carcinoma
TRAE	Treatment-related adverse event
irAE	Immune-related adverse event
NER	Neutrophil/eosinophil ratio
IQR	Interquartile range

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CTCAE	Criteria for Adverse Events
ROC	Receiver operating characteristic
CTCAE	Common Terminology Criteria for Adverse Events
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio

Renal cell carcinoma (RCC) is one of the most common urologic malignancies, with over 43,000 new cases diagnosed annually worldwide [1, 2]. Among these cases, approximately 30% present with advanced or metastatic disease (mRCC).

Over the past 5 years, the treatment landscape for mRCC has been changed due to rapid advancements in immune checkpoint inhibitor (ICI) combination therapies, including ICI/ICI and ICI/tyrosine kinase inhibitor (TKI) regimens. ICIs have emerged as a cornerstone in the management of mRCC, offering promising efficacy.

The current major guidelines recommended ICI/ICI therapy as first-line treatment for intermediate- and poor-risk mRCC patients and ICI/TKI therapy for patients in all International Metastatic RCC Database Consortium (IMDC) risk groups [3, 4]. While these therapies have demonstrated significant anticancer efficacy, their use is often accompanied by treatment-related adverse events (TRAEs) including immune-related adverse events (irAEs). Severe TRAEs are likely to result in treatment discontinuation and, in some cases, mortality. Consequently, the balance between efficacy and safety is crucial for determining the optimal therapeutic regimen for mRCC patients.

Identifying reliable predictors of TRAEs is essential to guide treatment decision-making and improve oncological outcomes. While several studies have explored potential biomarkers of TRAEs, such as the proportion of eosinophils 5, in patients treated with ICI combination therapies, the predictive value of eosinophils remains poorly understood, particularly in the context of different ICI regimens. This study aims to assess the proportion of eosinophils as a predictive biomarker of grade ≥ 3 TRAEs in patients with mRCC receiving first-line ICI/ICI or ICI/TKI therapy.

Materials and methods

Patient selection and study design

We conducted a multi-institutional, retrospective observational study following the World Medical Association Declaration of Helsinki and approval by the institutional review board of the principal institution (Osaka Medical and Pharmaceutical University; approval number: RIN–750–2571). This study included data from 21 hospitals across Japan collected between January 2018 and August 2023. Eligible patients were those with mRCC who received systematic treatment, including ICI/ICI and ICI/TKI therapies. Patients treated with TKI monotherapy in the first-line setting or those with missing data regarding TRAEs were excluded. Eventually, 180 patients in the ICI/ICI group and 216 patients in the ICI/TKI group were included for analysis (Fig. 1). The following data were retrieved from individual medical records: patient demographics (age, sex, Karnofsky performance), tumor characteristics (clinical stage, histology, metastatic site, IMDC classification), laboratory parameters before first-line therapy (eosinophil proportion and neutrophil-eosinophil ratio (NER)), and the details of the TRAEs (i.e., type of TRAEs, grade). The NER is defined as neutrophil count debited by eosinophil count. TRAEs were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The primary outcome of interest was the relationship between the eosinophil proportion

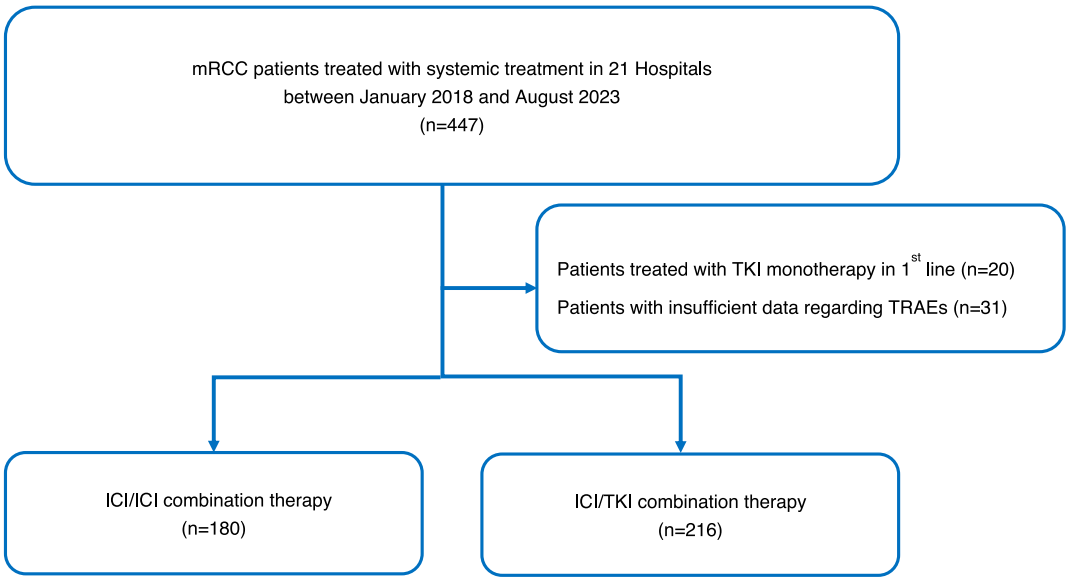

Fig. 1. Flow chart of the patient selection process.

and occurrence of grade ≥ 3 TRAEs in patients treated with ICI/ICI or ICI/TKI therapy. The secondary outcome was the association between the NER and occurrence of grade ≥ 3 TRAEs.

Statistical analysis

We depicted patient demographics, tumor characteristics, and analysis results in the ICI/ICI and ICI/TKI groups separately. Continuous variables are expressed as medians with interquartile range (IQR), whereas categorical variables are expressed as frequencies (percentages). Differences between the groups were analyzed using the chi-square test for categorical variables and Mann–Whitney U test for continuous variables.

Univariate and multivariate logistic regression analyses were conducted to evaluate the associations between clinical factors, such as hematological markers (i.e., eosinophil proportion and NER) and the occurrence of grade ≥ 3 TRAEs. To account for multicollinearity, multivariate logistic regression analyses of factors including the eosinophil proportion and NER were analyzed separately in multivariate models. The optimal cut-off values of hematological predictive factors for predicting grade ≥ 3 TRAEs were determined using the Youden index derived from receiver operating characteristic (ROC) curves [5]. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a modified version of R Commander (The R Foundation for Statistical Computing, Vienna, Austria) designed to add statistical functions frequently used in biostatistics [6].

Results

Patient and tumor characteristics

Of the 396 patients with mRCC were included in this study, 180 patients received ICI/ICI therapy, and 216 patients received ICI/TKI therapy. The patient demographics and tumor characteristics are summarized in Table 1. The median patient age (IQR) was 70 years. The predominant histology was clear cell carcinoma. Patients with intermediate- or poor-risk disease, based on the IMDC classification, were more frequently observed in the ICI/ICI group compared to the ICI/TKI group.

Treatment-related adverse events

Overall, 140 patients (35.4%) experienced grade ≥ 3 TRAEs. The detailed prevalence and distributions of the grade ≥ 3 TRAEs are shown in Table 2. Among the patients in the ICI/ICI and ICI/TKI groups, 71 (39.4%) and 69 (31.9%) reported grade ≥ 3 TRAEs, respectively. The most commonly observed grade ≥ 3 TRAE was pneumonitis (9.4%) in the ICI/ICI group and elevated ASL/ALT levels (8.8%) in the ICI/TKI group. Notably, pneumonitis occurred more frequently in the ICI/ICI group than in the ICI/TKI group (9.4% vs. 2.8%; $p = 0.009$), whereas the occurrence of other TRAEs showed no significant difference between the groups.

Associations of grade ≥ 3 TRAEs with the eosinophil proportion and NER in the ICI/ICI group.

In the ICI/ICI group (n = 180), 71 patients (39.4%) developed grade ≥ 3 TRAEs. Univariate logistic regression analyses identified a higher eosinophil proportions (≥ 2.0%) and lower NER values (≤ 40.0) as significant

All	Total	ICI/ICI	ICI/TKI	*p* value
n	396	180	216	
Age (median, IQR)	70 (60; 75)	68(60; 74)	71 (62; 75)	0.069
Female	95 (24.0%)	36 (20.0%)	59 (27.3%)	0.099
Kamofsky PS < 80	59 (14.9%)	37 (20.6%)	22 (10.2%)	0.005
Histology				0.566
Clear cell	289 (72.2%)	127 (70.6%)	162 (75.0%)	
Non-clear cell	65 (16.4%)	33 (18.3%)	32 (14.8%)	
ND	42 (10.6%)	20 (11.1%)	22 (10.2%)	
IMDC classification				< 0.001
Favorable	67 (16.9%)	12 (6.7%)	55 (25.5%)	
Intermediate	210 (53.0%)	100 (55.6%)	110 (50.9%)	
Poor	119 (30.0%)	68 (37.8%)	51 (23.6%)	
Metastatic site				
Lung	228 (57.6%)	75 (41.7%)	93 (43.1%)	0.84
Bone	95 (24.0%)	44 (24.4%)	51 (23.6%)	0.91
Liver	41 (10.4%)	15 (8.3%)	26 (12.0%)	0.25
Brain	13 (3.3%)	6 (3.3%)	7 (3.2%)	1
Other	106 (26.8%)	54 (30.0%)	52 (24.1%)	0.21
Follow up period (month) (median, IQR)	16.0 (7.0; 31.0)	19.5 (7.0; 35.0)	14.5 (7.0; 24.0)	0.003

Table 1. Patient demographics in the ICI/CI and ICI/TKI groups. *ICI* immune checkpoint inhibitor, *TKI* tyrosine kinase inhibitor, *ND* no data, *IMDC* International Metastatic RCC Database Consortium, *IQR* Interquartile range.

All	Total (n = 396)	ICI-ICI (n = 180)	ICI-TKI (n = 216)	*p* value
n	140 (35.4%)	71 (39.4%)	69 (31.9%)	0.14
Gastrointestinal toxicity				
Enteritis and diarrhea	13 (3.3%)	7 (3.9%)	6 (2.8%)	0.72
Decreased appetite	2 (0.5%)	1 (0.6%)	1 (0.5%)	1
Endocrine-related events				
Adrenal deficiency	18 (4.5%)	9 (5.0%)	9 (4.0%)	0.80
Pituitary insufficiency	6 (1.5%)	5 (2.8%)	1 (0.5%)	0.10
Hypothyroidism	11 (2.8%)	6 (3.3%)	5 (2.3%)	0.57
Renal Toxicity				
Proteinuria	2 (0.5%)	0	2 (0.9%)	0.50
Increased creatinine	7 (1.8%)	4 (2.2%)	3 (1.4%)	0.71
Cutaneous				
Rash	8 (2.0%)	4 (2.2%)	4 (1.9%)	1
Pruritus	1 (0.3%)	0	1 (0.5%)	1
Bullous pemphigoid	1 (0.3%)	1 (0.6%)	0	0.46
Hepatobiliary system				
AST/ALT elevation	27 (6.8%)	8 (4.5%)	19 (8.8%)	0.14
Serum lipase elevation	1 (0.2%)	1 (0.6%)	0	0.46
Angiocholecystitis	2 (0.5%)	2 (1.1%)	0	0.21
Musculoskeletal disorder				
Arthritis	1 (0.2%)	1 (0.6%)	0	0.46
Rhabdomyolysis	1 (0.2%)	1 (0.6%)	0	0.46
Myasthenia gravis	1 (0.2%)	1 (0.6%)	0	0.46
Others				
Hypertension	7 (1.8%)	1 (0.6%)	6 (2.8%)	0.13
Pneumonitis	23 (5.8%)	17 (9.4%)	6 (2.8%)	0.009
Diabetes				
Fatigue	3 (0.8%)	3 (1.7%)	0	0.09
Cardiac toxicity	1 (0.2%)	0	1 (0.5%)	1
Thromboembolism	2 (0.5%)	0	2 (0.9%)	0.50
Dysphonia	1 (0.2%)	0	1 (0.5%)	1
Stomatitis	3 (0.8%)	0	3 (1.4%))	0.25
Hand-foot syndrome	3 (0.8%)	0	3 (1.4%))	0.25
Uveitis	1 (0.2%)	0	1 (0.5%)	1
Hematological toxicity				
Anemia	1 (0.2%)	0	1 (0.5%)	1
Thrombocytopenia	1 (0.2%)	1 (0.6%)	0	0.46
Hemophagocytic syndrome	2 (0.5%)	1 (0.6%)	0	0.46
Hypercalcemia	3 (0.8%)	0	3 (1.4%))	0.25

Table 2. CTCAE grade ≥ 3 TRAEs experienced in the ICI/ICI and ICI/TKI groups. *CTCAE* Common Terminology Criteria for Adverse Events, *ICI* immune checkpoint inhibitor, *TKI* tyrosine kinase inhibitor.

predictors of grade ≥ 3 TRAEs. In the multivariate analysis after adjusting for the effects of age, sex, BMI, and allergy history, the eosinophil proportion remained an independent predictor of grade ≥ 3 TRAEs (odds ratio [OR]: 2.36, 95% confidence interval [confidential interval]: 1.23–4.54, p = 0.01), and NER (OR: 2.78, 95% CI: 1.39–5.53, p = 0.004) remained independent predictors of grade ≥ 3 TRAEs (Table 3).

Associations of grade ≥ 3 TRAEs with the eosinophil proportion and NER in the ICI/TKI group

In the ICI/TKI group (n = 216), 69 patients (31.9%) experienced grade ≥ 3 TRAEs. Unlike the ICI/ICI group, no significant association of the eosinophil proportion (OR: 0.65, 95% CI 0.28–1.53, p = 0.33) or NER (OR: 0.75, 95% CI 0.42–1.36, p = 0.35) with the occurrence of grade ≥ 3 TRAEs was observed (Table 4).

Discussion

Based on robust evidence from several phase III trials with long-term follow-up periods [7–10], ICI combination therapy is now a crucial part of mRCC treatment. However, in daily practice, some patients have difficulty continuing this treatment due to early progression or serious side effects. Hence, the number of publications focusing on identifying optimal biomarkers beneficial for clinical decision-making in such patients is glowing.

A) Univariate analysis of Eosinophil proportion and NER on the occurrence of TRAEs			
	Cut-off value	**OR (95% CI)**	***p* value**
Eosinophil (%)	≥ 2.00	2.03 (1.08–3.81)	0.027
NER (Neut./Eo.)	≤ 40.0	2.49 (1.28–4.86)	0.007
B) Multivariate analysis on the occurrence of TRAEs including eosinophil proportion			
		OR (95% CI)	***p* value**
Age ≥ 70		1.47 (0.78–2.80)	0.24
Sex (Female)		0.83 (0.37–1.85)	0.65
BMI ≥ 25		0.79 (0.36–1.76)	0.57
KPS < 80		0.94 (0.43–2.07)	0.88
Allergy history		1.36 (0.58–3.19)	0.48
Eosinophil ≥ 2%		2.36 (1.23–4.54)	0.01
C) Multivariate analysis on the occurrence of TRAEs including NER			
		OR (95% CI)	***p* value**
Age ≥ 70		1.41 (0.73–2.71)	0.31
Sex (Female)		0.90 (0.40–2.03)	0.80
BMI ≥ 25		0.83 (0.37–1.85)	0.64
KPS < 80		1.05 (0.47–2.34)	0.90
Allergy history		1.29 (0.53–3.10)	0.58
NER ≤ 40.0		2.78 (1.39–5.53)	0.004

Table 3. Univariate and multivariate logistic regression analyses of factors predicting the occurrence of TRAEs in the ICI/ICI group. *TRAEs* treatment-related adverse events, *NER* neutrophil/eosinophil ratio, *OR* odds ratio, *CI* confidential interval.

D) Univariate analysis of Eosinophil proportion and NER on the occurrence of TRAEs			
	Cut-off value	**OR (95% CI)**	***p* value**
Eosinophil (%)	≥ 2.0	0.69 (0.31–1.55)	0.37
NER (Neut./Eo.)	≤ 40	0.75 (0.42–1.36)	0.35
E) Multivariate analysis on the occurrence of TRAEs including eosinophil proportion			
		OR (95% CI)	***p* value**
Age ≥ 70		2.37 (0.96–5.87)	0.06
Sex (Female)		0.81 (0.31–2.09)	0.66
BMI ≥ 25		0.60 (0.23–1.59)	0.31
KPS < 80		0.00 (0.00–inf)	0.99
Allergy history		0.57 (0.18–1.76)	0.32
Eosinophile ≥ 2%		0.65 (0.28–1.53)	0.33
F) Multivariate analysis on the occurrence of TRAEs including NER			
		OR (95% CI)	***p* value**
Age ≥ 70		1.16 (0.63–2.14)	0.63
Sex (Female)		1.01 (0.52–1.95)	0.99
BMI ≥ 25		0.98 (0.52–1.90)	0.96
KPS < 80		1.03 (0.39–2.77)	0.95
Allergy history		0.50 (0.20–1.23)	0.13
NER ≤ 40.0		0.75 (0.41–1.37)	0.12

Table 4. Univariate and multivariate logistic regression analyses of factors predicting the occurrence of TRAEs in the ICI/TKI group. *TRAEs* treatment-related adverse events, *NER* neutrophil/eosinophil ratio, *OR* odds ratio, *CI* confidential interval

Several factors, including, sex, age, BMI, laboratory tests, pre-existing autoimmune disease (pAID), PD-L1 expression, and tumor mutation burden [11], are potentially associated with adverse reactions. However, their integration into routine clinical practice has been limited by insufficient accuracy, inconsistent results, or economic burden. Recent studies have highlighted the eosinophil proportion, a widely implementable, easily evaluated, and low-cost biomarker, as a promising biomarkers of irAEs [12]. On the other hand, previous studies have not differentiated ICI/ICI from ICI/TKI therapies when assessing the value of eosinophil levels for predicting TRAEs. Our large multi-institutional study evaluated the utility of the eosinophil proportion as a predictor of TRAEs in mRCC patients treated with ICI/ICI therapies separately from those treated with ICI/TKI therapies, which is important for developing treatment strategies.

Eosinophils are a type of white blood cell that participates in various cellular processes, contributes to defense against parasitic, bacterial, and viral infections, and plays a role in cancer immunology. Eosinophils have several receptors for cytokines, chemokines, and adhesion molecules, enabling responses to stimuli and maintenance of homeostasis. In response to stimuli, eosinophils release various granule proteins, suggesting numerous effector functions during the immune response to pathogens. They perform considerable roles in metabolism, fat deposition, and glucose homeostasis; tissue remodeling and development; liver and muscle repair; neuronal regulation; and immunoregulation. On the other hand, they are widely recognized for their potent cytotoxic capabilities, primarily driven by granule proteins [13]. This activity may play a role in the organ damage associated with autoimmune inflammation [14]. In line with the present results, several studies reported more abundant eosinophils associated with a higher occurrence of irAEs in patients treated with ICIs. For example, Diehi et al. showed that a higher baseline count of lymphocytes, especially eosinophils, was related to the risk of grade ≥ 2 irAEs in patients with solid tumors treated with a PD-1 inhibitor [15]. More specifically, some studies have documented an association between the baseline eosinophil count and specific irAEs, such as endocrine disorders, pneumonitis, and adrenal insufficiency, in patients with malignant tumors [16–18]. A recent study by Tasaki et al. reported that upregulation of the eosinophil proportion within 2 weeks of ICI/ICI initiation was associated with a greater incidence of irAEs in mRCC patients [19].

In addition to the eosinophil proportion, we evaluated the predictive value of the NER, a novel inflammatory biomarker previously reported to be correlated with oncological outcomes in mRCC patients treated with ICIs [20, 21]. Gil et al. showed that the NER is not only a prognostic biomarker for mRCC patients treated with nivolumab in second or later lines but also a predictive biomarker of irAEs [22]. The present study, involving a relatively larger number of mRCC patients treated with ICIs as first-line treatment, confirmed the NER as a potential predictive marker of TRAEs during ICI/ICI treatment. Similar to the eosinophil proportion, the NER was also a significant predictive factor of the incidence of grade ≥3 TRAEs during ICI/ICI but not ICI/TKI therapy. Considering the hypothesis that CD8-positive lymphocytes induced by neutrophils that have infiltrated tissues with irAEs may develop non-specific inflammation and autoimmune response [23], the NER could be a more specific biomarker compared with the eosinophil proportion (although difficult to compare). These results warrant further investigation via larger well-designed studies.

Despite the strengths of this study, the generalizability of our results is limited. The principal limitation was the retrospective nature, although the analyses were performed by logistic cox regression model to avoid the bias, which can potentially lead to selection bias and incomplete data collection, particularly for symptom-based TRAEs. Second, the optimal cut-off values for the eosinophil proportion and NER were derived from this specific cohort and may not be generalizable to other populations. Validation by prospective, well-designed studies is essential to confirm these findings and establish standardized thresholds. Third, the analyses were not divided into histological subtypes (e.g. papillary, chromophobe), it is unclear whether the results can be applied to all histological subtypes. However, this is the first study to analyze ICI/ICI and ICI/TKI therapies separately with regard to the usefulness of the eosinophil proportion and NER as predictors of TRAEs during first-line treatment in mRCC patients; the results could help guide decision-making. Further prospective studies need to be carried out in order to validate the relationships between TRAEs and eosinophil in mRCC patients treated with ICI therapies.

Conclusion

This study confirmed that an increased eosinophil proportion and NER were significant predictors of grade ≥ 3 TRAEs in mRCC patients treated with ICI/ICI therapy, but not ICI/TKI therapy. Given the easier accessibility and cost-effectiveness, the eosinophil proportion and NER hold promise as practical biomarkers guiding first-line treatment selection and shared decision-making in mRCC patients. Further prospective validation is warranted for clinical implementation of these biomarkers.

Data availability

The data supporting the findings of this study are available from the corresponding authors (MA and T. Kawada) on request.

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Author contributions

T. Kawada contributed to the project development, data collection, management, analysis, and manuscript writing/editing. SK, T. Yanagisawa, and KM contributed to the project development, data analysis, and manuscript editing. WF contributed to the data analysis. K. Komura, TT, RM, TN, LI, ST, TH, YH, KE, T. Kobayashi, BK, SN, TI, TS, YT, T. Yamanoi, KY, KT, YK, AT, and K. Kurose contributed to the data curation and manuscript writing/editing. T. Kimura, HA, RS, KF, and YO contributed to the project development. MA contributed to the project development/management and manuscript editing.

Declarations

Competing interests

Kazutoshi Fujita received honorarium from Ono, Bristle, MSD, Eisai, Pfizer, Merk, and Takeda. Takahiro Kimura is a paid consultant/advisor of Astellas, Bayer, Janssen, Sanofi and Takeda. The other authors declare no conflicts of interest associated with this manuscript.

Ethical approval

This study was approved by the ethical review board at Osaka Medical and Pharmaceutical University; approval number: RIN–750–2571 executed in accordance with the principles outlined in the World Medical Association Declaration of Helsinki, with the participants' informed consent.

Additional information

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