



# Elicitation of Rheumatologist Preferences for the Treatment of Patients with Rheumatoid Arthritis After the Failure of a First Conventional Synthetic Disease-Modifying Anti-Rheumatic Agent

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## ABSTRACT

**Introduction:** Rheumatoid arthritis (RA) clinical guidelines do not provide strong recommendations for the choice of disease-modifying anti-rheumatic drugs (DMARD) in patients with an inadequate response to methotrexate (MTX), and only limited evidence is available on factors influencing rheumatologist treatment decisions. We aimed to describe therapeutic preferences after the failure of a first-line strategy of MTX in simulated cases of patients with RA.

**Methods:** Fictional but realistic case-vignettes ( $n = 64$ ) of patients with RA and an inadequate response to MTX were developed with a combination of RA-poor prognostic factors and comorbidities. Physicians were presented with

eight vignettes and chose the most and least appropriate therapeutic option from the following six options randomly proposed 3 by 3: (1) replacing MTX with another csDMARD; (2) combining MTX with one or more csDMARDs; (3) adding a bDMARD of either TNF inhibitors (TNFi), tocilizumab (TCZ), abatacept (ABA), or rituximab (RTZ). A total of 1605 complete case vignettes were produced and randomly assigned to a representative sample of French rheumatologists. For each vignette, whenever a treatment was preferred, one point was incremented for this treatment; if this treatment was the least desired, one point was removed. Preferences were elicited using a normalized best–worst score.

**Results:** Two hundred and four French rheumatologists participated in the study with each vignette being assessed 20–28 times for a completion rate of 94%. TNFi was the first-choice strategy (80% of vignettes), except in cases with a history of infection and pulmonary comorbidity, where ABA was the first preference (85%). TCZ came third in 83% of the cases. Other options were never preferred and repeatedly yielded negative scores.

**Conclusions:** We observed a conservative trend with TNFi as the main therapeutic choice for patients with RA and inadequate response to MTX. Preference for bDMARD-based strategies increased with the number of RA-poor prognosis factors, whereas an increase in the number of comorbidities resulted in an increased

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preference for ABA. Understanding clinical decision-making will be particularly important as the therapeutic landscape for RA continues to evolve.

**Keywords:** Case-vignette; Discrete choice experiment; Disease-modifying anti-rheumatic drugs; Methotrexate; Rheumatoid arthritis; Therapeutic preference

### Key Summary Points

#### Why carry out this study?

There are limited data available on therapeutic decision-making for the treatment of rheumatoid arthritis (RA) following the failure of first-line therapy.

Multiple factors influence therapeutic decision-making including those related to the disease (prognostic factors), patient (comorbidities, socio-demographics), and physician (experience, conditions of practice, frequency of consultation).

The purpose of the study was to describe the therapeutic preferences of physicians involved in the management of RA, according to predefined profiles of fictitious RA patients, in cases of inadequate response to a first-line strategy of methotrexate (MTX).

#### What was learned from the study?

We observed a conservative trend with TNF inhibitors (TNFi) being the main therapeutic choice and abatacept (ABA) a choice for patients with pulmonary involvement and a history of serious or recurrent infection.

We conclude that prescribing physicians are typically conservative in their approach to treating RA patients with an inadequate response to MTX and that factors related to the physician (years and mode of practice, number of RA patients seen per week) have little or no impact on therapeutic decisions.

We also found that the presence of comorbidities resulted in a decreased preference for adding TNFi and tocilizumab (TCZ) and an increased preference of ABA and rituximab (RTX), as well as the other strategies.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14423927>.

## INTRODUCTION

Rheumatoid arthritis (RA), a chronic inflammatory condition, results in persistent and symmetrical inflammation of joints and affects about 1% of the global adult population [1]. The disease can lead to major joint destruction, resulting in disability, impaired quality of life, and reduced life expectancy. The therapeutic management of RA is primarily based on the use of disease-modifying anti-rheumatic drugs (DMARDs). According to the international guidelines for the management of RA, conventional synthetic (cs) DMARDs, as monotherapy or in combination, are the recommended first-line strategy for patients with active RA. Methotrexate (MTX) should be prescribed unless contraindicated [2, 3]. In cases of therapeutic failure, the next strategy should be guided by the presence of poor prognostic factors such as structural progression, high clinical, and/or biological activity and autoantibodies, namely rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) [4]. The addition of biological (b) DMARDs, or targeted synthetic (ts) DMARDs, is recommended in cases with poor prognostic factors.

Therapeutic decisions remain relatively complex in RA, particularly after MTX failure, which occurs in a significant proportion of patients [5]. There are several DMARDs available and several possible uses including replacing or

in conjunction with MTX. Up to 2017, several bDMARDs were approved for use following failure of first-line therapy, these include compounds with five different mechanisms of action: tumor necrosis factor inhibition (TNFi), interleukin-6 receptor inhibition, B-cell depletion, and T-cell co-stimulation blockade [6]. However, only a few published face-to-face randomized controlled trials and network meta-analyses are available to inform therapeutic decision-making [7, 8]. All failed to identify superiority of one of these agents over the others when used in combination with MTX or a csDMARD equivalent. This resulted in clinical practice guidelines positioning all these compounds at the same level for RA patients with inadequate response to MTX or another csDMARD and failing to propose a hierarchy of these agents or a therapeutic sequence for their use in daily practice [2].

Besides RA characteristics and prognosis, patient characteristics (e.g., age, comorbidities, lifestyle, social issues) and factors related to the physician (e.g., experience, conditions of practice) and health system (e.g., prescription conditions) may have an influence on therapeutic decisions (including route of administration) [9]. However, these topics are only marginally addressed by clinical practice guidelines, which provide a general framework for therapeutic decisions but only limited guidance on the best course of treatment in a specific clinical situation. There is growing interest in studying clinical decisions with several approaches available based on real-life situations (trained actors) or fictional simulations of clinical cases in the form of case-vignettes [10].

Data on therapeutic decisions for the management of RA remain limited, particularly for second-line strategies. Fautrel et al. described rheumatologists' therapeutic decisions in patients with RA receiving a first-line strategy and the criteria associated with these decisions based on simulated clinical cases [11]. A more recent study by Hifinger et al. examined rheumatologists' preferences regarding the attributes of a hypothetical DMARD (efficacy, safety, patient preference, cost-effectiveness, and overall cost) in several European countries [12]. Rheumatologists were willing to reduce

efficacy in favor of other attributes, albeit with variations between countries.

In this context, a deeper understanding of rheumatologists' prescription preferences is required to better understand how targeted DMARDs are used in daily practice. Preference elicitation for such complex situation is always a challenge since direct and concise questions rarely cover the full spectrum of possible clinical situations or therapeutic options. Thus, the discrete choice experiment (DCE) methodology, based on the Thurstone pairwise method, has been proposed to facilitate preference elicitation in difficult decision-making processes [13–15]. This approach disentangles complex clinical situations with a series of simplified scenarios in which different attributes reflect the patient and disease characteristics, thus producing multiple variants of one single scenario. The therapeutic choice options are then presented against one another, i.e., in pairs. Unlike other expert opinion approaches, such as the RAND Appropriateness Method [16] in which respondents are asked to rate the appropriateness of a specific option, the pairwise method does not require any direct or absolute rating (or ranking) of the proposed options. An alternative approach is to present more than 2 therapeutic options and to ask respondents to identify what they would consider the best and the worst therapeutic choices for each scenario. The compilation of the expert responses enables the ranking of the different options, which expresses respondents' overall preferences for each clinical situation [17].

Using a set of formatted clinical case-vignettes and associated questionnaires, adopting the discrete choice experiment (DCE) approach, we conducted a study to describe the therapeutic preferences of French rheumatologists when selecting a second therapeutic strategy after the failure of MTX in simulated patients with RA. This work also aimed at evaluating the impact of selected factors related to RA, the patient, and physician on the decision-making process.

## METHODS

### Study Design

This was a non-interventional multicenter study that took place from May 15, 2018 to December 21, 2018. The study methodology was based on the presentation to physicians of case-vignettes, i.e., fictional but realistic and formatted clinical cases in which patient and disease characteristics were randomly varied to cover a wide spectrum of clinical possibilities [10]. Cases were associated with questionnaires on therapeutic decisions using the DCE approach [13–15]. Answers reported by physicians were anonymous. Physicians were remunerated for their participation; this study was conducted in accordance with French regulatory requirements. The protocol and all administrative documents, including the financial agreement, were approved by the National Medical Council (Conseil National de l'Ordre des Médecins [CNOM]). The database was declared to the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés [CNIL]). Submission to an ethics committee was not required under French law.

### Selection of Participants

We wanted to conduct the study in a representative sample of rheumatologists who were hospital-based, office-based, or with a mixed practice (i.e., both hospital and office-based). Contacted physicians were required to be members of the French medical council (CNOM) with no limits in terms of age or number of years of practice. Practicing rheumatologists were identified in a database provided by IQVIA. It included 828 French rheumatologists who were offered to participate in the study. The goal of participant recruitment was to obtain a sample representative of the geographic distribution of French rheumatologists. A socio-demographic questionnaire was presented at the beginning of the study. The questionnaire collected data related to the physician and his/her usual clinical practice. It

also requested information regarding mode of practice, sex, age category, number of years of clinical practice in the current specialty, frequency of patients with RA seen in consultation, referral hospital, and whether they were initiating bDMARD or csDMARD treatments for patients with RA.

### Case-Vignettes Development

Case-vignettes were developed and pretested in collaboration with two experts in the treatment of RA (ES and BF). The basic structure of a vignette briefly described a patient living with RA, stable over the past 5 years thanks to an initial therapeutic strategy (optimized MTX 20 mg weekly and 5 mg of prednisone daily) and presenting with a recent increase in disease activity (see example Figure S1a in the electronic supplementary material). The medical history and examination included six specific clinical characteristics selected from a review of the literature (Table 1). These study variables were either poor prognostic factors (3) or comorbidities (3) (Table 1). The three poor prognostic factors have been consistently used for guiding treatment decisions in RA, namely disease activity according to Disease Activity Score in 28 Joints (DAS28), presence of structural damage, and presence of autoantibodies [2, 3]. The selected comorbidities were chosen as variables of interest because of their frequency in patients with RA [18]. None of the comorbidities were associated with an absolute or relative contraindication for any therapeutic option.

The set of vignettes was developed using a random combination of the six predefined study variables [19]. Each variable had two categories, and the number of possible combinations was  $2^6 = 64$ . An exploratory analysis was performed on disease activity; for each category (high and moderate), two additional sub-categories were defined according to the predominance of subjective (tender joint [TJ]; patient global assessment on a 0–100 VAS [Global VAS]) or objective (swollen joint [SJ]; C-reactive protein [CRP]) components of the DAS28. The final drafting of vignettes was conducted in a way as

**Table 1** Study variables and their respective categories

Variables of interest		Categories
RA prognostic factors	DAS28 score	High activity: DAS28 > 5.1
		Moderate activity: DAS28 > 3.2 and ≤ 5.1
	RF and/or ACPA	Seropositive (RF <sup>+</sup> and/or ACPA <sup>+</sup> )
		Seronegative (RF <sup>-</sup> and ACPA <sup>-</sup> )
Progression of structural damage	Presence Absence	
RA comorbidities	Serious or recurrent infection	Hospitalization due to pneumococcal pneumonia 2 years ago, or repetitive urinary tract infections with an episode of pyelonephritis, or recurrent herpes labialis
		Absence
	Cardiovascular disease	History of myocardial infarction, or pectoris angina with stent
		Absence
Pulmonary disease	Rheumatoid lung nodules, or diffuse interstitial lung disease	
	Absence	

*ACPA* anti-citrullinated protein antibodies, *DAS* disease activity score, *RA* rheumatoid arthritis, *RF* rheumatoid factor

to obtain clinical cases that were realistic and as close as possible to the current practice of physicians while maintaining a strong homogeneity. To avoid the participants being confronted with only the variables of interest, and to ensure that the vignettes would present patient complexity similar to actual practice, each vignette also included information regarding the patient's age (ranging from 41 to 59 years), sex (male-to-female ratio 1:3), occupation, and comorbidity without impact on RA management (see Figure S1b in the electronic supplementary material for details) [10].

### Physician Preference Assessment

The assessment of the physicians' therapeutic preferences was based on the DCE approach, a quantitative technique for revealing individual preferences in complex decision situations when direct questioning is not possible [13–15]. All participants were asked to complete eight vignettes via an online platform. Upon the presentation of a vignette, each participant had to assess the six following therapeutic options, randomly proposed 3 by 3: replacing MTX by another csDMARD (csDMARD switch), adding one or more csDMARD to MTX (csDMARDs combination), adding a TNFi, adding tocilizumab (TCZ), adding abatacept (ABA), or adding rituximab (RTX). For each vignette, ten different combinations of three therapeutic options were assessed. For each combination of three therapeutic options, the participants had to select the most and least appropriate therapeutic option (best–worst [BW] scaling method) [20].

### Statistical Analysis

Sample size calculations revealed that 216 participants were needed to conduct this cross-sectional study based on the following elements: (1) a Balanced Incomplete Block Design was used to randomly distribute the 64 vignettes (each rheumatologist needed to evaluate the same number of vignettes); (2) each vignette had to be evaluated the same number of times by 25–30 different rheumatologists to obtain



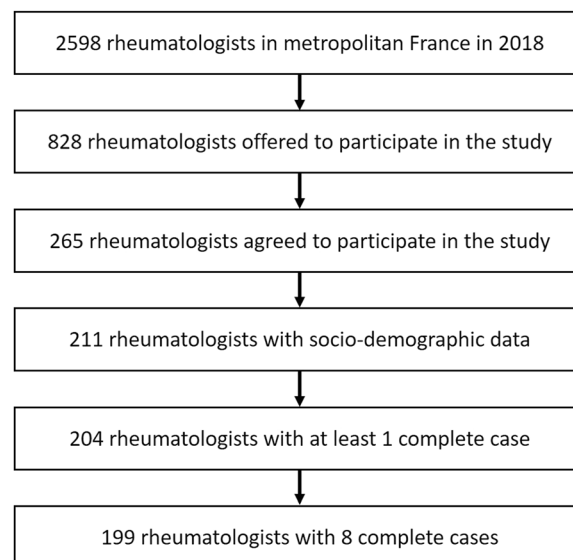
precise estimates; and (3) each rheumatologist needed to evaluate a maximum of ten vignettes [21].

Analyses were mainly descriptive, as the study was observational. Therapeutic option preference was expressed using a score. A bonus of 1 point was attributed to a therapeutic option when it was considered as the preferred choice, and a penalty of  $-1$  point was attributed when it was considered as the worst option. Therapeutic option scores were calculated as the difference between the number of bonus points and penalty points, and they ranged from  $-5$  to  $+5$  for each vignette. A normalized BW score (BWS) was then computed for each therapeutic option ranging from  $-1$  (worst option) to  $+1$  (best option); this normalized score was used to rank the therapeutic options separately in each vignette and then to rank them globally. The multiplication of vignettes and therapeutic options associated with the score-based ranking enabled the analysis of physician preferences. Statistical analysis was carried out using SAS software Version 9.4, except graphs for which the R software Version 3.5.1 were used.

## RESULTS

### Participants

A total of 211 French rheumatologists took part in the study (signed a contract and received a center number), 204 (97%) assessed at least one vignette, and 199 (94%) of the investigators who started the study evaluated all eight vignettes (Fig. 1). A detailed description of the participants is found in Table 2. Investigators were predominantly women (56.9 vs. 43.1%), 46.9% were hospital-based, 26.5% office-based, and the remaining 26.5% had a mixed practice. The average practice duration was 16.8 years, and most participants (84.4%) reported seeing more than one patient with RA per week. Only 2.8% reported seeing a patient with RA less than once per month. The majority of participants reported initiating both csDMARDs and bDMARDs (80.1%), while 19.9% reported initiating csDMARDs only. The geographical distribution of respondents was representative of the



**Fig. 1** Diagram depicting the recruitment of rheumatologists

rheumatologist distribution in mainland France (data not shown).

### Vignettes

A total of 1605 vignettes were assessed in this study with each of the 64 individual vignettes being assessed between 20 and 28 times. Of the 1605 vignettes, 87% included at least one poor prognostic factor while 12.5% included all three poor prognostic factors. Additionally, 87.5% of the vignettes included at least one comorbidity of interest and 12.5% included the three comorbidities of interest.

### Therapeutic Preferences

A full algorithm with the ranking of all therapeutic options for each vignette is presented in Fig. 2. A TNFi was the preferred strategy in 80% of the vignettes and ABA was the first option in the remaining cases. In all the cases where ABA was the first option, there was a history of infection and, in most (85%), a pulmonary involvement. Abatacept was the most frequently selected second option in 75% of the vignettes, while TNFi was selected in 20% and TCZ in 5%. Tocilizumab was chosen as the third

**Table 2** Socio-demographic data of participating physicians

	<b>Total (n = 211)</b>
Sex	
Male	91 (43.1%)
Female	120 (56.9%)
Age (years)	
20–30	12 (5.7%)
31–40	65 (30.8%)
41–50	43 (20.4%)
51–60	62 (29.4%)
≥ 61	29 (13.7%)
Mode of exercise	
Hospital-based	99 (46.9%)
Office-based	56 (26.5%)
Mixed	56 (26.5%)
Number of years practice in current speciality	
Mean (SD)	16.8 (10.3)
Median (Q1–Q3)	15.0 (7.0–27.0)
Number of years practice in current speciality	
≤ 10	85 (40.3%)
10–19	36 (17.1%)
≥ 20	90 (42.7%)
Frequency of consultations with RA patients	
> 1 per week	178 (84.4%)
< 1 per week but > 1 per month	27 (12.8%)
≤ 1 per month	6 (2.8%)
Initiation of DMARD in patients with moderate-to-severe RA	
Yes, csDMARDs only (e.g., MTX)	42 (19.9%)

**Table 2** continued

	<b>Total (n = 211)</b>
Yes, csDMARDs, and bDMARDs	169 (80.1%)

*bDMARDs* biological disease-modifying anti-rheumatic drugs, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *MTX*, methotrexate, *n* number of patients in a group, *SD* standard deviation

strategy in most cases (83%). Tumor necrosis factor inhibitor, ABA, and TCZ were ranked in this order in 70% of the vignettes. The average normalized BW score was computed globally for each strategy and showed that TNFi, ABA, and TCZ were associated with a positive BW score while all other strategies, including RTX, were associated with a negative BW score (Fig. 3).

The analysis of the BW score according to the presence of each disease variable of interest yielded similar findings to the one based on the global normalized BW score (Fig. 4). An increase in the number of poor prognostic factors increased physician preference for a strategy based on the addition of a bDMARD, i.e., TNFi, ABA, and TCZ (more positive score), as well as RTX (less negative score, i.e., less rejected strategy). Inversely, an increase in the number of poor prognostic factors decreased physician preference for csDMARD-based strategies, i.e., csDMARD replacement or combination (Fig. 5a). An increase in the number of comorbidities resulted in a decreased preference for adding TNFi and TCZ, and in an increased preference for ABA and RTX, as well as for the csDMARD-based strategies (Fig. 5b). An exploratory analysis by disease activity with four categories (high objective, high subjective, moderate objective, and moderate subjective) revealed a marked increase in preference for TCZ in cases where patients presented with high disease activity and predominance of DAS28 objective components (SJ and CRP) (data not shown). However, TCZ remained the third preferred option even in such patients. Factors related to the prescribing physician appeared to have either a limited or no impact on

Poor Prognostic Factors			Comorbidity				Ranking according to BW score												
DAS28	Auto-antibodies	Structural Progression	History of Infection	Cardiovascular Involvement	Pulmonary Involvement	Option 1	BWS	Option 2	BWS	Option 3	BWS	Option 4	BWS	Option 5	BWS	Option 6	BWS		
High >5.1	RF + and/or ACPA +	+	+	+	+	ABA	0.57	TNFI	0.39	TCZ	0.10	RTX	-0.30	1+ csDMARD	-0.33	csDMARD Sw	-0.41		
						TNFI	0.66	ABA	0.48	TCZ	0.11	RTX	-0.32	1+ csDMARD	-0.35	csDMARD Sw	-0.58		
						ABA	0.56	TNFI	0.48	TCZ	0.13	RTX	-0.13	1+ csDMARD	-0.42	csDMARD Sw	-0.62		
						TNFI	0.52	ABA	0.50	TCZ	0.35	RTX	-0.41	1+ csDMARD	-0.45	csDMARD Sw	-0.52		
						TNFI	0.50	ABA	0.42	TCZ	0.34	RTX	-0.13	1+ csDMARD	-0.55	csDMARD Sw	-0.58		
						TNFI	0.57	ABA	0.49	TCZ	0.26	RTX	-0.30	1+ csDMARD	-0.33	csDMARD Sw	-0.70		
		-	-	-	-	-	-	TNFI	0.55	ABA	0.48	TCZ	0.34	RTX	-0.13	1+ csDMARD	-0.50	csDMARD Sw	-0.74
								TNFI	0.86	TCZ	0.44	ABA	0.34	RTX	-0.32	1+ csDMARD	-0.54	csDMARD Sw	-0.78
								ABA	0.54	TNFI	0.18	TCZ	-0.01	1+ csDMARD	-0.19	csDMARD Sw	-0.23	RTX	-0.29
								TNFI	0.38	ABA	0.34	TCZ	0.06	1+ csDMARD	-0.12	csDMARD Sw	-0.13	RTX	-0.54
								ABA	0.43	TNFI	0.21	TCZ	-0.07	1+ csDMARD	-0.19	RTX	-0.19	csDMARD Sw	-0.20
								ABA	0.55	TNFI	0.52	TCZ	0.04	1+ csDMARD	-0.14	csDMARD Sw	-0.36	RTX	-0.61
	RF - and/or ACPA -	+	+	+	+	+	TNFI	0.28	ABA	0.22	TCZ	-0.03	1+ csDMARD	-0.09	RTX	-0.16	csDMARD Sw	-0.22	
							TNFI	0.48	ABA	0.43	TCZ	0.32	1+ csDMARD	-0.32	csDMARD Sw	-0.45	RTX	-0.45	
							TNFI	0.58	ABA	0.24	TCZ	0.15	1+ csDMARD	-0.24	csDMARD Sw	-0.36	RTX	-0.37	
							TNFI	0.61	ABA	0.32	TCZ	0.23	csDMARD Sw	-0.27	1+ csDMARD	-0.35	RTX	-0.53	
							TNFI	0.63	ABA	0.51	TCZ	0.15	RTX	-0.27	1+ csDMARD	-0.48	csDMARD Sw	-0.55	
							TNFI	0.66	ABA	0.50	TCZ	0.17	1+ csDMARD	-0.32	RTX	-0.35	csDMARD Sw	-0.65	
		-	-	-	-	-	-	TNFI	0.50	ABA	0.34	TCZ	0.22	csDMARD Sw	-0.32	RTX	-0.36	1+ csDMARD	-0.39
								TNFI	0.76	ABA	0.48	TCZ	0.28	1+ csDMARD	-0.39	RTX	-0.56	csDMARD Sw	-0.57
								TNFI	0.66	ABA	0.34	TCZ	0.07	RTX	-0.13	1+ csDMARD	-0.46	csDMARD Sw	-0.50
								TNFI	0.81	TCZ	0.36	ABA	0.21	RTX	-0.38	1+ csDMARD	-0.42	csDMARD Sw	-0.59
								TNFI	0.55	ABA	0.33	TCZ	0.30	RTX	-0.22	1+ csDMARD	-0.48	csDMARD Sw	-0.48
								TNFI	0.83	TCZ	0.39	ABA	0.34	RTX	-0.39	1+ csDMARD	-0.50	csDMARD Sw	-0.68
Moderate ≥ 3.2, ≤ 5.1	RF + and/or ACPA +	+	+	+	+	ABA	0.37	TNFI	0.30	1+ csDMARD	0.08	TCZ	-0.10	csDMARD Sw	-0.17	RTX	-0.47		
						TNFI	0.52	ABA	0.40	TCZ	0.09	1+ csDMARD	-0.28	RTX	-0.34	csDMARD Sw	-0.38		
						ABA	0.40	TNFI	0.27	TCZ	0.09	csDMARD Sw	-0.15	RTX	-0.28	1+ csDMARD	-0.34		
						TNFI	0.47	ABA	0.39	TCZ	0.18	1+ csDMARD	-0.22	csDMARD Sw	-0.40	RTX	-0.43		
						TNFI	0.40	ABA	0.40	TCZ	0.02	1+ csDMARD	-0.14	csDMARD Sw	-0.23	RTX	-0.45		
						TNFI	0.71	ABA	0.32	TCZ	0.05	1+ csDMARD	-0.18	RTX	-0.42	csDMARD Sw	-0.48		
	RF - and/or ACPA -	+	+	+	+	+	TNFI	0.50	ABA	0.33	TCZ	0.33	RTX	-0.34	csDMARD Sw	-0.36	1+ csDMARD	-0.45	
							TNFI	0.75	ABA	0.18	TCZ	0.13	csDMARD Sw	-0.17	1+ csDMARD	-0.40	RTX	-0.50	
							TNFI	0.67	ABA	0.53	TCZ	0.04	RTX	-0.22	csDMARD Sw	-0.47	1+ csDMARD	-0.55	
							TNFI	0.72	ABA	0.54	TCZ	0.07	1+ csDMARD	-0.29	RTX	-0.47	csDMARD Sw	-0.56	
							ABA	0.57	TNFI	0.41	TCZ	0.16	RTX	-0.09	1+ csDMARD	-0.48	csDMARD Sw	-0.57	
							TNFI	0.50	ABA	0.45	TCZ	-0.02	csDMARD Sw	-0.29	1+ csDMARD	-0.29	RTX	-0.34	
Moderate ≥ 3.2, ≤ 5.1	RF + and/or ACPA +	+	+	+	+	TNFI	0.53	ABA	0.39	TCZ	0.29	RTX	-0.01	1+ csDMARD	-0.52	csDMARD Sw	-0.68		
						TNFI	0.78	ABA	0.40	TCZ	0.10	1+ csDMARD	-0.26	RTX	-0.33	csDMARD Sw	-0.70		
						TNFI	0.49	ABA	0.37	TCZ	0.30	RTX	-0.16	csDMARD Sw	-0.50	1+ csDMARD	-0.50		
						TNFI	0.75	ABA	0.40	TCZ	0.26	RTX	-0.35	1+ csDMARD	-0.42	csDMARD Sw	-0.64		
						ABA	0.43	TNFI	0.34	1+ csDMARD	-0.11	csDMARD Sw	-0.16	TCZ	-0.19	RTX	-0.31		
						TNFI	0.35	ABA	0.28	TCZ	-0.01	csDMARD Sw	-0.05	1+ csDMARD	-0.06	RTX	-0.52		
	RF - and/or ACPA -	+	+	+	+	+	ABA	0.32	TNFI	0.26	1+ csDMARD	-0.03	TCZ	-0.03	csDMARD Sw	-0.10	RTX	-0.42	
							TNFI	0.42	ABA	0.25	TCZ	0.00	1+ csDMARD	-0.03	csDMARD Sw	-0.14	RTX	-0.49	
							TNFI	0.49	ABA	0.28	TCZ	0.03	1+ csDMARD	-0.13	csDMARD Sw	-0.23	RTX	-0.44	
							TNFI	0.79	ABA	0.28	TCZ	0.00	1+ csDMARD	-0.23	csDMARD Sw	-0.25	RTX	-0.59	
							TNFI	0.32	ABA	0.13	csDMARD Sw	-0.02	1+ csDMARD	-0.03	TCZ	-0.08	RTX	-0.32	
							TNFI	0.61	ABA	0.21	TCZ	0.13	1+ csDMARD	-0.16	csDMARD Sw	-0.26	RTX	-0.54	
Moderate ≥ 3.2, ≤ 5.1	RF + and/or ACPA +	+	+	+	+	ABA	0.49	TNFI	0.36	TCZ	0.04	RTX	-0.19	1+ csDMARD	-0.27	csDMARD Sw	-0.43		
						TNFI	0.54	ABA	0.46	TCZ	-0.09	1+ csDMARD	-0.18	csDMARD Sw	-0.29	RTX	-0.44		
						TNFI	0.51	ABA	0.49	TCZ	0.37	RTX	-0.27	1+ csDMARD	-0.53	csDMARD Sw	-0.57		
						TNFI	0.77	ABA	0.46	TCZ	0.12	RTX	-0.36	1+ csDMARD	-0.39	csDMARD Sw	-0.59		
						TNFI	0.48	ABA	0.41	TCZ	0.15	1+ csDMARD	-0.19	RTX	-0.23	csDMARD Sw	-0.62		
						TNFI	0.66	ABA	0.42	TCZ	0.04	1+ csDMARD	-0.32	RTX	-0.38	csDMARD Sw	-0.43		
	RF - and/or ACPA -	+	+	+	+	+	TNFI	0.50	ABA	0.43	TCZ	0.28	RTX	-0.22	csDMARD Sw	-0.40	1+ csDMARD	-0.58	
							TNFI	0.83	ABA	0.43	TCZ	0.28	RTX	-0.41	1+ csDMARD	-0.47	csDMARD Sw	-0.66	
							TNFI	0.51	ABA	0.42	TCZ	-0.11	csDMARD Sw	-0.15	1+ csDMARD	-0.30	RTX	-0.37	
							ABA	0.40	TNFI	0.38	csDMARD Sw	-0.03	TCZ	-0.10	1+ csDMARD	-0.14	RTX	-0.52	
							ABA	0.26	TNFI	0.24	1+ csDMARD	0.08	csDMARD Sw	0.03	TCZ	-0.09	RTX	-0.52	
							TNFI	0.57	ABA	0.30	TCZ	0.05	csDMARD Sw	-0.10	1+ csDMARD	-0.18	RTX	-0.64	
Moderate ≥ 3.2, ≤ 5.1	RF - and/or ACPA -	+	+	+	+	TNFI	0.50	ABA	0.32	TCZ	0.07	csDMARD Sw	-0.22	1+ csDMARD	-0.32	RTX	-0.35		
						TNFI	0.55	ABA	0.31	1+ csDMARD	0.23	TCZ	-0.22	csDMARD Sw	-0.29	RTX	-0.58		
						TNFI	0.55	ABA	0.18	csDMARD Sw	-0.04	TCZ	-0.08	1+ csDMARD	-0.23	RTX	-0.39		
						TNFI	0.59	ABA	0.14	TCZ	0.06	csDMARD Sw	0.00	1+ csDMARD	-0.17	RTX	-0.63		

**Fig. 2** Summary of standardized BW scores (six study variables, six preferred options) for all 64 case-vignettes. 1 + csDMARD conventional synthetic disease-modifying anti-rheumatic drug combination, ABA abatacept, ACPA

anti-citrullinated protein antibodies, csDMARD Sw conventional synthetic disease-modifying anti-rheumatic drug switch, RF rheumatoid factor, RTX rituximab, TCZ tocilizumab, TNFI tumor necrosis inhibitors

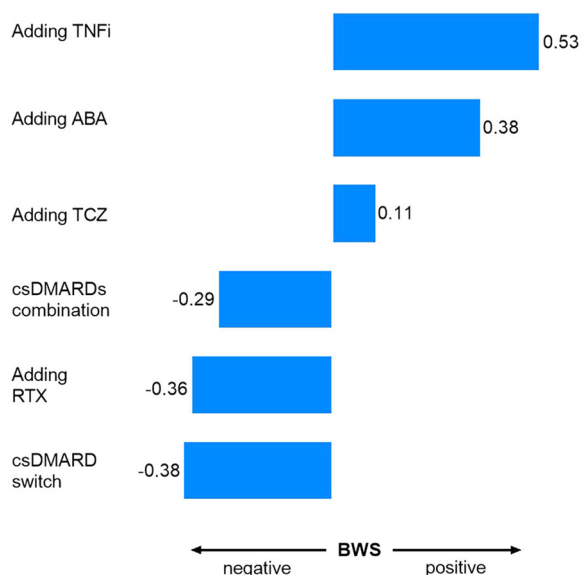
therapeutic decisions (see Figure S2 in the electronic supplementary material for details)..

## DISCUSSION

This study aimed to describe therapeutic preferences in RA after failure of MTX and to

evaluate the impact of selected factors related to RA, the patient, and physician on the decision-making process. It is important to point out that French rheumatologists have no consistent constraint in their prescription of targeted therapies in RA patients with inadequate response to MTX; all six proposed options are accepted by the health authorities and





**Fig. 3** Standardized global BWS score for all six therapeutic options. *ABA* abatacept, *BWS* best–worst scores, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *RTX* rituximab, *TCZ* tocilizumab, *TNFi* tumor necrosis inhibitors

reimbursed for all patients by the national public health insurance. This substantial drug prescription freedom led to reasonable use of targeted therapies, which are used in approximately 31% of RA patients [22].

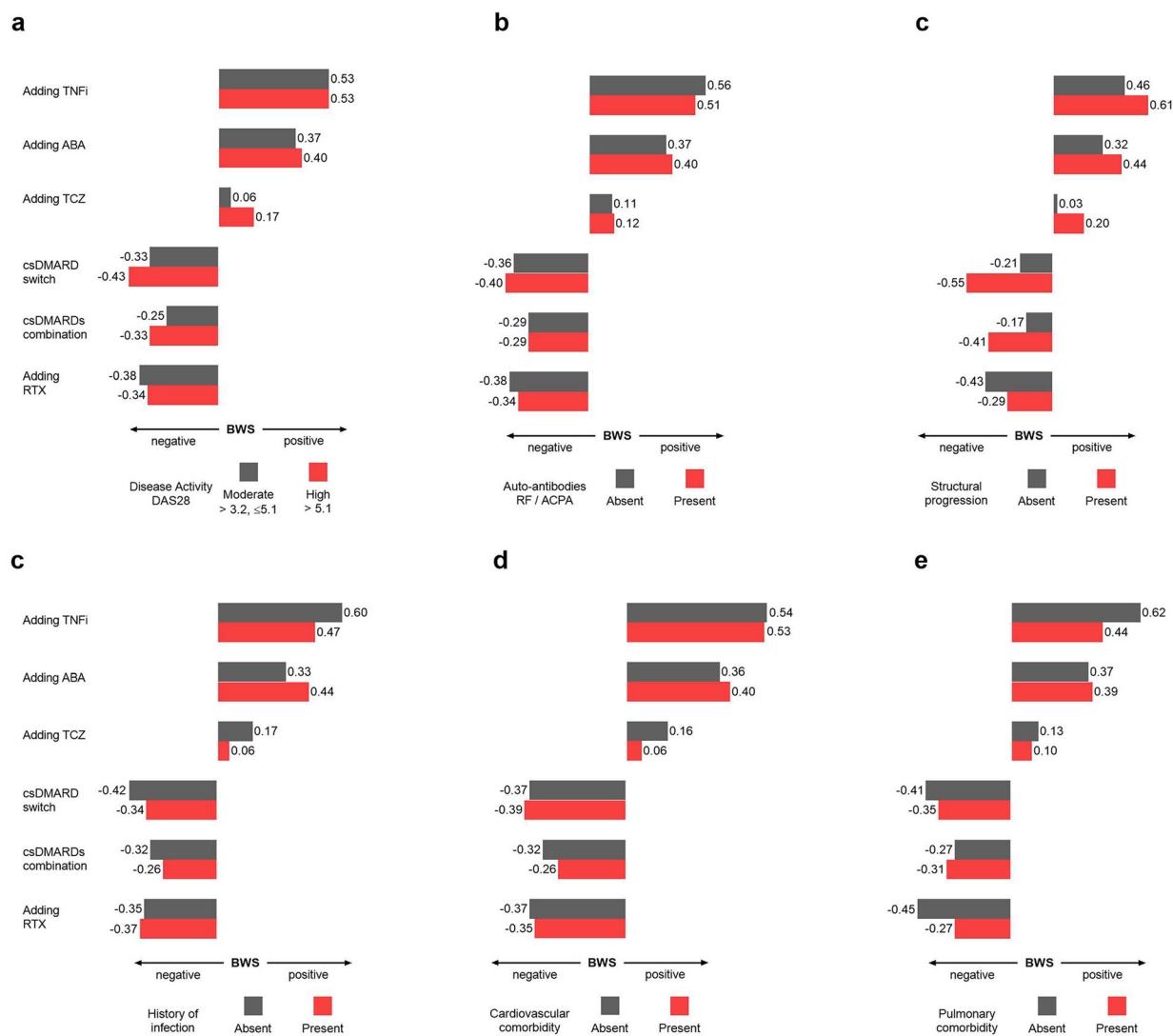
We developed 64 fictional, but realistic, clinical case-vignettes to elicit the therapeutic preferences of 211 French rheumatologists. In the current study, case-vignettes were associated with questionnaires on therapeutic decisions using the well-established DCE approach. The multiplication of vignettes and therapeutic options associated with a score-based ranking enabled the assessment of physician preferences.

Our study demonstrates an overall conservative trend among physicians, with TNFi being the strategy of choice in 80% in these simulated patients with RA. This is aligned with the results of several publications on treatment pattern in real patients [23–25]. The exception to this trend was found in patients with a history of infection and pulmonary comorbidity, where ABA was the preferred option. This result was not unexpected, as some guidelines have

proposed to favor ABA over TNFi in patients with history of serious infections based on very low-quality evidence [3]. On the other hand, there is only limited evidence to support the use of ABA in interstitial lung disease associated with RA and no evidence to support its use in the case of rheumatoid lung nodules [26]. Rituximab was consistently ranked after the other bDMARDs strategies; this could be explained by the instructions-for-use on its label, which describes RTX as being indicated for use in patients with RA who display inadequate response or intolerance to one or more TNFi.

Poor prognostic factors have been identified as an important decision-criteria for treatment intensification with bDMARDs [2, 27]. This was reflected in our work, as an increase in the number of poor prognostic factors had a positive impact on the preference of all bDMARD-based strategies, i.e., TNFi, ABA, and TCZ (more positive score), as well as RTX (less negative score). Reliability of DAS28 in the individual patient has been questioned as the presence of subjective components (i.e., TJ and VAS) can lead to misclassification of disease activity and potentially overtreatment [28]. Some authors have argued that patient global assessment should be removed from composite measures of disease activity [29]. While the added value of subjective components to guide treatment intensification is still debated, the impact on therapeutic decision after MTX failure is not known. In our study, an analysis performed according to the predominance of objective or subjective components of DAS28 showed mainly an increased preference for TCZ in case of high disease activity with predominance of objective components. The effect on the BW score of the other strategies was more limited.

Guidelines for RA invite physicians to include comorbidities in treatment decisions [2, 18]. We found that an increase in the number of comorbidities resulted in a decreased preference for adding TNFi and TCZ, and an increased preference for ABA and RTX, as well as for the csDMARD-based strategies. The influence of comorbidities on therapeutic decisions in RA is not well understood. Previous studies have shown a higher prevalence of



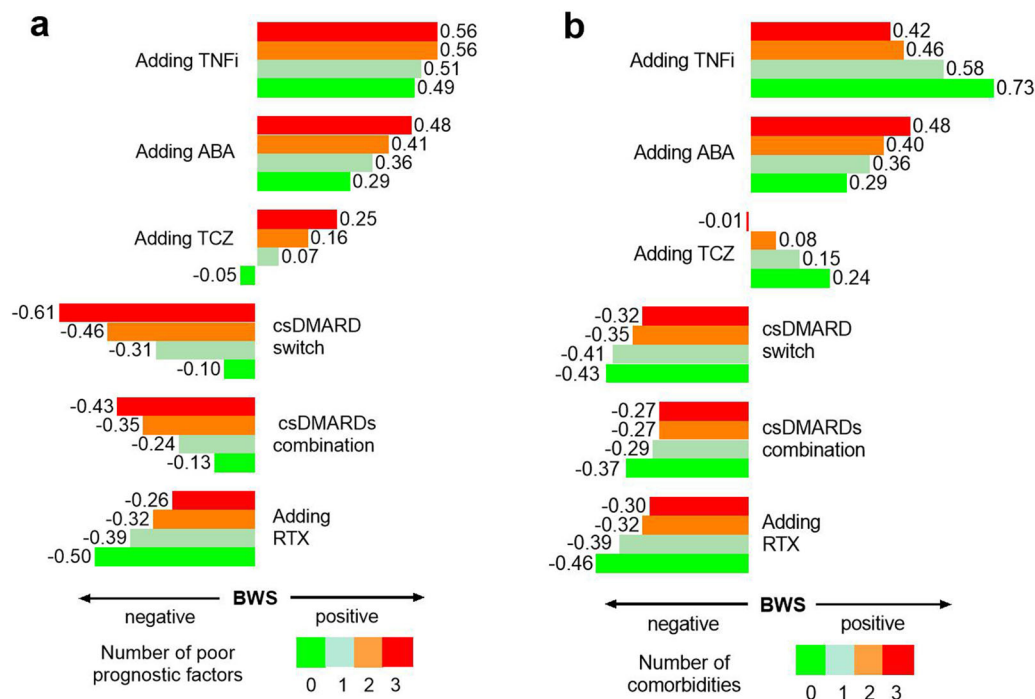
**Fig. 4** Standardized BW scores by **a** disease activity (DAS28), **b** presence of autoantibodies (RF/ACPA), **c** structural progression, **d** history of infection, **e** cardiovascular comorbidity, and **f** pulmonary comorbidity. *ABA* abatacept, *ACPA* anti-citrullinated protein antibodies,

*BWS* best–worst scores, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drug, *RF* rheumatoid factor, *RTX* rituximab, *TCZ* tocilizumab, *TNFI* tumor necrosis inhibitors

comorbidities in patients on csDMARDs in comparison to patients on bDMARDs [24, 30, 31]. Frisell et al. observed substantial differences in baseline characteristics of patients at the start of a first bDMARD with patients starting on ABA or RTX more likely to have a history of comorbidity (e.g., serious infection, pulmonary disease) than patients starting a TNFi or TCZ [25]. The comorbidities selected as

variables of interest in this study were neither associated with an absolute nor relative contraindication, nor with a recommendation for any therapeutic option. This was done to limit the weight that such comorbidities would have had on the therapeutic decision.

There is limited and conflicting evidence regarding the impact of prescribers' demographic characteristics and mode of practice on



**Fig. 5** Standardized BW score according to the **a** number of poor prognostic factors and **b** number of comorbidities. *ABA* abatacept, *BWS* best–worst scores, *csDMARDs*

conventional synthetic disease-modifying anti-rheumatic drug, *RTX* rituximab, *TCZ* tocilizumab, *TNFi* tumor necrosis inhibitors

treatment decisions in RA [32, 33]. Results may vary according to geographic location. For instance, in France, bDMARDs used to treat RA should only be initiated by rheumatologists who are hospital-based, and those with a mixed practice (both private office- and hospital-based). Office-based rheumatologists will usually refer patients with RA to hospital clinics to receive their first bDMARD prescription, while renewal of bDMARD prescriptions may be done in the office-setting thereafter. In our study, the mode of practice (office-, hospital-, or mixed) did not appear to influence physician preference. Other factors related to the prescribing physician, such as years of practice and number of RA patients seen per week also appeared to have either a limited or no impact on physician preference.

Physician preference has been identified in previous research as a significant determinant of treatment decisions in RA [34, 35]. With an increasing number of therapeutic options available for patients in RA, it is important for

physicians to better understand treatment decisions in clinical practice. Preference for a given therapeutic option may lead to a non-random allocation of treatment. This decision can be motivated by scientific evidence, prescribing experience, or a mere misconception about the therapy [25, 36]. Evaluating medical practices and behaviors is essential to improving the quality of care. The methods used must be accurate, valid, and closely mimic cases encountered in daily practice. There are several methods available including the audit of clinical practices, trained actors to present as patients, or the use of case-vignettes. Case-vignettes have been increasingly used in various chronic conditions to assess decision-making [37]. Results from case-vignettes studies have been shown to be comparable to those obtained with practice audits or standardized patients while also measuring the quality of care [10]. Case-vignettes have the added advantage of avoiding differences in recruitment, the variability introduced by the disease severity, as

well as other potential confounding factors that could interfere with the decision-making process.

The strengths of our study include the representativeness of participating rheumatologists with each region proportionally represented based on national demographics at the time of participation. We also note that only a small minority of the participants (15.6%) reported seeing less than one RA patient per week. An additional strength of the work was the high level of engagement obtained, as 94% of the participants with socio-demographic data completed all evaluations [38]. Finally, we believe that the design of our study, using case-vignettes with questionnaires following the DCE approach, enabled the assessment of preferences while limiting the risk of response bias.

A potential weakness of these findings relates to timeliness. As tsDMARDs had been available for less than 1 year for the treatment of RA in France, we focused this work on well-established csDMARD- and bDMARD-based strategies. Repeated or longitudinal studies will be needed to monitor the changing preferences of physicians as the field gains hands-on experience with the use of newer therapies. We also recognize that other factors, such as patient preference and continually evolving treatment recommendations, influence treatment decisions. We had to limit the number of variables of interest during the development of case-vignettes since the number of combinations increases quickly as more variables and categories are considered. The limited number of factors does not impact the validity of our results, but future studies should be carried out to understand the impact that patient preference and shared decision-making has on therapy selection [3, 39–42]. This is particularly important with the emergence of Janus kinase inhibitors, a new class of oral DMARDs, the first of which was approved by the European Medicines Agency and became available in France in 2017 [43, 44]. We note that the simulated population of patients may not be representative of the population seen by all rheumatologists, which may affect the generalizability of some of our results. However, this should be limited to the overall ranking of ABA

and TCZ as results regarding the other options were aligned with findings from the literature.

## CONCLUSIONS

This study provides information on the prescribing habits of French rheumatologists in RA after failure of a first-line strategy with MTX. We found a conservative trend with TNFi being the main therapeutic choice for most RA patients and ABA as the primary therapeutic choice for patients with pulmonary involvement or high risk of infection. We also found that an increase in the number of comorbidities resulted in a decreased preference for adding TNFi and TCZ, and in an increased preference of ABA and RTX, as well as of the other strategies. Understanding clinical decision-making will be particularly important as the therapeutic landscape for RA continues to evolve. The study should be repeated in the future to include new therapeutic options and explore patient preferences in the context of shared decision-making.

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**Authorship** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval this version for to be published.

**Authors' Contributions** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Baptiste Roux, Eric Senbel, Bruno Fautrel, and Frederick Durand. Bruno Fautrel, Frederick Durand, Eric Senbel, and Baptiste Roux planned and directed data interpretation. All authors contributed to manuscript drafting, provided critical revision throughout, and approved the final version for submission.

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**Compliance with Ethics Guidelines** This study involved the elicitation of physician preference and was conducted in accordance with French regulatory requirements. The protocol and all administrative documents, including the financial agreement, were approved by the National Medical Council (Conseil National de l'Ordre des Médecins [CNOM]). The database was declared to the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés [CNIL]). Submission to an ethics committee was not required under French law.

**Data Availability** All data generated or analyzed during this study are included in this published article as a supplementary information file.

**Prior Presentation** Preliminary results from this analysis were presented in poster format at the European League Against Rheumatism (EULAR) 2020 Annual Meeting.

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