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When Usual Care Is Not So Usual: Protocol Violations and Generalizability in a Treat-to-Target Strategy Trial in Patients With Axial Spondyloarthritis

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Objective. The objective of this study was to evaluate the impact of protocol violations in the treat-to-target group in the Tight Control in Spondyloarthritis (TICOSPA) trial and to compare the proportion of patients optimally treated according to the Assessment of Spondyloarthritis International Society (ASAS)/EULAR 2016 recommendations for patients with axial spondyloarthritis (axSpA) between the treat-to-target versus usual care (UC) arms.

Methods. This study was a cluster-randomized, controlled 48-week trial including patients with axSpA who fulfilled the ASAS criteria, had an Axial Spondyloarthritis Disease Activity Score >2.1, and were biologic disease-modifying antirheumatic drug naive. Eighteen axSpA expert centers were randomly allocated to one treatment arm: (a) treat-to-target prespecified management strategy (four-week visits), and (b) UC treatment decisions at the rheumatologist's discretion (12-week visits). Protocol violations in the treat-to-target arm and the fulfillment of the 2016 ASAS/EULAR recommendations in both arms were evaluated at every visit. ASAS Health Index (ASAS-HI) and disease activity outcomes at 48 weeks were compared between treat-to-target violators versus nonviolators. Patients treated according to the ASAS/EULAR recommendations were compared between both arms.

Results. A total of 160 patients initiated the trial (80 patients with treat to target; 80 patients with UC). In the treat-to-target arm, 51.2% patients violated the protocol at least once (62.2% of violations resulting in maintenance/reduction of treatment against protocol). After 48 weeks, treat-to-target violators versus nonviolators showed similar ratios of ASAS-HI improvement. The proportion of patients managed according to the ASAS/EULAR recommendations after the first 12 weeks were 63.9% versus 61.8% for the treat-to-target and UC arms, respectively.

Conclusion. Protocol violations in the treat-to-target arm in the TICOSPA trial were frequent, although they did not have an impact on the rate of the primary outcome. The groups with UC was optimally treated, partly explaining the nonachievement of the primary objective in the TICOSPA trial.

INTRODUCTION

In the field of chronic inflammatory rheumatic diseases and in particular rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA), recommendations issued from international societies are emphasizing the importance of a treat-to-target approach.[1,2] To follow this recommendation, the target must be clearly defined. However, there is a gap between recommendations and daily practice.[3,4] Barriers to changing clinical practice can arise at different levels in the health care system: the patient, professional, health care team, and health care organization.[3] Several potential solutions have been proposed to close this gap.[5] One of these is to show the benefit in daily practice of following these recommendations. For the treat-to-target management recommendation, the evidence of this benefit might come from trials comparing the treatment effect

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SIGNIFICANCE & INNOVATIONS

- In this secondary analysis of the Tight Control in Spondyloarthritis trial comparing a tight-control treatment strategy with "usual care" in patients with early spondyloarthritis, we document the co-occurrence of two important challenges of such trials:
  - High rates of protocol violations in the tight-control group.
  - Better-than-expected care in the usual care group.
- We also showed that protocol violations had no impact on the overall outcome.
- This study provides new information related to challenges and pitfalls in the development of future pragmatic strategy trials in the field of rheumatic diseases.

between patients managed and not managed in accordance with the recommendations related to the treat-to-target strategy.

Treat-to-target strategy trials are considered nonpharmacological trials because they primarily focus on treatment strategies and protocols rather than testing the efficacy or safety of specific pharmacological agents. To optimally conduct these trials, recommendations have been provided by the Consolidated Standards of Reporting Trials (CONSORT) group. One of the recommendations of this consort statement is to conduct strategy trials according to cluster design, in which the unit of randomization and intervention are communities or health care institutions.[6]

Based on these preliminary remarks, one could anticipate two issues when running strategy trials in chronic inflammatory rheumatic diseases. The first issue is related to the risk of protocol violations in the active arm. Obviously, the consequence of a treat-to-target strategy is that the treatment should be intensified in case the target is not achieved. In the field of axial SpA (axSpA), an Axial Spondyloarthritis Disease Activity Score (ASDAS) value of <2.1 has been proposed to define this target.[7] An investigator could consider the target too stringent, and that an intensification of the treatment should not be mandatory even in the context of a strategy therapeutical trial. Similarly, an investigator could prescribe a treatment intensification despite achieving the target. On the other hand, a patient could consider a treatment escalation too fast, refusing to initiate a new drug. These scenarios are resulting in protocol violations that might have an impact on the primary outcome, namely decreasing the treatment effect in the active arm. For this reason, the evaluation of protocol violations and their associated factors are important to better interpret the results of these trials.

The second issue is related to the risk of a "remarkable" treatment effect in the control ("usual care" [UC]) arm, patients who are supposed to be managed according to routine clinical practice. Usually, to facilitate the enrollment of the centers and consequently the enrollment of the patients in this trial, only experienced centers, experts in the field of the disease, are invited to participate. These expert centers in the disease are usually familiar with the recommendations issued from the scientific societies (and may even have participated in their conception) and might potentially have adopted the recommendations related to the treat-to-target strategy in their daily practice. Therefore, the results observed in the UC arm are only reflecting the treatment effect observed in the UC of patients managed in centers with experts of the disease. These centers are possibly not representative of the general UC in daily practice. This attitude might result in a remarkable treatment effect in the control arm, hampering the generalizability of the treatment effect observed on the control arm and reducing the treatment effect.

The Tight Control in Spondyloarthritis (TICOSPA) was the first trial aiming at evaluating the benefits of a treat-to-target strategy in patients with axSpA in comparison with UC.[8] The trial did not meet its primary objective (ie, a statistically significant difference in the proportion of patients reaching an ≥30% improvement of the Assessment of Spondyloarthritis International Society Health Index [ASAS-HI] after 48 weeks of follow-up), but it did show positive results in secondary outcomes in favor of the treat-to-target arm in terms of disease activity and cost-effectiveness analysis.[9] We took the opportunity of the TICOSPA study to evaluate the two hypotheses described above (ie, the risk of protocol violations in the active arm and the risk of a remarkable treatment effect in the control group), which could explain the nonsignificance of the primary outcome. Thus, the objectives of this analysis were as follows: (a) to evaluate the proportion of patients who violated the tight-control protocol in the treat-to-target group during the 48 weeks of follow-up and the step of the treat-to-target algorithm in which this violation was made, (b) to determine factors associated with protocol violation, (c) to determine the impact of protocol violation on efficacy outcomes, and (d) to compare the proportion of patients treated according to the Assessment of Spondyloarthritis International Society (ASAS)/EULAR 2016 recommendations for biologic disease-modifying antirheumatic drug (bDMARD) initiation in patients with axSpA[10] over the first 12 weeks of follow-up in both arms.

PATIENTS AND METHODS

Study design. TICOSPA was a pragmatic, prospective, parallel, cluster-randomized, open, controlled trial with the center of the cluster (NCT03043846). Patients were observed for 48 weeks with visits scheduled differently depending on the arm (treat to target every 4 weeks and UC every 12 weeks). The study was conducted according to the local good clinical practice and the Declaration of Helsinki. Additional information on the study design can be found elsewhere.[8]

Centers and patients. Eighteen selected centers with experts in axSpA from France, the Netherlands, and Belgium were randomly allocated (1:1) to one of two treatment arms (treat to target or UC). Adult patients younger than 65 years with a diagnosis of axSpA according to the treating rheumatologist and fulfilling the ASAS classification criteria for axSpA were selected. At inclusion, the patient had to be biologic naive with active disease (ASDAS ≥ 2.1) and nonoptimally treated with nonsteroidal anti-inflammatory drugs (NSAIDs). In addition, a pelvic radiograph, magnetic resonance imaging (MRI) of the sacroiliac joints and HLAB27 status was mandatory to assess the ASAS classification criteria (https://ard.bmj.com/content/68/6/777.long). All patients provided written consent to participate in the study.

Study treatment regimens. *Treat-to-target arm.* Visits were scheduled every four weeks for a year (a total of 13 visits), and the management strategy was prespecified and based on the strict application of the 2016 ASAS/EULAR axSpA management recommendations. An electronic algorithm guided treatment decisions at each visit after collection and entry of the ASDAS value in an electronic case report form (eCRF). The target was low disease activity (LDA) according to the ASDAS (ie, ASDAS < 2.1). If the target was not met, the eCRF proposed intensification of the treatment to the investigator. If the recommendation was to initiate a bDMARD, the selection of the specific drug was at the rheumatologist's discretion. Per protocol, a negative tuberculosis test before recruitment and available C-reactive protein (CRP) in all visits were mandatory to avoid delays in bDMARD initiation. The full algorithm providing the predetermined recommendations at each visit is available in the main manuscript.[8]

UC arm. Visits were scheduled every 12 weeks for a year (a total of five visits), and all treatment decisions were left to the investigator's discretion, including the frequency of follow-up in between visits. Per protocol, physicians in the UC arm had to collect ASDAS and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at each visit in the UC group.

Outcomes. *Protocol violation.* Protocol violation was evaluated in the eCRF only for the treat-to-target arm using the question "Recommendation followed by physician and patient? (yes/no)," at each four-week visit and answered by the investigator. Patients from the treat-to-target arm who violated the protocol at least once according to this variable were considered as "violators," and those who never violated the algorithm during the follow-up were considered as "nonviolators." In addition, the reason for not following the recommendation (ie, protocol violation) was evaluated by the investigator with the variable "Reason for nonrespect (patient related/physician related/other)." The step of the treat-to-target algorithm in which the protocol was violated was also collected.

Efficacy outcomes. Efficacy outcomes were evaluated not only in the treat-to-target arm (in patients who were protocol violators and nonviolators) but also in the UC arm. The primary outcome in the TICOSPA trial was the percentage of patients achieving an improvement of at least 30% in the ASAS-HI at the 48-week visit. Additional secondary activity outcomes, such as the ASDAS states (ie, LDA defined as ASDAS <2.1 and inactive disease [ID] defined as ASDAS <1.3)[7] and changes (major improvement, defined as ΔASDAS ≥2.0, and clinically important improvement [CII], defined as the change in ASDAS ≥1.1),[11] ASAS responses (ASAS criteria for 20% improvement [ASAS20] and ASAS criteria for 40% improvement),[12] ASAS partial remission, and BASDAI criteria for 50% improvement (BASDAI50) were evaluated.[13]

Adherence to the 2016 ASAS/EULAR management recommendations. Because only 12-week visits were available for both arms, adherence to the 2016 ASAS/EULAR management recommendations for bDMARD initiation was evaluated every 12 weeks. According to these recommendations, bDMARDs could be initiated in patients with a definite diagnosis of axSpA according to the rheumatologist, with objective signs of inflammation (abnormal CRP, positive MRI, or radiographic sacroiliitis), inefficacy or intolerance to two different NSAIDs, and active disease defined either by BASDAI ≥4 or ASDAS ≥2.1. A patient was considered to be adherent to the recommendations for bDMARD initiation if they met the conditions for initiating bDMARD at one visit and had indeed received a bDMARD at the next visit but also, if they did *not* meet the conditions for initiating a bDMARD at one visit and indeed did *not* receive the treatment at the next visit. The remaining patients were considered as nonadherent to the ASAS/EULAR recommendations.

Statistical methods. The number of patients who violated the tight-control algorithm in the treat-to-target arm were described, as well as the absolute number of violations (one patient could violate the protocol in several visits). The proportion of violations at each algorithm's step, the direction of the violation (ie, intensification or maintenance/reduction of the treatment against protocol), and whether these violations were physician or patient driven were described. Baseline predictive factors associated with at least one protocol violation in the treat-to-target group were evaluated using univariate analyses adjusted for multiple testing using the Benjamini–Hochberg procedure, as well as with multivariate logistic regressions. Interactions and confounding factors were tested, and variables with P less than 0.20 from the univariate analysis were included in the multivariate model.

The prevalence of patients achieving efficacy outcomes at the 48-week visit was compared between treat-to-target nonviolators versus treat-to-target violators versus UC using generalized estimating equation models adjusted by country and sex and using the groups with the aim of evaluating whether the violation of the tight-control algorithm had an impact on the outcome

measures at the end of the trial. Finally, the prevalence of patients treated according to the 2016 ASAS/EULAR recommendations for bDMARD initiation at each follow-up visit was compared between both arms (treat to target and UC). All contrasts were two-sided and considered significant with *P* less than 0.05. Data were analyzed using RStudio 1.4.1106.

RESULTS

A total of 160 patients fulfilling the inclusion criteria were enrolled (80 in the treat-to-target arm and 80 in the UC arm), although 144 patients (72 per arm) completed the last visit. At baseline, the mean (±SD) age was 37.9 (±11.0) years, 82 patients (51.2%) were male, and the mean (±SD) disease duration was 3.7 (±6.2) years. A total of 120 patients (75.0%) were HLA-B27 positive, 75 patients (46.9%) had radiographic sacroiliitis, and 131 patients (81.9%) had positive MRI of the sacroiliac joints (Table 1). The treat-to-target group exhibited a higher prevalence of university studies, a history of anterior uveitis, and higher levels of Physician Global Assessment in comparison with the UC group (Table 1).

Prevalence of the protocol violations in the treat-to-target arm. A total of 41 of 80 patients (51.2%) violated the treat-to-target protocol at least once over the 48 weeks. Among the 41 patients who violated the protocol, 17 violated it once, 9 patients at two visits, and 3 patients at three or more visits. Only two patients violated the protocol systematically at all visits.

The absolute number of protocol violations in these patients was 119, of which 45.5% were physician driven (eg, pain not related to SpA according to the physician, interruption of bDMARDs due to surgical intervention), 37.0% were patient driven (eg, refusal by the patient to take NSAIDs, the patient missed the appointment), and 17.6% were due to other reasons (eg, treatment change by the general practitioner). The discrepancies between the recommended treatment by the tight-control algorithm and the treatment given to the patient are described in Supplementary Table 1. A total of 5 of 119 violations (4.2%) involved a lack of NSAID full dose escalation, 26 of 119 violations (21.8%) involved a lack of switching to a second NSAID, 23 of 119 violations (19.3%) were explained by a lack of treatment maintenance with NSAIDs, physiotherapy, and analgesics, and 17 of 119 violations (14.3%) because of a lack of a first bDMARD initiation. In addition, 15 of 119 violations (12.6%) were represented by a lack of continuation of the first bDMARD, and 9 of 119 patients (7.6%) violated the protocol because a lack of switching to a second bDMARD if no response to the first one.

Overall, 33 of 119 violations (27.7%; represented by four patients) led to an intensification of the treatment against the recommendations provided by the algorithm (ie, an earlier initiation of bDMARD in all of them). On the other hand, 74 of 119 violations (62.2%; represented by 37 patients) led to a maintenance or reduction of the treatment (28 of 74 violations leading to lack of change or intensification of NSAIDs and 46 of 77 violations leading to a lack of the change or initiation of bDMARD). Finally, 12 of 119 violations (10.1%) were represented by a second violation due to a nonadherence to previous step of the algorithm.

Baseline predictive factors associated with protocol violation in the treat-to-target arm. The univariate analysis evaluating predictive factors of at least one protocol violation is represented in Table 2. The multivariate analysis showed that baseline factors independently associated with protocol violations in the treat-to-target arm were to be a French center (odds ratio [OR] 3.7, 95% confidence interval [CI] 1.1–15.0), female sex (OR 4.4,

Table 1. Baseline characteristics of patients included in the Tight Control in Spondyloarthritis trial*

Characteristic	Total (n = 160)	Treat-to-target arm (n = 80)	UC arm (n = 80)
Age, mean (±SD), y	37.9 (±11.0)	37.6 (±10.8)	38.1 (±11.4)
Female, n (%)	78 (48.8)	35 (43.8)	43 (53.8)
Current smoking status, n (%)	61 (38.1)	29 (36.2)	32 (40.0)
University studies, n (%)	99 (61.9)	57 (71.3)	42 (52.2)
Disease duration, mean (±SD), y	3.7 (±6.2)	4.2 (±6.6)	3.3 (±5.8)
Radiographic sacroiliitis, n (%)	75 (46.9)	42 (52.5)	33 (41.2)
MRI sacroiliitis, n (%)	131 (81.9)	63 (78.8)	68 (85.0)
HLA-B27 positive, n (%)	120 (75.0)	62 (77.5)	58 (72.5)
History of anterior uveitis, n (%)	22 (13.8)	16 (20.0)	6 (7.5)
History of psoriasis, n (%)	8 (5)	3 (3.8)	5 (6.3)
History of IBD, n (%)	2 (1.3)	0 (0)	2 (2.5)
Good NSAID response, n (%)	118 (73.8)	63 (78.8)	55 (68.8)
Physician Global Assessment, mean (±SD)	5.2 (±1.9)	5.7 (±1.7)	4.7 (±1.9)
ASDAS, mean (±SD)	3.0 (±0.7)	3.0 (±0.7)	3.0 (±0.6)
BASDAI, mean (±SD)	5.2 (±1.8)	5.2 (±1.7)	5.2 (±1.9)
ASAS-HI (0–17), mean (±SD)	8.6 (±3.7)	8.2 (±3.8)	9.0 (±3.6)

* ASAS-HI, Assessment of Spondyloarthritis International Society Health Index; ASDAS, Axial Spondyloarthritis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; UC, usual care.

Table 2. Baseline predictive factors associated with protocol violation in the treat-to-target arm*

Characteristic	Protocol violators (n = 41)	Protocol nonviolators (n = 39)	*P* value	Adjusted *P* value[a]
Country (France vs others), n (%)	33 (80.5)	23 (59.0)	0.036	0.630
Age, mean (±SD), y	38.6 (±10.3)	36.6 (±11.3)	0.426	0.991
Female, n (%)	24 (58.5)	11 (28.2)	0.006	0.210
Current smoking status, n (%)	16 (39.0)	13 (33.3)	0.769	1.000
University studies, n (%)	30 (73.2)	27 (69.2)	0.697	1.000
Married or living in couple, n (%)	33 (80.5)	27 (69.2)	0.245	0.779
BMI, mean (±SD)	25.6 (±5.3)	25.2 (±3.7)	0.732	1.000
Disease duration of at least four years, n (%)	27 (65.9)	26 (66.7)	0.939	1.000
Symptom duration of ≤10 years, n (%)	23 (56.1)	18 (46.2)	0.374	0.935
Diagnostic delay of at least seven years, n (%)	27 (65.9)	20 (51.3)	0.186	0.742
X-ray SIJ structural damage, n (%)	21 (51.2)	21 (53.8)	0.814	1.000
MRI sacroiliitis, n (%)	30 (73.2)	33 (84.6)	0.211	0.742
HLA-B27 negative, n (%)	12 (29.3)	6 (15.4)	0.137	0.742
History of arthritis, n (%)	8 (19.5)	8 (20.5)	0.911	1.000
History of heel enthesitis, n (%)	14 (34.1)	11 (28.2)	0.566	0.991
History of anterior uveitis, n (%)	8 (19.5)	8 (20.5)	0.911	1.000
History of psoriasis, n (%)	1 (2.4)	2 (5.1)	0.611	0.991
History of IBD, n (%)	0 (0)	0 (0)	–	–
Family history of SpA, n (%)	17 (41.5)	16 (41.0)	0.968	1.000
History of abnormal CRP, n (%)	25 (61.0)	24 (61.5)	0.959	1.000
Good NSAID response, n (%)	31 (75.6)	32 (82.1)	0.481	0.991
Articular peripheral involvement (last three months), n (%)	11 (26.8)	8 (20.5)	0.507	0.991
Current number of swollen joints, mean (±SD)	0.1 (±0.3)	0.6 (±1.1)	0.205	0.742
Current number of tender joints, mean (±SD)	1.4 (±1.5)	2.3 (±1.8)	0.282	0.823
Entheseal peripheral involvement (last three months), n (%)	15 (36.6)	9 (23.1)	0.188	0.742
MASES, mean (±SD)	0.9 (±1.4)	1.4 (±3.2)	0.346	0.932
Dactylitis (last three months), n (%)	1 (2.4)	1 (2.5)	1.000	1.000
CRP ≥6 mg/L, n (%)	21 (51.2)	16 (41.0)	0.175	0.742
ASDAS-CRP ≥2.1, n (%)	40 (97.6)	39 (100)	1.000	1.000
BASDAI, mean (±SD)	5.1 (±1.4)	5.3 (±1.9)	0.544	0.991
Physician global, mean (±SD)	5.4 (±1.7)	5.9 (±1.7)	0.185	0.742
BAS-G, mean (±SD)	6.0 (±1.8)	5.9 (±1.8)	0.899	1.000
BASFI, mean (±SD)	3.3 (±2.3)	3.0 (±1.9)	0.644	1.000
ASAS-HI (0–17), mean (±SD)	8.2 (±3.1)	7.2 (±3.7)	0.212	0.742

* ASAS-HI, Assessment of Spondyloarthritis International Society Health Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BAS-G, Bath Ankylosing Spondylitis Patient Global Score; BMI, body mass index; CRP, C-reactive protein; IBD, inflammatory bowel disease; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; SIJ, sacroiliac joint; SpA, spondyloarthritis.
[a] *P* values were adjusted for multiplicity according to the Benjamini–Hochberg procedure.

95% CI 1.4–15.1), diagnostic delay ≤7 years (OR 3.4, 95% CI 1.1–11.9), negative HLA-B27 (OR 6.3, 95% CI 1.6–32.2), and CRP ≥6 mg/L (OR 4.2, 95% CI 1.3–15.9; Figure 1). When evaluating variables associated with violators leading to an intensification (n = 4 patients) compared to violators leading to maintenance or reduction of treatment (n = 36 patients) and nonviolators (n = 39 patients), the only two significant factors found in the univariate analysis were female sex (50% vs 59.5% vs 28.2%, $P < 0.01$) and current smokers (100% vs 32.4% vs 33.3%, $P = 0.04$; Supplementary Table 2). However, when adjusting for multiplicity, the significance disappeared.

Impact of protocol violation in the treat-to-target arm on the efficacy outcomes. After 48 weeks of follow-up, the comparison between treat-to-target protocol violators (n = 41) and nonviolators (n = 39) showed that ASAS-HI improvement was similar in both groups (39.0% vs 35.9%, $P = 0.77$) after adjusting for country and sex, with no significant differences. ASAS20, ASDAS-LDA, ASDAS-ID, and ASDAS-CII outcomes were less prevalent in treat-to-target protocol violators than in nonviolators, although these differences did not reach statistical significance (Table 3). When compared with the UC group after adjusting for confounders, the prevalence of patients achieving BASDAI50 was more frequent in the treat-to-target protocol violator group (51.2% vs 31.6%, $P = 0.04$), although no differences were found in the other efficacy outcomes. A sensitivity analysis was conducted to evaluate the impact of violators, leading to intensification versus violators leading to maintenance or reduction of the treatment versus nonviolators after 48 weeks of follow-up in treat-to-target patients (Supplementary Table 3). No differences were found in the efficacy outcomes among the three groups after adjusting for country and sex.

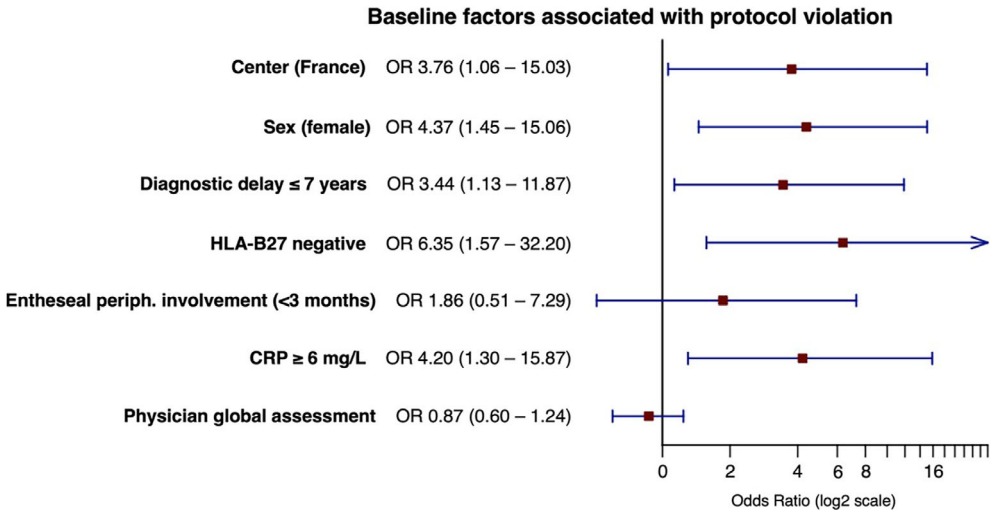

Figure 1. Multivariate analysis evaluating predictive factors associated with protocol violation in the treat-to-target arm. Values are given as OR (95% confidence interval). CRP, C-reactive protein; OR, odds ratio; periph., peripheral.

Adherence to the 2016 ASAS/EULAR management recommendations in both arms after 12 weeks of follow-up. After 12 weeks of follow-up, the proportion of patients managed according to the 2016 ASAS/EULAR recommendations for bDMARD initiation were 63.9% and 61.8% in the treat-to-target and UC arms, respectively ($P = 0.80$; Supplementary Table 4). After the 48 weeks of follow-up, almost all patients were adherent to the recommendations at least once (100% and 97.2% in the treat-to-target and UC arms, respectively; Figure 2).

DISCUSSION

This secondary analysis of the TICOSPA treat-to-target strategy trial showed that there were many protocol violations in the tight-control group, mostly in the direction of nonintensification of the treatment. These violations had no apparent effect on the trial outcome, as ASAS-HI was similar in violators and nonviolators at the end of the study. Also, as the proportion of patients managed according to the 2016 ASAS/EULAR recommendations for bDMARD initiation was similar in both treatment arms, this suggests UC approached optimal care in the study centers.

The first common risk in strategy trials was confirmed in the TICOSPA study: a high rate of patients (>50%) violated the protocol at least once in the treat-to-target arm during the follow-up. The majority of these protocol deviations in the treat-to-target algorithm were physician driven, and they were mainly represented by the maintenance or reduction of the treatment against protocol, suggesting that treat to target represents a challenging approach even in a randomized clinical trial scenario. The absence of the treatment escalation in some patients likely reflects two contexts: on one hand, a physician's consideration of factors beyond just measuring the ASDAS, including other clinical characteristics and comorbidities in making decisions; on the other hand, a lack of confidence in the beneficial effect of treatment intensification, particularly in situations in which disease activity is acceptably controlled. In fact, we found that the mean ASDAS of patients who did not escalate treatment against protocol was 2.3, suggesting a potential acceptable disease activity close to the "official" recognized LDA (ie, the target in the trial). The remaining question is whether this tight-control strategy might be applied in daily clinical practice. Recently, a Dutch study evaluated the extent to which treat-to-target recommendations were applied in daily clinical practice in patients with axSpA and found that they were applied to a limited extent.[14] In addition, they found that disease activity scores were not frequently used for determining the frequency of re-evaluation or treatment escalation, suggesting a gap between axSpA treat-to-target recommendations and daily practice management. These results highlight the necessity of evaluating the real-life implementation of treat-to-target strategies for patients with rheumatic diseases.

Some factors related to these protocol violations were found. The first factor was the country of treatment, likely due to differences in health systems and bDMARD reimbursement, which could lead to a delay in treatment initiation. The second factor was the patients who were HLA-B27 negative and female. One hypothesis is that this patient profile could have introduced doubts in the rheumatologists' minds regarding diagnosis or been considered as a less severe disease, and consequently, rheumatologists did not intensify the treatment. The third factor was an elevated CRP level at baseline, suggesting that in patients with higher disease activity and possibly more severe disease, decisions were made irrespective of the algorithm. One could assume a lower treatment efficacy in violators compared to nonviolators due to the poorer management in the former group. However, this was not confirmed in this analysis because both

Table 3. Impact of protocol violation on the efficacy outcomes at week 48*

Characteristic	Treat-to-target nonviolators (n = 39), n (%)	Treat-to-target violators (n = 41), n (%)	UC[a] (n = 80), n (%)	Global GEE, *P* value	Treat-to-target nonviolators vs treat-to-target violators, *P* value	Treat-to-target nonviolators vs UC, *P* value	Treat-to-target violators vs UC, *P* value
ASAS-HI improvement at week 48	14 (35.9)	16 (39.0)	21 (26.6)	0.330	–	–	–
ASAS20 at week 48	33 (84.6)	33 (80.5)	61 (77.2)	0.640	–	–	–
ASAS40 at week 48	14 (35.9)	16 (39.0)	19 (24.1)	0.180	–	–	–
BASDAI50 at week 48	24 (61.5)	21 (51.2)	25 (31.6)	0.006	0.314	0.002	0.037
ASDAS-CII at week 48	22 (56.4)	16 (39.0)	26 (32.9)	0.053	–	–	–
ASDAS-MI at week 48	6 (15.4)	8 (19.5)	9 (11.4)	0.480	–	–	–
ASDAS-LDA at week 48	24 (61.5)	19 (46.3)	32 (40.5)	0.092	–	–	–
ASDAS-ID at week 48	11 (28.2)	8 (19.5)	10 (12.7)	0.130	–	–	–

* GEE models were used with the group as the dependent variable and the disease activity outcome as the covariate. All comparisons have been adjusted by country and sex. Post hoc analyses were conducted if the global *P* value <0.05. ASAS20, Assessment of Spondyloarthritis International Society criteria for 20% improvement; ASAS40, Assessment of Spondyloarthritis International Society criteria for 40% improvement; ASAS-HI, Assessment of Spondyloarthritis International Society Health Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI50, Bath Ankylosing Spondylitis Disease Activity Index criteria for 50% improvement; CII, clinically important improvement; GEE, generalized estimating equation; ID, inactive disease; LDA, low disease activity; MI, major improvement; UC, usual care.
[a] There were 79 patients as the denominator in the UC group.

groups showed similar efficacy outcomes at the end of the trial, suggesting that these protocol deviations in the context of this treat-to-target strategy had little impact.

The second common risk in strategy trials was also confirmed in this study: the UC arm was optimally treated according to the ASAS/EULAR recommendations for bDMARD initiation during the first 12 weeks of follow-up, which could explain, at least partially, the nonsignificant differences in the primary outcome (ASAS-HI) in the TICOSPA trial. In fact, previous studies in recent patients with axSpA demonstrated that adherence to the 2016 ASAS/EULAR recommendations in the initiation of bDMARD therapy leads to better long-term outcomes in terms of quality of life and sick leave.[15] The unexpectedly high rate of adherence to the recommendations in the UC arm can be explained by two reasons. First, the cluster-trial design, as only SpA expert centers could be selected to participate and were thus aware of these recommendations and applying them in their UC. This suggests that in carefully selected centers, the implementation of the management guidelines is already quite optimal. This could mean that the design of future pragmatic trials may need to include nonexpert centers in the clustering randomization with the aim to achieve a "true" UC management in the control arm. However, this would not be in line with the CONSORT group recommendations, which suggest that the participating institutions may be atypically well resourced or experienced because the feasibility of the trial will depend on these attributes.[6] The second reason is the obligation to collect ASDAS and BASDAI at each visit in the UC group, which could

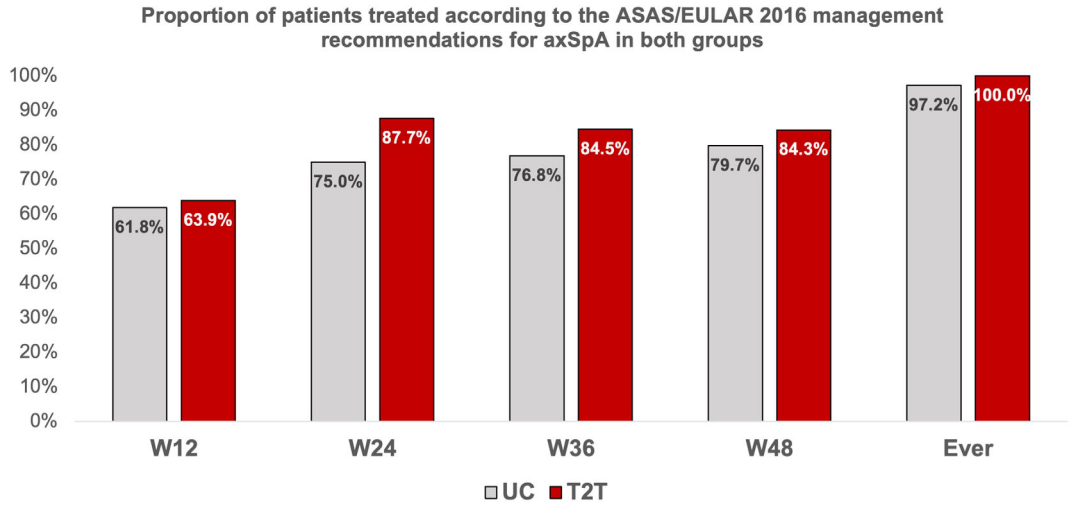

Figure 2. Proportion of patients treated according to the ASAS/EULAR 2016 management recommendations for axSpA in both groups. ASAS, Assessment of Spondyloarthritis International Society; axSpA, axial spondyloarthritis; T2T, treat to target; UC, usual care; W, week. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.25387/abstract.

lead to treatment intensification by physicians. Thus, this may not accurately reflect "true" UC because previous studies have shown that only around 40% of patients have the ASDAS measurements included in their clinical records in clinical practice.[16] In any case, the limited treatment options for treating patients with axSpA and the easily understandable recommendations facilitate the fact that many patients already follow UC in clinical practice.

Not only the optimal management of the UC group but also the choice of the primary outcome could explain the absence of statistical significance in the ASAS-HI in the TICOSPA trial. In fact, this is another challenging issue when planning strategy trials in the field of treat to target. One could propose as main outcome the percentage of patients achieving the target at the end of follow-up, which was the case in patients with RA when running the Tight Control of Rheumatoid Arthritis (TICORA) trial.[17] Another possibility is to propose the percentage of patients achieving a response in terms of composite indices evaluating the same construct (ie, disease activity), which was the case of the Tight Control of Inflammation in Early Psoriatic Arthritis (TICOPA) trial in patients with PsA.[18] These choices can be criticized because of the bias of circularity (eg, the choice of the outcome is related to the choice of the target). This was the reason why in the TICOSPA trial the target was disease activity (ie, ASDAS), whereas the main outcome was a consequence of disease activity (ie, ASAS-HI, which evaluates function and health). The selection of a primary outcome similar than in the TICORA or TICOPA trials would result in a higher significant difference in favor of the treat-to-target strategy in the TICOSPA trial. For this reason, the selection of the main outcome in these strategy trials represents a critical moment in the design of future studies.

The main strength of this study is the cluster-randomized design, allowing us to evaluate the treat-to-target strategy with a reliable comparator and with a balanced population. One limitation is that the UC strategy was conducted by expert SpA centers, which prevented the evaluation of the characteristics of UC management in nonexpert centers. Another limitation is that protocol violations, such as the nonescalation of treatment based on shared decisions between the physician and the patient, have been considered as protocol deviations. This scenario is very common in clinical practice, and some authors may not consider this situation as a violation of the protocol.

In summary, these results confirm that protocol violations in the treat-to-target arm in the TICOSPA trial were frequent, although they did not have an impact on the rate of primary outcome. On the other hand, the proportion of patients managed according to the 2016 ASAS/EULAR recommendations for bDMARD initiation in the UC arm was very high, suggesting that the UC group was optimally treated and explaining the nonachievement of the primary objective in the TICOSPA trial. To document any improvement of treat to target over UC in a trial, the treatment in the control group should really be representative of UC.

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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 López-Medina 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.

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