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Towards the Lowest Efficacious Dose: Results From a Multicenter Noninferiority Randomized Open-Label Controlled Trial Assessing Tocilizumab or Abatacept Injection Spacing in Rheumatoid Arthritis in Remission

Joanna Kedra ¹, Philippe Dieudé ², Caroline Giboin ¹, Hubert Marotte ³, Carine Salliot ⁴, Thierry Schaevebeke ⁵, Aleth Perdriger ⁶, Martin Soubrier ⁷, Jacques Morel ⁸, Arnaud Constantin ⁹, Emmanuelle Dernis ¹⁰, Valérie Royant ¹¹, Jean-Hugues Salmon ¹², Thao Pham ¹³, Jacques-Eric Gottenberg ¹⁴, Edouard Pertuiset ¹⁵, Maxime Dougados ¹⁶, Valérie Devauchelle-Pensec ¹⁷, Philippe Gaudin ¹⁸, Grégoire Cormier ¹⁹, Philippe Goupille ²⁰, Xavier Mariette ²¹, Francis Berenbaum ²², Didier Alcaix ²³, Sid-Ahmed Rouidi ²⁴, Jean-Marie Berthelot ²⁵, Agnès Monnier ²⁶, Christine Piroth ²⁷, Frédéric Lioté ²⁸, Vincent Goëb ²⁹, Cécile Gaujoux-Viala ³⁰, Isabelle Chary-Valckenaere ³¹, David Hajage ¹, Florence Tubach ¹, Bruno Fautrel ¹; CRI-IMIDIATE clinical research network

Affiliations

¹ Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Pitié Salpêtrière, Paris, France.

² Université de Paris Cité, INSERM UMR 1152 and Hôpital Bichat-Claude Bernard, AP-HP, Paris, France.

³ Université Jean Monnet Saint-Étienne, Centre Hospitalier Universitaire de Saint-Etienne, Mines Saint-Etienne, INSERM, SAINBIOSE U1059, Saint-Étienne, France.

⁴ Orleans Regional Hospital, Orleans, France.

⁵ Bordeaux-Pellegrin University Hospital, Bordeaux, France.

⁶ Rennes University Hospital, Rennes, France.

⁷ Clermont-Ferrand University Hospital, Clermont-Ferrand, France.

⁸ Montpellier University Hospital and University of Montpellier, INSERM, CNRS, Montpellier, France.

⁹ Pierre-Paul Riquet University Hospital, Toulouse III - Paul Sabatier University, and INSERM UMR 1291, Purpan University Hospital, Toulouse, France.

¹⁰ Le Mans General Hospital, Le Mans, France.

¹¹ Chartres Hospital, Chartres, France.

¹² University of Reims Champagne-Ardenne, Faculty of Medicine, UR 3797 and Maison Blanche Hospital, Reims University Hospitals, Reims, France.

- ¹³ Sainte-Marguerite Hospital, Assistance Publique - Hôpitaux de Marseille, Marseille, France.
- ¹⁴ Hautepierre Hospital, Strasbourg University Hospital, Strasbourg, France.
- ¹⁵ Nord-Ouest Val-d'Oise Hospital, Pontoise, France.
- ¹⁶ University of Paris, Hôpital Cochin. AP-HP, INSERM U1153, pôle de recherche et d'enseignement supérieur Sorbonne Paris-Cité, Paris, France.
- ¹⁷ Brest University Hospital, INSERM U1227, Brest, France.
- ¹⁸ Grenoble Alpes University Hospital, Grenoble, France.
- ¹⁹ La Roche sur Yon Hospital, La Roche sur Yon, France.
- ²⁰ University Hospital of Tours and University of Tours, Tours, France.
- ²¹ Université Paris-Saclay, Hôpital Bicêtre, AP-HP, INSERM UMR1184, Le Kremlin Bicêtre, France.
- ²² Sorbonne University-INSERM Centre De Recherche scientifique Saint-Antoine, AP-HP Saint-Antoine Hospital, Paris, France.
- ²³ Le Havre Hospital, Le Havre, France.
- ²⁴ Châteaudun General Hospital, Châteaudun, France.
- ²⁵ Nantes University Hospital, Nantes, France.
- ²⁶ Cote Basque Hospital, Bayonne, France.
- ²⁷ Dijon University Hospital, Dijon, France.
- ²⁸ Université de Paris and INSERM UMR1132 Bioscar (Centre Viggo Petersen), Hôpital Lariboisière, AP-HP, Paris, France.
- ²⁹ University Hospital of Amiens, Université de Picardie Jules Verne, Amiens, France.
- ³⁰ Institut Pierre Louis d'Epidémiologie et de Santé Publique, University of Montpellier, INSERM, Centre Hospitalier Universitaire de Nîmes, Montpellier, France.
- ³¹ Nancy University Hospital, Nancy, France.

Collaborators

- **CRI-IMIDIATE clinical research network:**

B Banneville, V Foltz, A Ameer, M Afshar, F Desmoulins, S Pavy, R Seror, A Mamoune, J Champey, J Sellam, C Richez, N Mehsen, N Poursac, S Brousseau, M E Truchetet, E Ducourau, A Saraux, D Cornec, M L Tanguy, S Varache, T Marhadour, S Jousse-Jolin, C Kergoulay, N Bihannic, A Clarysse, D Abdi, T Frayssac, S Mathieu, J F Maillefert, P Ornetti, C Fortunet, M Gilson, A Sudre, L Grange, R Gruel, A Sicaud, A Baillet, C Chollet, C Chantreau, L Bessonnet, C Cozic, S Varin, M Caulier, G Tanguy, V Andre, C Zarnitsky, E Thuillier, V Dutot, X Puecha, E Rouanet, V André, F Medina Ortiz, G Direz, B Haettich, J M Piot, S Trijau, C Lukas, S Gouilloux, M C Gomes Martins, S Barrat, G Mouterde, A Guillardau, C Sordet, E Ravet, A Henne, V Segard, J Sibila, E Chatelus, A Cantagrel, B Mazieres, B Jammard, M Laroche, M H Cerato, D Thuillez, O Peyr, J Ora, H K Ea, A Frazier, C Briere, S Ottaviani, G Jelin, H Zylberman-Yona, E Palazzo, M Forien, M Nguyen, A Molto, K Batard, B Pallot-Prades, T Thomas, H Locrelle, I Griffoul, S Mammou, N Charron, J Jusseaume, N Muguet, M L Lepilliez, S Boddaert, M Delaunay, V Dos Santos, F Flaisler, F Erny, V Martaille, C Ruet, B Gareau, C Salliot, S Loiseau-Peres, C Bloino-Ayoul, C Mot, G Coiffier, S Rio, R Damade, N Karaazbidi, A Ouldhennia, S Aprelon, R Mangouka, D Loeuille, I Cerf-Payrastre, M Delattre, S Goulvent, J Peschard, J Lambrecht, P Brochot, E Durand, E Vincent, L Cerloth, C L Gaudron, M Sulpice, S Paulus, F Charbonnier, H Saadia-Tounsi, S Maouel, Y Aboulola, C Le Tiec, G Bensasson, A Nianzou, A Daguanel-Nguyen, B Ghezzoul, V Cogulet, C Poullaouec, C Guimard, F Stephan, E Elequet, S Corny, C Coudert, E Jouffray, P Fagnoni, A Lehmann, Y Poirier, M L Martin, E Morice, D Bolle, A M Caminondo, V Amirat-Combralier, A Martinez, A Hutt, L Caturla, S Houet, E Frantz, S Marque, S Le, R Putrus, Z Sari, S Edet, C Guerin, L Flet, J Mordini, J Perichou, C Chittaro, C Calas, B Darricau, T Page, F Girault, H Bourgoïn, M Blandin, S Bauer, S Boddaert, C Maillard, S Tollec, L Navarro, I Hermelin, P Roge, K Benbekhaled, M Prevot, G Laurennès, P Benoit, A Chambon, M Gerard, C Burtin, C Ligier

Abstract

Objective: We assess the clinical and structural impact at two years of progressively spacing tocilizumab (TCZ) or abatacept (ABA) injections versus maintenance at full dose in patients with rheumatoid arthritis in sustained remission.

Methods: This multicenter open-label noninferiority (NI) randomized clinical trial included patients with established rheumatoid arthritis in sustained remission receiving ABA or TCZ at a stable dose. Patients were randomized to treatment maintenance (M) at full dose (M-arm) or progressive injection spacing (S) driven by the Disease Activity Score in 28 joints every 3 months up to biologics discontinuation (S-arm). The primary end point was the evolution of disease activity according to the Disease Activity Score in 44 joints during the 2-year follow-up analyzed per protocol with a linear mixed-effects model, evaluated by an NI test based on the one-sided 95% confidence interval (95% CI) of the slope difference (NI margin 0.25). Other end points were flare incidence and structural damage progression.

Results: Overall, 202 of the 233 patients included were considered for per protocol analysis (90 in S-arm and 112 in M-arm). At the end of follow-up, 16.2% of the patients in the S-arm could discontinue their biologic disease-modifying antirheumatic drug, 46.9% tapered the dose and 36.9% returned to a full dose. NI was not demonstrated for the primary outcome, with a slope difference of 0.10 (95% CI 0.10-0.31) between the two arms. NI was not demonstrated for flare incidence (difference 42.6%, 95% CI 30.0-55.1) or rate of structural damage progression at two years (difference 13.9%, 95% CI -6.7 to 34.4).

Conclusion: The Towards the Lowest Efficacious Dose trial failed to demonstrate NI for the proposed ABA or TCZ tapering strategy.

INTRODUCTION

Over the last two decades, the treatment strategy in rheumatoid arthritis (RA) has considerably evolved. Biologic disease-modifying antirheumatic drugs (bDMARDs) have greatly improved RA outcomes, and sustained remission is an achievable goal.¹ Long-term drug maintenance is usual in patients with RA who have achieved remission. However, some authors emphasized that drug maintenance may result in patient over treatment because the dose to maintain remission is potentially different from doses required to induce remission.^{2–5} Furthermore, bDMARDs may represent a certain burden for patients with RA.⁶ Additionally, bDMARDs were found to be associated with increased risk of infection: the overall incidence of serious infections in patients with RA receiving bDMARDs ranged from 3 to 7 per 100 patient-years, with no major differences among the different classes of biologics.⁷ Furthermore, the risk of a subsequent infectious episode is increased three- to five-fold for patients receiving bDMARDs.⁸ An increased risk of cancer is also suspected, particularly non melanoma skin cancers with tumor necrosis factor inhibitor (TNFi) treatment.⁹ Finally, bDMARDs are expensive.¹⁰ The reimbursement of these treatments varies among countries, and the treatments may represent a significant financial burden for patients and society.¹¹

Hence, recent international clinical practice guidelines recommended considering a careful and progressive tapering of bDMARDs in the case of sustained remission (after glucocorticoid discontinuation and eventually conventional synthetic DMARD[csDMARD] tapering).^{12,13} Thus, bDMARD tapering in patients with RA in sustained remission is frequently discussed and was considered feasible when applying the treat-to-target and tight-control strategies.^{14–16} Most published studies have investigated TNFi tapering and discontinuation but provided contradictory results. Most failed to demonstrate noninferiority (NI) in terms of the incidence of flares.^{17–22} Two studies demonstrated NI for the primary outcome but also found a significantly increased rate of flare or structural damage progression.^{16,23}

The amount of evidence on the potential benefit of non-TNFi bDMARD tapering is more limited. Tocilizumab (TCZ) is a monoclonal antibody targeting the interleukin-6 receptor. The first observational study of patients enrolled in a long-term extension phase of a TCZ clinical trial, the Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study, showed that TCZ discontinuation resulted in high flare rates, with 35.1% of patients in sustained remission at week 24 and only 13.4% at 1 year.²⁴ The Study on Abatacept and Tocilizumab Attenuation (SONATA) retrospective exploratory cohort study found that tapering TCZ or abatacept (ABA), a co-stimulation molecule blocking cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), was possible at 12 months in only 42% and 27% of patients with RA, respectively, and that complete discontinuation was achievable in 10% of patients for both treatments.²⁵ Conversely, change in the Disease Activity Score in 28 joints (DAS28) or Health Assessment Questionnaire (HAQ) scores at 6 and 12 months did not significantly differ between patients with a dose reduction and those with the usual care.²⁵ To date, no randomized control trial (RCT) has been implemented to bring more robust conclusions. Therefore, the Towards the Lowest Efficacious Dose (ToLEDo) trial aimed to assess the NI of progressively spacing TCZ or ABA driven by DAS28 versus maintenance at full dose on disease activity, relapse, structural lesion progression, and function in patients with established RA in sustained remission.

MATERIALS AND METHODS

Study design.

ToLEDo is a multicenter open-label two-arm NIRCT of patients with RA who achieved remission with TCZ or ABA treatment as monotherapy or combined with methotrexate or leflunomide. The study methodology followed the Prospective Randomized Open Blinded End Point methodologic recommendations.²⁶ This trial was approved by the Committee for the Protection of Persons Ile-de-France 1 on January 12, 2012 (number 12-780) and was registered at ClinicalTrials.gov (NCT01557374). For a list of CRI-IMIDIATE Network members, see Appendix A.

Patients.

All patients included had to fulfill the following criteria: age ≥ 18 years; RA diagnosis according to the American College of Rheumatology-EULAR 2010 criteria²⁷; documented DAS28-erythrocyte sedimentation rate (DAS28ESR) ≤ 2.6 for at least 6 months; no documented structural damage progression on x-rays for at least 1 year; ongoing treatment with TCZ or ABA at as table dose for at least 1 year, used in combination with a csDMARD or as monotherapy; prednisone at a stable low dose (ie, ≤ 5 mg/day); and the ability to provide informed written consent. Of note, similar inclusion criteria have been chosen in RCTs aiming to assess the possibility of tapering bDMARDs in RA, such as Spacing of TNF-blocker injections in Rheumatoid Arthritis Study (STRASS) or Dose Reduction Strategy of Subcutaneous TNF inhibitors (DRESS).¹⁴ Exclusion criteria were ongoing participation in another RCT for RA, planned surgery within the coming 2 years, ongoing or planned pregnancy, no health insurance coverage, a language barrier, and being under guardianship. Patients or the public were not involved in the design, conduct, or reporting of our research.

Randomization.

The randomization list was computer generated, balanced by blocks of variable and undisclosed size, and stratified according to the center and biologic (TCZ or ABA). Patients were randomly assigned in a 1:1 ratio to progressive spacing (S) of TCZ or ABA driven by DAS28 (S-arm) versus maintenance (M) at full dose (M-arm). Concealment of the study group assignments was achieved with the use of a centralized, secure, interactive, Web-based response system (CleanWeb, Tele medicine Technologies) that was accessible from each study center.

Procedures.

Treatments of interest were used at their labeled doses (Supplementary Material 1).^{28,29} In the M-arm, patients were to remain on the labeled dosage of TCZ or ABA (as well as csDMARD in case of combination). All comedications, including corticosteroids, had to

remain unchanged during the 2-year follow-up. In the S-arm, bDMARD injections were progressively spaced every 3 months according to a predetermined four-step algorithm based on the DAS28ESR, up to bDMARD discontinuation at step 4. Spacing was reversed to the previous step in case of an RA flare, defined as DAS28ESR > 3.2 (detailed algorithm in Supplementary Material 1). Similarly, all other co-medications had to remain unchanged during the 2-year follow-up. This procedure was consistent with tapering algorithms from previous RCTs conducted with TNFi in RA.^{14,17}

Outcomes.

Patients were followed up every 3 months for 2 years (details in Supplementary Material 2). The primary endpoint was change in RA disease activity as assessed by the DAS44.³⁰ Disease activity was measured by an assessor who was unaware of the randomization arm, clinical assessment, and treatment administration and management. Several secondary end points were considered: change in RA disease activity as assessed by the DAS28; flare and major flare frequency at 1 and 2 years, defined, respectively, as a resumption of RA inflammatory activity resulting in a DAS28ESR > 3.2 and DAS28ESR > 3.2 not recovered at the visit 3 months later despite bDMARD re-escalation at a previous step; and structural damage progression at 1 and 2 years assessed according to the van der Heijde–modified Sharp score (vSHS) on radiographs of hands, wrists, and forefeet performed at inclusion and 1- and 2-year follow-up. Significant radiographic progression was defined as vSHS change (Δ vSHS) greater than or equal to the smallest detectable change (SDC) (SDC 6.9 points at 2 years).³¹ Finally, the HAQ Disability Index (HAQ-DI) was used to assess functional limitation at baseline, 6, 12, 18, and 24 months of follow-up. The two arms were compared for change in the HAQ-DI from baseline to 2 years.

Statistical analysis.

This trial was designed to detect NI based on the slope of DAS44 score measured from baseline to 2-year follow-up in the S-arm versus the M-arm. The primary analysis compared the difference between the slopes. Under the assumption of an SD of 0.65 for the DAS44 score in patients with RA,^{32a} a correlation of 0.25 between DAS44 measures, and nine repeated DAS44 measures (every 3 months), we needed 105 patients per arm to demonstrate the NI defined by an NI margin of 0.25 points of the DAS44 score, with power of 90% and alpha risk of 5%. To account for the 10% potential lost to follow-up, we planned to include 232 patients (116 per arm). Two population sets were considered: intention to treat (ITT) and per protocol (PP).

For the primary outcome analysis, disease activity was modeled with a linear mixed-effects model to account for repeated measurements in the same individual and the action of time in treatment strategies in the two arms. The NI of the S-arm versus the M-arm was evaluated by an NI test based on the one-sided 95% confidence interval (95% CI) of the slope difference of DAS44 evolution. Two-sided precision 95% CIs were also provided. A sensitivity analysis was performed, considering the use or not of co-medications with csDMARDs (methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine) at baseline. A full description of

secondary outcome analyses (evolution of DAS28, flares, major flares, structural damage progression, and evolution of HAQ-DI) is provided in Supplementary Material 3.

Multiple imputations were used in ITT analyses to replace missing values, assuming that data were missing at random; a sensitivity analysis was performed without imputing missing data in ITT analyses. No imputation was applied in PP analyses. All analyses were performed with R (R Core Team 3.5.0; 2019 R Foundation for Statistical Computing).

Anonymous participant data are available under specific conditions. Proposals will be reviewed and approved by the sponsor, scientific committee, and staff based on scientific merit and absence of competing interests. Once the proposal has been approved, data can be transferred through a secure online platform after the signing of a data access agreement and a confidentiality agreement.

RESULTS

Study population and tapering procedure. Overall, 233 patients were recruited in 31 centers in mainland France and Monaco from March 1, 2012, to May 31, 2016. Five patients withdrew consent before receiving the first dose of the allocated intervention, which led to 228 patients in the ITT population. A total of 165 patients (72.%) received TCZ and 63 (27.6%) ABA. Four patients were lost to follow-up after the baseline visit, and 22 showed major deviation from the protocol (Supplementary Material 4). Thus, the PP population included 202 patients: 90 in the S-arm and 112 in the M-arm (Figure 1). Among them, 148 (73.4 %) received TCZ and 54 (26.6%) ABA.

Patient baseline characteristics are in Table 1. In the PP population, patients were mostly female ($n = 155$, 76.7%); the mean age was 55.7 years (SD 12.4 years). Patients frequently had established and severe RA, with a mean RA duration of 13.4 years (SD 9.1 years), erosive disease in 160 (80.4%), rheumatoid factor positivity in 160 (81.2%), and anticitrullinated peptide antibody positivity in 155 (79.9%). Additionally, a substantial proportion of patients had received previous lines of bDMARDs: one for 51 patients (25.3%), two for 47 (23.3%), and at least three for 47 (23.3%). ABA and TCZ were mostly prescribed with methotrexate ($n = 120$, 59.4%). In the M-arm, almost all patients continued their medication unchanged; only one patient switched to another bDMARD because of loss of efficacy. In the S-arm, according to the tapering algorithm, 41 patients (36.9%) in the ITT population could not taper their bDMARD during the 2-year follow-up, but 70 (63.1%) could taper or discontinue their bDMARD (Figure 2). Tapering was more frequent in patients receiving ABA. Six of the 117 patients in the S-arm (4 receiving ABA and 2 TCZ) experienced loss of efficacy of the

ongoing bDMARD at a mean \pm SD delay of 18.9 ± 5.6 months from inclusion and did not respond to bDMARD re-escalation, so they switched to another bDMARD.

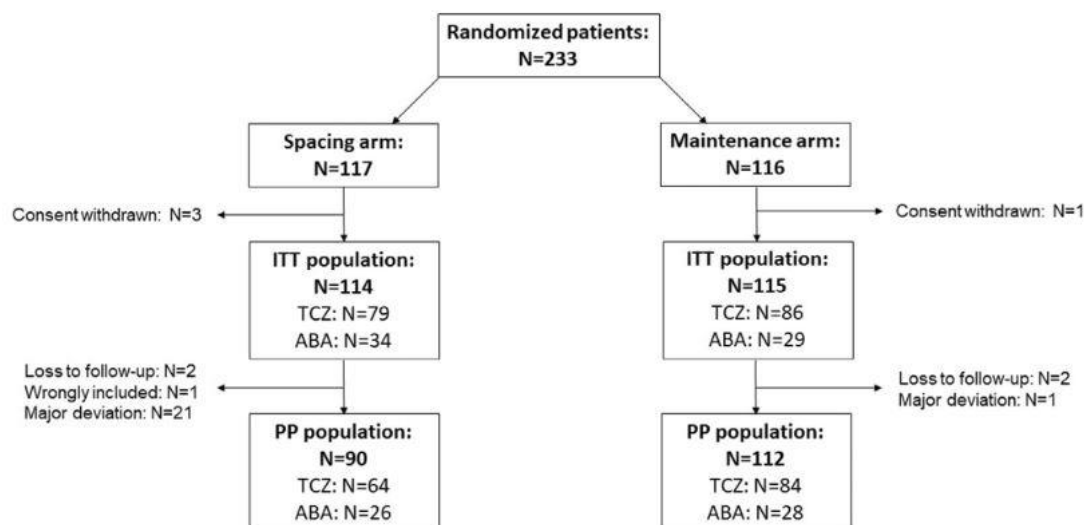


Figure 1. Flow chart of the patients in the trial. A major deviation was defined as a situation in which the inclusion criteria were not fulfilled (except for language barrier, minor fluctuation of Disease Activity Score in 28 joints before inclusion, no stable doses of methotrexate or glucocorticoids before inclusion) and/or a deviation from the tapering strategy likely to have an impact on the evaluation of the primary outcome. Three patients (two in the S-arm and one in the M-arm) had missing data for Disease Activity Score in 44 joints and were therefore removed from the PP primary outcome analysis. ABA, abatacept; ITT, intention to treat; M-arm, maintenance arm; PP, per protocol; S-arm, spacing arm; TCZ, tocilizumab.

Primary outcome analysis.

The primary analysis was performed PP in 199 patients; 3 patients had missing data for the primary outcome. The slope difference between the curves representing the evolution of DAS44 in the S-arm and M-arm during the 2-year follow-up was 0.10 (95% CI–0.10 to 0.31) in the whole population, 0.34 (95% CI–0.07 to 0.74) in the ABA subgroup, and 0.02 (95% CI–0.22 to 0.26) in the TCZ subgroup (Figure3). The upper limit of the one-sided 95% CI of the slope difference exceeded the NI margin of 0.25 in the whole population and ABA subgroup (0.28 and 0.68, respectively) but not in the TCZ subgroup, for whom the upper limit was 0.22 ($P=0.032$). Thus, NI was achieved in the TCZ subgroup but not demonstrated in the whole population or in the ABA subgroup. Similar findings were found on ITT analyses (Supplementary Material 5) as well as PP and ITT analyses regarding the evolution of DAS28 (Figure3 and Supplementary Material 6) and sensitivity analysis taking into account the use or not of co-medication at baseline (Supplementary Material 7).

Secondary outcomes analyses.

In the PP population, 60 patients experienced disease flare in the S-arm ($n=42$ of 90 [46.7%] receiving TCZ, and $n=18$ of 90, [20.0%] receiving ABA), corresponding to a cumulative flare incidence of 66.6%. In the M-arm, 26 patients experienced flare (ie, cumulative flare incidence of 23.6%). The difference in flare incidence between the two arms was +42.6% (95% CI 30.0–55.1), +44.2% (95% CI 20.3–68.1), and +41.8% (95% CI 27.0–56.6) in the whole population and ABA and TCZ subgroups, respectively (Figure4). NI was not demonstrated, including in the sensitivity analysis taking into account whether or not baseline co-medication was used (Supplementary Material 8). Factors remaining significantly

associated with increased risk of flare were allocation to the S-arm (hazard ratio [HR] 3.30, 95%CI 2.11–5.17), baseline HAQ score (HR 1.10, 95% CI 1.03–1.18 for each additional 0.5 points), and baseline ESR (HR 1.03, 95% CI 1.01–1.05) (Table 2 and Supplementary Material 9).

Table 1. Baseline characteristics of the ITT and PP populations*

Randomization arm		ITT population		PP population	
	Monotherapy n (%)	Spacing (n = 113)	Total (n = 228)	Monotherapy n (%)	Spacing (n = 90)
Female sex, n (%)	85 (73.3)	85 (77.3)	170 (75.0)	82 (73.2)	73 (81.1)
Age, mean \pm SD, median (IQR)	54.9 \pm 13.6 (55.9)	56.1 \pm 11.5 (56.0)	55.5 \pm 12.6 (56.0)	55.3 \pm 13.5 (56.0)	56.2 \pm 11.1 (57.5)
Active smokers, n (%)	20 (17.4)	29 (25.7)	49 (21.5)	20 (17.8)	23 (25.6)
Respiratory, n (%)	92 (81.4)	85 (77.3)	177 (78.5)	90 (81.4)	70 (78.7)
RF, n (%)	87 (77.1)	91 (82.0)	178 (79.5)	85 (75.4)	75 (83.3)
RF, n (%)	218.5 \pm 272.6	196.4 \pm 244.7	206.8 \pm 257.7	219.6 \pm 276.5	199.3 \pm 259.9
ACPA, n (%)	85 (77.1)	92 (82.0)	177 (78.5)	82 (73.2)	73 (81.1)
ACPA level, mean \pm SD	925.1 \pm 574.8	926.9 \pm 580.1	926.0 \pm 577.5	927.5 \pm 583.1	942.9 \pm 582.9
RA duration, mean \pm SD	12.5 \pm 8.1	13.4 \pm 9.7	12.9 \pm 9.0	12.5 \pm 8.1	14.4 \pm 10.1
Previous DMARDs, mean \pm SD	3.1 \pm 2.0	3.0 \pm 2.2	3.0 \pm 2.1	3.1 \pm 2.1	3.1 \pm 2.1
Previous DMARDs, n (%)	30 (26.4)	34 (30.1)	64 (28.2)	29 (25.9)	28 (31.1)
Combination with MTX	67 (58.3)	69 (61.1)	136 (59.7)	64 (56.2)	62 (68.9)
Combination with other than MTX	11 (9.6)	12 (10.6)	23 (10.1)	11 (9.6)	9 (10.0)
Monotherapy	37 (32.2)	32 (28.3)	69 (30.3)	37 (32.2)	25 (27.8)
Overall, mean \pm SD	36 (31.3)	26 (23.0)	62 (27.1)	35 (30.7)	19 (21.1)
Pre-treatment	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
Pre-treatment	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
Hydrocortisone	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
Parent global assessment	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
VAS G-10, mean \pm SD	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
Physician global assessment	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
ESR, mean \pm SD, mm/h	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
CRP, mean \pm SD, mg/L	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
SG 44, mean \pm SD	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
TC 44, mean \pm SD	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
DMARDs, mean \pm SD	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)
HAQ, mean \pm SD	31 (27.0)	26 (23.0)	57 (25.0)	30 (26.5)	18 (20.0)

95% CI, 95% confidence interval; ABA, abatacept; ACPA, anticitrullinated peptide antibodies; DMARD, disease-modifying antirheumatic drug; CRP, C-reactive protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IgM, immunoglobulin M; IQR, interquartile range; ITT, intention to treat; MTX, methotrexate; PP, per protocol; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TC2, total count; TC4, tender joint count; VAS, visual analog scale.

95% CI, 95% confidence interval; ABA, abatacept; ACPA, anticitrullinated peptide antibodies; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IgM, immunoglobulin M; IQR, interquartile range; ITT, intention to treat; MTX, methotrexate; PP, per protocol; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TCZ, tocilizumab; TJC, tender joint count; VAS, visual analog scale.

Similarly, major flares were more frequent in the S-arm than M-arm: 15 in the S-arm (n = 8 of 90 [8.9%] receiving TCZ and n = 7 of 90 [7.8%] ABA), corresponding to a cumulative incidence of 16.85%, and 8 in the M-arm (cumulative incidence 7.27%). The difference between the two arms was +9.6% (95% CI 0.4–18.7), +15.8% (95% CI –5.0 to 36.6), and +6.7% (95% CI –3.0 to 16.4) in the whole population and ABA and TCZ sub-groups, respectively, as compared with the M-arm (Figure 4). NI was not demonstrated, including in the sensitivity analysis taking into account whether or not baseline co-medication was used (Supplementary Materials 8 and 10).

In the multivariable Cox model, an increased risk of major flare was associated with ESR at baseline (HR 1.04, 95% CI 1.01–1.07), DAS44 (HR 4.21, 95% CI 1.66–10.72), and HAQ score (HR 1.21, 95% CI 1.08–1.36), and decreased risk of major flare was associated with the absence of swollen joints (HR 0.09, 95% CI 0.02–0.35) (Table 2 and Supplementary Material 9).

The concordance was good between the radiograph readers in terms of evaluating radiographic damage (Supplementary Material 11). Overall, 80 patients (44 in the M-arm and 36 in the S-arm), whose baseline characteristics did not substantially differ from the whole PP population (Supplementary Material 12), had radiograph data at inclusion and at least one of the two reading times and were considered for radiographic damage analysis. A total of 62 patients (34 in the M-arm and 28 in the S-arm) were considered for the analysis of radiographic progression at 2 years. Mean baseline vSHS was 40.8 (SD 59.6) in the S-arm and 35.8 (SD 57.6) in M-arm. The progression between baseline and two years was 5.0 in the S-arm and 2.5 in the M-arm, corresponding to a difference of 2.5 (95% CI –0.3 to 5.3); NI was not demonstrated (Supplementary Material 13).

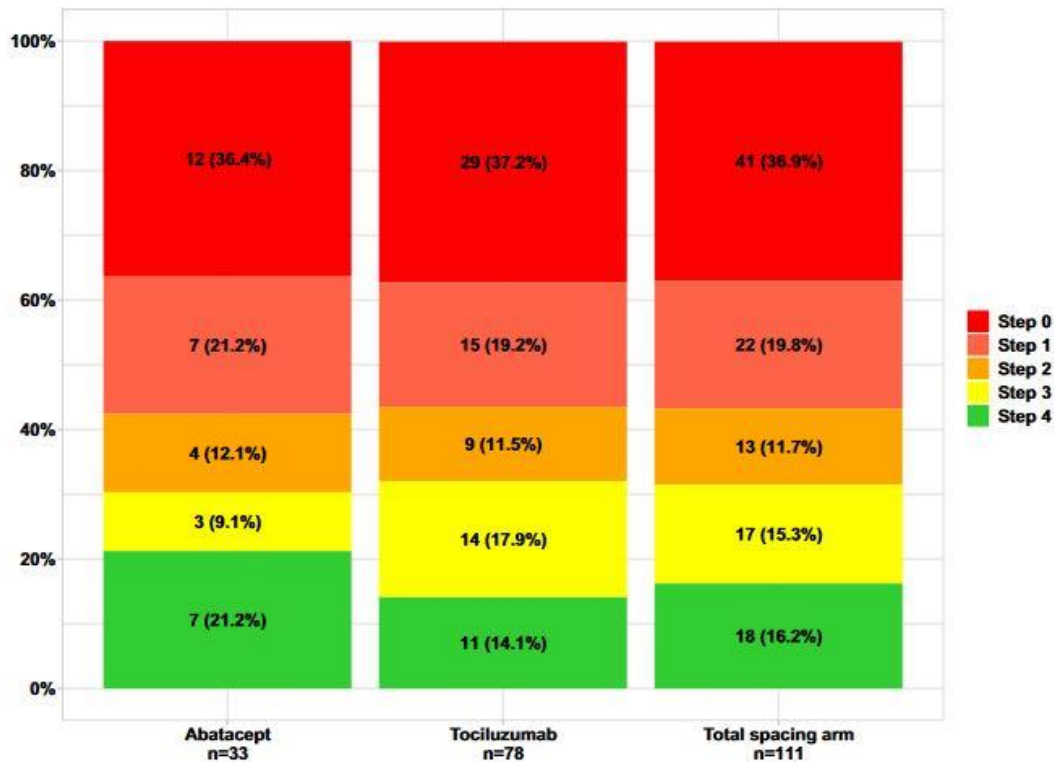


Figure 2. Therapeutic regimen at the end of follow-up in the spacing arm for the intention-to-treat population. Step 0 refers to the standard dose of biologic, steps 1 to 3 refer to a tapered dose, and step 4 refers to the complete discontinuation of biologic disease-modifying antirheumatic drugs. Of note, two patients had missing data for the tapering step at the end of follow-up.

The rate of patients with structural damage progression at 2 years with Δ vSHS greater than SDC was 28.6% in the S-arm and 14.7% in the M-arm, corresponding to a difference of 13.9% (95% CI -6.7 to 34.4); the upper limit of the one-sided 95% CI was 31.1%, and NI was not demonstrated. A multivariable logistic regression model identified independent risk factors for radiographic progression at 2 years: the number of erosions at baseline (odds ratio 0.11, 95% CI 0.02–0.54) and allocation to the S-arm (odds ratio 5.80, 95% CI 1.24–27.09) (Table 2 and Supplementary Material 14).

Overall, 194 patients with complete data for the HAQ-DI at baseline and at least once during the follow-up were included in the analysis of the evolution of HAQ-DI: 106 in the M-arm and 88 in the S-arm. The mean baseline HAQ-DI was 0.5 in the M-arm and 0.6 in the S-arm. At the end of the 2-year follow-up, the difference in evolution of HAQ-DI between the two arms was 0.0 (95% CI -0.1 to 0.1). The upper limit of the one-sided 95% CI of the slope difference was 0.08, so NI was demonstrated (Supplementary Material 15).

Safety.

Adverse events reported during the study are in Supplementary Material 16. Overall, 82 adverse events (72.6%) occurred in the S-arm and 78 (67.8%) in the M-arm. The most frequent adverse event was symptoms suggesting a flare ($n = 174$, 76.3%), which was significantly more frequent in the S-arm than in the M-arm ($n = 100$ [88.5%] vs $n = 74$ [64.4%]; $P = 0.01$). The difference in serious adverse events did not significantly differ between the two arms ($n = 18$ [15.7%] in the M-arm vs $n = 12$ [10.6%] in the S-arm; $P =$

0.261). Serious infections were more frequent in the M-arm than in the S-arm ($n = 13$ [11.3%] vs $n = 4$ [3.5%]; $P = 0.026$). Overall, three deaths occurred during follow-up: two in the M-arm and one in the S-arm. One death was related to a pulmonary infection in a context of amyotrophic lateral sclerosis, the second one was related to a pulmonary infection complicated by pulmonary and heart failure, and the third patient had a history of chronic pulmonary disease and was found dead at home.

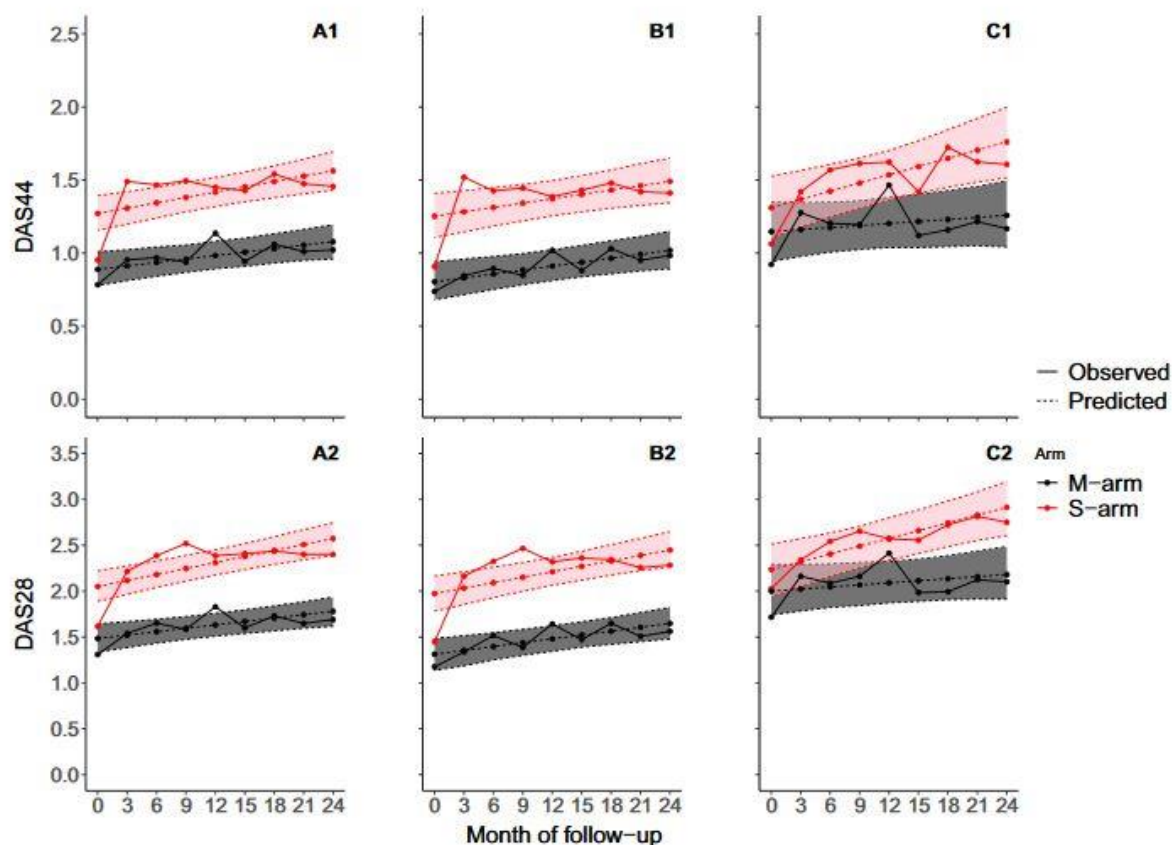


Figure 3. Evolution of (1) DAS44 and (2) DAS28 between the two trial arms. (A) S-arm versus M-arm in the whole population. (B) S-arm versus M-arm in the tocilizumab subgroup. (C) S-arm versus M-arm in the abatacept subgroup. Nota bene: the graphical representations of the predicted models are accompanied by their 95% confidence intervals (in gray for the maintenance arm and in light red for the spacing arm). DAS28, Disease Activity Score in 28 joints; DAS44, DAS in 44 joints; M-arm, maintenance arm; S-arm, spacing arm.

DISCUSSION

In this open-label RCT aiming to evaluate the NI of a progressive spacing strategy of TCZ and ABA compared with maintenance at full dose, 60% of patients in the spacing arm were able to space or discontinue their treatment at the end of the 2-year follow-up. However, we could not demonstrate NI between the two arms for the main or any of the secondary study out-comes (ie, evolution of disease activity according to DAS44 or DAS28, occurrence of flare and major flare, and radiographic progression). Therefore, bDMARD tapering and discontinuation in patients with established RA can result in risk of flare and potential structural damage progression.

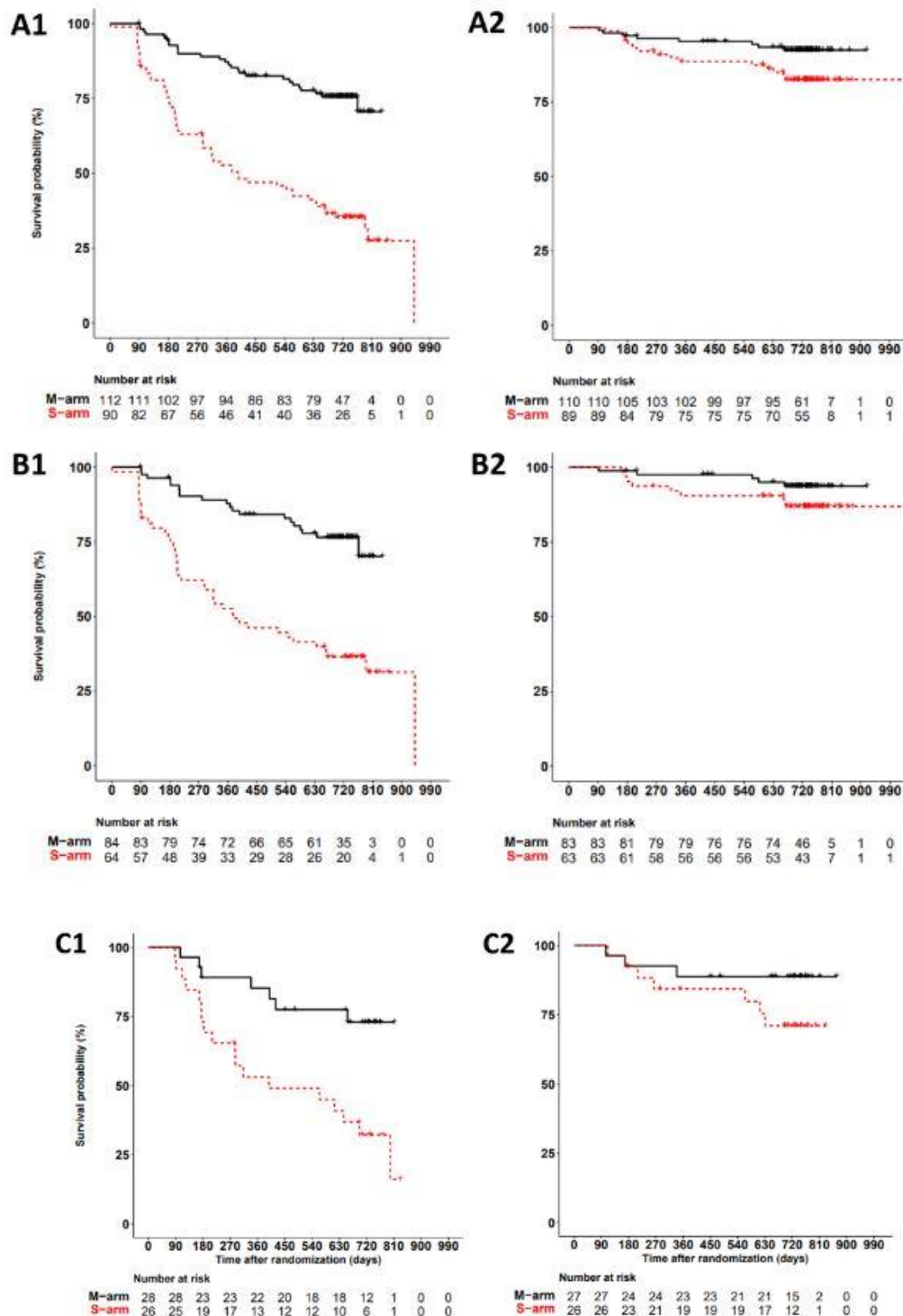


Figure 4. Kaplan-Meier curves for disease flare. (A) S-arm versus M-arm. (B) Tocilizumab subgroup. (C) Abatacept subgroup. The left-side panels show flares, and the right-side panels show major flares. M-arm, maintenance arm; S-arm, spacing arm.

This study has several strengths. First, to our knowledge, it is the first RCT aiming to assess the possibility of tapering TCZ or ABA, for which the published data are limited. Indeed, previous studies, such as DREAM or SONATA, were retrospective or had no control

group.^{24,25,33} Second, our trial proposed a progressive and DAS-driven tapering strategy, whereas the two previous studies used an abrupt discontinuation of TCZ, which could explain why the outcomes in these studies were worse than in our findings.²⁴ Although guidelines report that tapering of bDMARDs would be a relevant strategy in patients in sustained remission when drug tapering is considered,^{12,13} our study suggests no benefit when this strategy is applied to patients receiving TCZ or ABA.

Table 2. Results of the multivariable Cox models for risk of flare and major flares and the multivariable logistic regression model for radiographic progression in the intention-to-treat population*

Variable	Data	P value
Flares, HR (95% CI)		
Randomization to the S arm	3.30 (2.11–5.17)	<0.001 ^a
HAQ score (for each additional 0.5 points)	1.10 (1.03–1.18)	0.005 ^a
DAS28 at baseline ≥ 2.6	1.35 (0.56–3.26)	0.51
ESR	1.03 (1.01–1.05)	0.007 ^a
DAS44 at baseline ≥ 1.6	1.65 (0.90–3.02)	0.125
Major flares, HR (95% CI)		
ESR	1.04 (1.01–1.07)	0.016 ^a
HAQ score (for each additional 0.5 points)	1.21 (1.08–1.36)	0.002 ^a
Absence of swollen joints	0.09 (0.02–0.35)	<0.001 ^a
DAS44 at baseline ≥ 1.6	4.21 (1.66–10.72)	0.007 ^a
Randomization to the S arm	2.07 (0.89–4.81)	0.081
Treatment with TCZ	0.52 (0.23–1.19)	0.131
Radiographic progression, OR (95% CI)		
Erosions	0.11 (0.02–0.54)	0.004 ^a
Randomization to the S-arm	5.80 (1.24–27.09)	0.016 ^a
Disease duration, years	0.90 (0.78–1.03)	0.092
ESR	1.06 (0.98–1.15)	0.142

* 95% CI, 95% confidence interval; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HR, hazard ratio; OR, odds ratio; S-arm, spacing arm; TCZ, tocilizumab.

^a P values < 0.05 are significant.

However, our study also has several limitations. First, we found several deviations from the protocol (21 in the S-arm and one in the M-arm), which could explain a lack of power to demonstrate NI of the S-arm for the primary outcome and for secondary outcomes (and particularly radiographic progression). These deviations occurred mainly between the inclusion and the first follow-up visit and were due to misunderstanding the tapering strategy. Second, we included patients with long-standing and severe RA; indeed, the mean disease duration was 13.4 years, 80% of participants had erosions and positive autoantibodies at the time of inclusion, and patients had taken a median of three previous DMARDs before TCZ or ABA. Thus, these patients were more likely to experience flare and structural damage progression with spacing of TCZ or ABA. Therefore, our results are probably not generalizable to patients with early and biologic-naïve RA who might have displayed better outcomes with the tapering strategy. In addition, although the tapering strategy was progressive and DAS-driven, we cannot exclude it was a little bit too fast for patients with severe RA (some physicians are likely to prefer 6-month steps).

Despite these limitations, our results agree with current knowledge on bDMARD discontinuation strategy. Trials assessing a disease activity–driven tapering strategy for TNFi treatment, such as STRASS or ARCTIC REWIND, did not demonstrate NI in terms of flare occurrence: flares occurred in 76.6% and 63% of patients tapering the TNFi, respectively, versus 46.5% and 5% of patients maintaining bDMARDs at a full dose.^{17,19} Only the DRESS trial demonstrated NI of tapering compared to maintenance strategy for major flares but not short-term flares.¹⁴ Thus, whatever the bDMARD, patients with RA seem likely to experience flare during the spacing procedure.

Similarly, NI of the S-arm was not demonstrated in terms of structural damage progression; however, radiographic progression did not significantly differ between the two study arms which limits the conclusions. Nonetheless, our findings agree with previous studies of TNFi treatment.^{14, 17}

Functional impairment, assessed by the HAQ-DI, was the only factor for which NI was reached. The implication of this result is ambiguous; given that NI was not demonstrated for structural damage progression, an impact of the tapering strategy on functional capacities remains possible. In studies of TNFi treatment, despite no significant difference in HAQ-DI between spacing and maintenance strategies, NI was not demonstrated.^{14, 17}

NI was only demonstrated for the primary outcome analysis in the TCZ subgroup; however, this result should be interpreted with caution, given that NI was not demonstrated for this subgroup in any secondary end-point analyses. Nevertheless, tapering TCZ might be feasible, and this question should be studied in a dedicated trial.

Finally, regarding safety, to our knowledge, this is the first study showing potentially fewer severe adverse events in the spacing versus maintenance arms in terms of infectious events.^{14–22} Actually, the common thinking for safety issues is a phenomenon called “depletion of the susceptible,” where by people at risk of the most common treatment side effects are likely to experience them in the first months after treatment initiation; consequently, patients with adequate and durable responses to the treatment are those with a low risk profile.³⁴

Our findings indicate that, as shown in many other chronic diseases, drug tapering can lead to disease reactivation, including severe flares and progression.^{35, 36} Despite significant progress in RA therapeutic management, drug-free remission remains rare, estimated at not more than 10% to 15% of patients,^{37, 38} and an RA cure seems to remain unattainable.⁴ However, this suggestion does not indicate that overtreatment is not possible for some patients²; some patients do maintain remission with reduced bDMARD doses, so achieving “remission at the lowest efficacious dose” could become the new relevant target to reach in RA care. Therapeutic drug monitoring (ie, monitoring the bDMARD plasma concentration) could be helpful in this purpose and may be more relevant than injection spacing with a fixed dose.³⁹ This move would have a positive impact on patient outcomes as well as societal (ie, economic) burden. An economic analysis of the trial is currently ongoing, which will enable us to assess whether the spacing strategy is associated with higher costs because of poorer

disease control or whether it reduces care-related costs while maintaining a quality of life comparable to the maintenance strategy.

In conclusion, the ToLEDo trial did not demonstrate NI of the proposed ABA or TCZ tapering strategy compared to maintaining full-dose therapy. The results for all outcomes are consistent and, as they stand, cannot support the recommendation to space TCZ and ABA injections in patients with advanced or erosive RA. Nevertheless, there seemed to be a positive signal for TCZ, which needs to be confirmed by a dedicated trial.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kedra had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design. Hajage, Tubach, Fautrel Acquisition of data. Dieudé, Marotte, Salliot, Schaefferbeke, Perdriger, Soubrier, Morel, Constantin, Dernis, Royant, Salmon, Pham, Gotten-berg, Pertuiset, Dougados, Devauchelle-Pensec, Gaudin, Cormier, Goupille, Mariette, Berenbaum, Alcaix, Rouidi, Berthelot, Monnier, Piroth, Lioté, Goëb, Gaujoux-Viala, Chary-Valckenaere, Fautrel. Analysis and interpretation of data. Kedra, Giboin, Hajage, Tubach, Fautrel.

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