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Factors associated with treatment intensification in patients with axial spondyloarthritis and high disease activity in clinical practice

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Abstract

Objective: To investigate which factors are associated with treatment intensification (TI) in axial SpA (axSpA) patients with high disease activity (HDA).

Methods: Patients with axSpA and HDA [Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1] from the Dutch SpA-Net registry were included. TI was defined as: (i) higher dose or shorter interval of the same drug, (ii) switch from current drug to another due to inefficacy or (iii) addition of a new drug. Only anti-inflammatory drugs were considered. Primary determinants considered were ASDAS, Assessment of SpondyloArthritis international Society Health Index (ASAS HI) and physician global assessment (PhGA). Acceptable symptom state according to patient (PASS-patient) or physician (PASS-physician) were included in sensitivity analyses. Patient-centred and physician-centred logistic regression models were used to investigate the association between potential determinants and TI.

Results: In total, 121 patients with HDA were included. TI was conducted in a minority (41/121, 33.9%), and mainly involved a switch or addition of a drug. In multivariable regression analyses, a higher ASDAS was associated with TI in the patient-centred model [odds ratio $(OR)_{ASDAS} = 1.94$ (95% CI 1.00–3.74)]. However, in the physician-centred model, this association attenuated, and PhGA or PASS-physician were the primary factors associated with TI [$OR_{PhGA} = 1.71$ (1.24–2.34); $OR_{PASS\text{-}physician} = 94.95$]. Interestingly, patient-centred factors (ASAS HI/PASS-patient/education level) did not contribute to TI.

Conclusion: In practice, treatment is intensified in a minority of axSpA patients with HDA. Physician-centred factors are associated with the decision to change treatment, independently of disease activity or patient perspective. Further research is needed to better understand these decisions.

Keywords: axial spondyloarthritis, disease activity, treatment, treatment intensification.

Rheumatology key messages

- Treatment is intensified in a minority of axial SpA patients with high disease activity.
- The physician's perspective on disease activity is driving the decision to change treatment in these patients.
- Patient-centred factors like disease impact and symptom state do not seem to contribute (substantially) to treatment decisions.

Introduction

The goal of disease management in axial SpA (axSpA) is to maximize quality of life, which is typically achieved by reducing disease activity [1]. Anti-inflammatory pharmacological treatments, such as NSAIDs, biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), have an important role in management of axSpA [1–3]. International recommendations highlight the importance of measuring disease activity regularly [4, 5]. This should preferably be done with the Ankylosing Spondylitis Disease Activity Score (ASDAS), a combination of patient-reported outcomes and laboratory parameters of inflammation [6]. Sustained inactive disease (ASDAS <1.3) or low disease activity (LDA, 1.3 ≤ ASDAS < 2.1) should be aimed for as part of treat-to-target (T2T), and it is advised to intensify treatment when disease activity is high according to the ASDAS (≥2.1) and the rheumatologist [1, 4].

In a recent Dutch study, only 38% of patients with axSpA in daily practice had inactive disease/LDA [7]. Furthermore,

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in only a small proportion (13%) of patients with high disease activity (HDA, ASDAS ≥2.1) was treatment intensified. Another study in axSpA reported similar findings on apparent T2T non-adherence [8]. The reasons for this discrepancy between recommendations and daily practice are unknown. The role of the ASDAS in current treatment decisions in axSpA is unclear, in particular its interplay with factors reflecting the patient's and rheumatologist's perspectives (such as patient-reported disease impact and physician-reported disease activity, respectively). The ASDAS was developed and validated in a selected population, more than a decade ago. Since then, the definition of axSpA has been broadened, and in clinical practice large heterogeneity is seen among patients. Furthermore, the context of a patient is important when making treatment decisions. The question is to what extent the decision to (not) intensify treatment is guided by patient-centred *vs* physician-centred factors.

Knowledge of the drivers of treatment decisions in patients with axSpA and HDA in current practice is a first step to optimize disease management in axSpA (given the available treatment armamentarium), as it would elucidate clinical decision-making. Therefore, our objectives were to assess the frequency of treatment intensification (TI) in axSpA patients with HDA in a clinical practice registry, and to investigate which patient-centred and physician-centred factors are associated with TI in this population.

Methods

Study design and population

For this observational study, we used data from SpA-Net [9]. SpA-Net is a disease-specific web-based quality registry for Dutch patients with SpA (ICTRP Registration NTR6740). SpA-Net has been operational between 2016 and 2023 in two large Dutch rheumatology centres.

All patients with a clinical diagnosis of SpA and under rheumatologist care in the two participating centres were consecutively included in SpA-Net as part of routine care. Both prevalent and incident cases were eligible. Besides a clinical diagnosis, no other inclusion or exclusion criteria applied. Patients were prospectively followed up over time. Patients completed questionnaires at home shortly before their routine outpatient consultations. In addition, data on patient-based outcomes, laboratory values and medication use were collected in SpA-Net. The frequency of visits in SpA-Net was not fixed but followed daily practice. Any changes in disease management were guided by the treating rheumatologist.

For the current study, patients with an axSpA diagnosis were eligible if they were in an HDA state (ASDAS ≥2.1). Additionally, they had to have data available on the primary potential determinants: ASDAS-based disease activity (always available, as HDA was an inclusion criterion), disease impact (Assessment of SpondyloArthritis international Society Health Index, ASAS HI) and physician-reported disease activity (physician global assessment, PhGA). If multiple timepoints for a patient met these criteria, one timepoint was selected, based on two criteria: (i) presence of TI (to enrich the dataset for this outcome and capture as many events as possible) and (ii) most secondary determinants available (see 'Outcome and potential determinants' below and Supplementary Fig. S1, available at *Rheumatology* online). Data from May 2016 to April 2023 were available for analysis.

The local ethics committee determined that observational studies in SpA-Net do not require official approval, as data are collected in routine care and are not subject to the Medical Research Involving Human Subjects Act (METC azM/UM 15-4-266). Written informed consent was obtained from each patient to use their data for research.

Outcome and potential determinants

The outcome was TI, defined as (i) a higher dose or shorter interval of the same drug, (ii) a switch of the current drug to another drug or (iii) an addition of a new drug to the current treatment regime. In addition, treatment modification had to be due to inefficacy, and only anti-inflammatory drugs [NSAIDs, conventional synthetic DMARDs (csDMARDs), bDMARDs, tsDMARDs, glucocorticoids] were considered.

Both patient-centred and physician-centred determinants of TI were included. The primary potential determinants were disease activity (assessed with the ASDAS [6]), patient-reported disease impact (assessed with the ASAS HI, 0–17 [10]) and physician-reported disease activity (assessed with the PhGA, 0–10). Secondary determinants included age, sex, educational level, peripheral symptoms and skin involvement. Educational level was dichotomized (higher education/university *vs* other). Peripheral symptoms were assessed with swollen joint (0–66), enthesitis (0–65) and dactylitis counts (0–20), and were dichotomized as present (count of swollen joints, enthesitis and/or dactylitis ≥1) or absent (count of 0). Skin involvement was assessed with the body surface area (BSA, 0–100%), and dichotomized as active (BSA ≥3%) or inactive (BSA <3%).

Additional determinants were explored in sensitivity analyses. These included acceptability of the current state (yes/no) according to the patient (patient acceptable symptom state, PASS-patient) or the physician (PASS-physician). As PASS-patient/physician were added to SpA-Net later (June 2020) and thus expected to be missing more frequently, they were only considered in sensitivity analyses.

In SpA-Net, the ASDAS, PASS and PhGA were completed on every visit, while the ASAS HI was completed with a minimum interval of 3 months, depending on the frequency of consultations. Joints/enthesitis/dactylitis counts were completed on indication.

Other population characteristics

The following patient and disease characteristics were included for descriptive purposes only: smoking status (current *vs* former/never), employment status (employed *vs* not employed), symptom duration, HLA-B27 status, history of extra-musculoskeletal manifestations (EMMs; uveitis, psoriasis, IBD), CRP and the Bath AS Disease Activity and Functional Indices (BASDAI/BASFI; 0–10) [11, 12].

Statistical analysis

Patient and disease characteristics were described for the overall study population, and for patients with TI and without TI (non-TI) separately. Characteristics were compared between TI and non-TI subgroups using independent *t*-tests or Mann–Whitney tests for continuous variables, and χ^2 tests or Fisher's exact tests for categorical variables, as appropriate. The number and characteristics of TI events were described.

Logistic regression analyses were conducted to assess whether the potential determinants were associated with TI. Patient-centred models and physician-centred models were generated. In the patient-centred models, determinants considered were ASDAS and ASAS HI (primary), and age, sex and education (secondary). The physician-centred models were an extension of the patient-centred models, adding physician-assessed factors. PhGA (primary), peripheral symptoms and BSA (secondary) were considered for these in addition to the patient-centred model determinants.

The modelling strategy consisted of several steps. Variable selection was conducted as the projected sample size and number of events would likely not allow for inclusion of all primary/secondary determinants. First, univariable analyses were conducted with the primary and secondary determinants, and only factors that were potentially associated with the outcome ($P < 0.20$) were selected for multivariable analysis. Next, in multivariable analysis, these selected factors were entered into the model one by one in a predefined order [primary before secondary determinants, and patient-centred factors first within primary/secondary determinant groups: ASDAS, ASAS HI, PhGA (primary determinants), education, peripheral symptoms, skin involvement (secondary determinants)], and retained if associated with the outcome ($P < 0.05$). Age and sex were always included in multivariable analysis.

Several sensitivity analyses were conducted: (i) not considering glucocorticoids for TI events, (ii) including all primary determinants in the model, regardless of results of univariable or multivariable analysis, (iii) replacing PhGA with PASS-physician in the physician-centred model (as these measures were strongly correlated, they were not explored in the same model) and (iv) adding PASS-patient to the patient-centred model as a primary determinant.

Finally, the analysis was repeated in a sample containing all patients with axSpA in SpA-Net, regardless of their ASDAS (thus also including patients in an LDA state, i.e. ASDAS <2.1). In the primary analysis, we made an *a priori* selection based on ASDAS (only including those with ASDAS ≥2.1). Consequently, the role of ASDAS itself as a driver for TI in the regression models could have been suppressed. Therefore, this additional analysis was conducted to confirm the role of ASDAS (or lack thereof) as a determinant for TI.

Missing data were not imputed. Collinearity and interactions between variables were checked for. In case of relevant interaction, analyses were stratified. *P*-values <0.05 were considered statistically significant. All analyses were conducted in Stata SE 14.0 (StataCorp, College Station, TX, USA).

Results

Population characteristics

In total, 266 patients in SpA-Net were in an HDA state (ASDAS ≥2.1) at 1171 observations over time. In this population, 121 patients also had data available on the other primary explanatory factors (ASAS HI and PhGA) at time of ASDAS, and a single observation per patient was selected for analysis. At this time point, their mean age was 50.4 (SD 13.6) years, 65 (53.7%) were female and mean symptom duration was 20.0 (S.D. 13.2) years (Table 1). Mean ASDAS was 2.9. Most of them were currently on an NSAID (61.2%) and/or bDMARD (57.9%).

The distribution of patients across the different primary explanatory factors for TI (ASDAS, ASAS HI, PhGA and in sensitivity analyses PASS-patient and PASS-physician) was moderately concordant (Table 2). Correlations between the continuous primary explanatory factors (ASDAS/ASAS HI/PhGA) were low, ranging from 0.15 to 0.25. Only a small minority scored poor (>12) on the ASAS HI, despite an unacceptable symptom state (Table 2).

TI characteristics

Although our study sample was enriched for observations with presence of TI, TI was conducted in only a minority of patients (41 TI events in 121 patients, 33.9%) (Table 3). In this group, the majority were already receiving an NSAID and/or bDMARD. TI was most often applied in the form of switching to another drug, typically within the same drug class, or addition of a drug. In most TI events, the new drug was a bDMARD. In patients already on a bDMARD, TI often involved switching to another bDMARD (Supplementary Table S1, available at *Rheumatology* online).

Patients receiving TI were younger, had a shorter symptom duration, worse patient global, more peripheral symptoms and higher PhGA compared with those not receiving TI (Table 1).

Determinants of TI

Multivariable logistic regression analyses showed that a higher ASDAS was associated with TI in the patient-centred model [odds ratio $(OR)_{ASDAS} = 1.94$, 95% CI 1.00–3.74]. However, when the physician perspective was introduced in the physician-centred model, this association attenuated, while several physician variables were prominent ($OR_{PhGA} = 1.71$, 95% CI 1.24–2.34; $OR_{peripheral} = 3.86$, 95% CI 1.41–10.58, Table 4). There was a significant interaction between PhGA and ASDAS, indicating that the association between PhGA and TI depended on the ASDAS. Because of this, additional physician-centred models with PhGA were stratified by ASDAS, using the median ASDAS value as cut-off (patient-centred models were not stratified, as PhGA was not considered for these). The stratified models showed that a higher PhGA was only significantly associated with TI in those with highest ASDAS (≥2.75), and the strength of association was also substantially higher in this subgroup ($OR_{PhGA} = 2.48$ in ASDAS ≥2.75 subgroup *vs* $OR_{PhGA} = 1.32$ if forced in model in 2.1 < ASDAS ≤ 2.75 subgroup) (Table 5). Of note, the very high disease activity threshold (ASDAS >3.5) was considered as cut-off for stratification, but the very high disease activity subgroup was too small ($n = 14$) for adjusted analyses. Unadjusted analyses showed a similar trend. Disease impact (ASAS HI) was not associated with TI in any of the models.

Of the secondary potential determinants, education, sex and BSA were not associated with TI. Older age was associated with a lower likelihood of TI in some of the models, although results were not consistent.

In *post hoc* analyses, adding centre to the models did not affect results, and centre itself was not associated with TI. Patients currently on a b/tsDMARD (at time of treatment decision) were numerically less likely to receive TI than those

Table 1. Population characteristics of patients with ASDAS ≥2.1 included in primary analysis

Characteristic	All ($n = 121$)	TI ($n = 41$)	Non-TI ($n = 80$)	P[a]
Age, years	50.4 (13.6)	46.4 (12.6)	52.4 (13.7)	0.02
Female, *n* (%)	65 (53.7)	23 (56.1)	42 (52.5)	0.71
High education, *n* (%)	47 (38.8)	18 (43.9)	29 (36.3)	0.41
Employment, *n* (%)	71 (58.7)	30 (73.2)	41 (51.3)	0.02
Current smoking, *n* (%)	26 (21.7)	8 (19.5)	18 (22.8)	0.91
Symptom duration, years	20.0 (13.2)	16.7 (12.5)	21.8 (13.4)	0.03
HLA-B27 positive, *n* (%)	68 (61.8)	23 (57.5)	45 (64.3)	0.48
History of uveitis, *n* (%)	30 (24.8)	10 (24.4)	20 (25.0)	0.94
History of psoriasis, *n* (%)	27 (22.3)	9 (22.0)	18 (22.5)	0.95
History of IBD, *n* (%)	17 (14.0)	3 (7.3)	14 (17.5)	0.13
Current NSAID[b], *n* (%)	74 (61.2)	25 (61.0)	49 (61.3)	0.98
Current csDMARD[b], *n* (%)	11 (9.1)	2 (4.9)	9 (11.3)	0.21
Current bDMARD[b], *n* (%)	68 (56.2)	20 (48.8)	48 (60.0)	0.24
Adalimumab	16 (22.9)	7 (35.0)	9 (18.0)	
Certolizumab	5 (7.1)	1 (5.0)	4 (8.0)	
Etanercept	14 (20.0)	3 (15.0)	11 (22.0)	
Golimumab	6 (8.6)	1 (5.0)	5 (10.0)	
Infliximab	9 (12.9)	2 (10.0)	7 (14.0)	
Secukinumab	18 (25.7)	6 (30.0)	12 (24.0)	
Current tsDMARD[b], *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	N/A
History of b/tsDMARDs[c], *n* (%)				
0	42 (34.7)	15 (36.6)	27 (33.8)	
1	30 (24.8)	6 (14.6)	24 (30.0)	
2	22 (18.2)	11 (26.8)	11 (13.8)	
≥3	27 (22.3)	9 (22.0)	18 (22.5)	
ASDAS	2.9 (0.6)	3.0 (0.7)	2.8 (0.5)	0.09
ASDAS >3.5 (VHDA), *n* (%)	14 (11.6)	8 (19.5)	6 (7.5)	0.07
BASDAI (0–10)	5.4 (1.8)	5.7 (1.8)	5.3 (1.7)	0.29
CRP, mg/L	6.8 (13.2)	9.2 (19.5)	5.6 (8.2)	0.48
Patient global (0–10)	5.7 (2.1)	6.4 (2.1)	5.3 (2.0)	<0.01
BASFI (0–10)	3.7 (2.4)	3.5 (2.3)	3.7 (2.4)	0.67
ASAS HI (0–17)	6.9 (3.5)	7.3 (3.3)	6.7 (3.6)	0.39
PASS-patient, *n* (%) ($n = 65$)[d]	38 (58.5)	8 (42.1)	30 (65.2)	0.09
PASS-physician, *n* (%) ($n = 60$)[d]	43 (71.7)	3 (17.6)	40 (93.0)	<0.01
Physician global	2.9 (1.8)	4.0 (1.5)	2.3 (1.6)	<0.01
TJC ≥1, *n* (%)	30 (27.0)	18 (50.0)	12 (16.0)	<0.01
SJC ≥1, *n* (%)	14 (12.6)	10 (27.8)	4 (5.3)	<0.01
Dactylitis (presence), *n* (%)	1 (0.8)	1 (2.5)	0 (0.0)	0.34
Enthesitis (presence), *n* (%)	24 (20.3)	15 (37.5)	9 (11.5)	<0.01

Data are presented as mean (S.D.) unless stated otherwise.
[a] For TI *vs* non-TI.
[b] Current = before current TI (if TI group).
[c] Number of bDMARDs and tsDMARDs ever received. Includes current b/tsDMARD drug use in current users.
[d] Data were missing in $n = 56/121$ (PASS-patient, 46%) or $n = 61/121$ (PASS-physician, 50%). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; HDA: high disease activity; HLA-B27: Human Leucocyte Antigen B27; PASS: patient acceptable symptom state; SJC: swollen joint count; TI: treatment intensification; TJC: tender joint count; tsDMARD: targeted synthetic DMARD; VHDA: very high disease activity.

not on a b/tsDMARD [20/68 (29%) *vs* 21/53 (40%); $P = 0.24$]. No clear relation was observed between the number of previous b/tsDMARDs and TI.

Sensitivity analyses

All sensitivity analyses confirmed the results (Supplementary Tables S2–S5, available at *Rheumatology* online). If glucocorticoids were not considered for definition of TI, results were similar. If the primary determinants (ASDAS, ASAS HI, PhGA; latter only for physician-centred model) were forced and retained in the models, ASAS HI was still not associated with the outcome in any model, and the effect size was small ($OR_{ASAS\ HI}$ range 0.96–1.01). When PhGA was replaced with PASS-physician in the physician-centred model, results were similar to the main analysis, with PASS-physician being very strongly associated with TI ($OR_{PASS\text{-}physician} = 94.95$). Adding PASS-patient to the patient-centred model as a primary driver did not change results, and PASS-patient itself was also not associated with the outcome ($OR_{PASS\text{-}patient} = 1.64$, 0.45–5.93). PASS-patient/physician were missing in a substantial number of patients, reducing the sample size in these analyses.

When the analysis was repeated in all patients, regardless of their ASDAS (thus also including patients with ASDAS <2.1), results were similar to in the primary analysis. ASDAS was associated with TI in the patient-centred model, either as a continuous variable or dichotomized as ASDAS ≥2.1 *vs* <2.1. In the physician-centred model, however, PhGA and peripheral symptoms—and not ASDAS—were associated with TI (Supplementary Table S6, available at *Rheumatology* online).

Table 2. Distribution of patients across primary explanatory factors

		ASAS HI			PhGA		PASS-patient		PASS-physician[d]	
		Good[b]	Moderate[b]	Poor[b]	Low[c]	High[c]	Yes	No	Yes	No
ASDAS	HDA[a]	40 (95.2)	60 (87.0)	7 (70.0)	88 (89.8)	19 (82.6)	36 (94.7)	22 (81.5)	40 (93.0)	14 (82.4)
	VHDA[a]	2 (4.8)	9 (13.0)	3 (30.0)	10 (10.2)	4 (17.4)	2 (5.3)	5 (18.5)	3 (7.0)	3 (17.6)
ASAS HI	Good[b]				36 (36.7)	6 (26.1)	19 (50.0)	5 (18.5)	17 (39.5)	6 (35.3)
	Moderate[b]				53 (54.1)	16 (69.6)	19 (50.0)	19 (70.4)	25 (58.1)	9 (52.9)
	Poor[b]				9 (9.2)	1 (4.3)	0 (0.0)	3 (11.1)	1 (2.3)	2 (11.8)
PhGA	Low[c]						34 (89.5)	22 (18.5)	40 (93.0)	11 (64.7)
	High[c]						4 (10.5)	5 (81.5)	3 (7.0)	6 (35.3)
PASS-patient[d]	Yes								29 (67.4)	6 (35.3)
	No								14 (32.6)	11 (64.7)

All values are *n* (%). Percentages represent proportion of patients within group in vertical direction.
[a] Defined as 2.1 ≤ ASDAS ≤ 3.5 (HDA) or ASDAS >3.5 (VHDA).
[b] Defined as ASAS HI ≤5 (good), 5 < ASAS HI < 12 (moderate) or ASAS HI ≥12 (poor).
[c] Defined as PhGA ≤4/10 (low) or PhGA >4/10 (high).
[d] PASS-patient and PASS-physician were available in *n* = 65/121 (PASS-patient, 54%) or *n* = 60/121 (PASS-physician, 50%). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; HDA: high disease activity; PASS: patient acceptable symptom state; PhGA: physician global assessment of disease activity; VHDA: very high disease activity.

Table 3. Treatment intensification event characteristics in patients with ASDAS ≥2.1

Characteristic	TI events in analysis[a] (*n* = 41)
Current[b] medication use, *n* (%)	
NSAID	25 (61.0)
csDMARD	2 (4.9)
bDMARD	20 (48.8)
tsDMARD	0 (0.0)
Glucocorticoid	1 (2.4)
No anti-inflammatory drug	8 (19.5)
Type of TI[c], *n* (%)	
Dose increase	0 (0.0)
Frequency increase	0 (0.0)
Switch within same drug class	24 (58.5)
Switch between drug classes	1 (2.4)
Switch within and between drug classes[d]	3 (7.3)
Addition	13 (31.7)
TI-related drug class, *n* (%)	
If switched to another drug	
NSAID	7 (25.0)
csDMARD	0 (0.0)
bDMARD	18 (64.3)
tsDMARD	0 (0.0)
Glucocorticoid	0 (0.0)
Multiple[e]	3 (10.7)
If addition of a drug	
NSAID	4 (30.8)
csDMARD	2 (15.4)
bDMARD	7 (53.8)
tsDMARD	0 (0.0)
Glucocorticoid	0 (0.0)
Multiple[e]	0 (0.0)

[a] TI events of observations that were used for regression analysis. Only one observation was considered per patient. Selection of observations was guided by presence of TI and available data on secondary determinants (Supplementary Fig. S1, available at *Rheumatology* online).
[b] Current = before current TI (if TI group).
[c] If a drug was stopped and another one was started, this was considered a 'switch'. If a drug was started but no drug was stopped, this was considered an 'addition'.
[d] If a drug was stopped and multiple drugs were added as part of TI (both within the same as between different classes).
[e] If multiple drugs were initiated as part of TI. ASDAS: Ankylosing Spondylitis Disease Activity Score; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; TI: treatment intensification; tsDMARD: targeted synthetic DMARD.

Discussion

Our study indicates that current recommendations for T2T for axSpA are not always followed in practice, as disease management is not changed in the majority of patients with axSpA and HDA. In particular, physician-centred factors such as the physician's perspective on disease activity and symptom state seem to drive decisions on TI, whereas patient-centred factors such as disease impact and the patient's perspective on symptom state do not seem to contribute significantly.

Another recent study on treatment decisions in axSpA came to a similar finding, with treatment adaptations often not being driven by patient-reported disease activity (BASDAI), but by the physician's opinion on disease activity status [8]. In RA, study results on drivers of treatment decisions are conflicting, with some also showing patient-centred factors to be strong drivers, although studies differed in design and type of drivers explored [13–16]. The strong influence of physician-centred factors on treatment adaptations is expected, as the rheumatologist's final decision to change treatment is based on their judgement. This clinical judgement is formed based on a combination of observable and unobservable factors. It is unlikely that a single measure such as the ASDAS can capture the same judgement, and thus more likely to be overruled in the decision-making process (note that this does not mean that the rheumatologist does not consider the ASDAS) [15]. Furthermore, patients and rheumatologists consider different factors when they judge disease activity, resulting in patient–physician discordance [17, 18]. Interestingly, if there is a rheumatologist–patient discrepancy, the treatment decision is more likely to align with the rheumatologist perspective [16]. Nonetheless, it is surprising that in our study both disease impact (ASAS HI) and the current symptom state according to the patient (PASS-patient) were not at all associated with TI. Especially for PASS-patient, one would expect a higher likelihood of TI if the patient considers their state to be not acceptable. The contrast between the strength of association between TI and PASS-patient (OR 1.6) *vs* PASS-physician (OR 95.0) was also substantial. The notion that the physician already takes these patient-centred aspects into account in their judgement

Table 4. Regression analysis of determinants of treatment intensification in patients with ASDAS ≥2.1

	Univariable ($n = 121$)			Multivariable patient-centred ($n = 121$)			Multivariable physician-centred ($n = 113$)		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age, years	0.97	0.94–1.00	0.02	0.97	0.94–1.00	0.02	0.97	0.94–1.00	0.09
Sex, female	1.16	0.54–2.46	0.71	1.14	0.52–2.52	0.74	0.95	0.35–2.55	0.92
ASDAS	1.91	1.01–3.61	0.05	1.94	1.00–3.74	0.05	1.52	0.71–3.24	0.28
PhGA (0–10)	1.90	1.44–2.53	<0.01	N/A[a]			1.71	1.24–2.34	<0.01
ASAS HI (0–17)	1.05	0.94–1.17	0.38	[b]			[b]		
Education, high	1.38	0.64–2.96	0.41	[b]			[b]		
Peripheral symptoms, yes	6.27	2.57–15.33	<0.01	N/A[a]			3.86	1.41–10.58	<0.01
Body surface area ≥3%, yes	2.00	0.12–32.93	0.63	N/A[a]			[b]		

[a] PhGA, peripheral symptoms (swollen joints, dactylitis, enthesitis) and psoriasis body surface area were considered for physician-centred models only.
[b] Factor not included in multivariable analysis, as it was not potentially associated with the outcome in univariable analysis ($P \geq 0.20$). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; N/A: not applicable; OR: odds ratio; PhGA: physician global assessment of disease activity; TI: treatment intensification.

Table 5. Regression analysis of determinants of treatment intensification in patients with ASDAS ≥2.1, stratified by median ASDAS value

	Multivariable: physician-centred					
	Group A: ASDAS ≥2.75 ($n = 57$)			Group B: 2.1 ≤ ASDAS < 2.75 ($n = 56$)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age, years	0.99	0.93–1.05	0.75	0.96	0.91–1.00	0.05
Sex, female	1.36	0.29–6.37	0.70	1.05	0.28-3.97	0.94
ASDAS	N/A[a]			N/A[a]		
PhGA (0-10)	2.48	1.43–4.31	<0.01	[c]		
ASAS HI (0-17)	[d]			[d]		
Education, high	[b]			[b]		
Peripheral symptoms, yes	4.62	1.03–20.66	0.05	4.36	1.06–17.84	0.04
Body surface area ≥3%, yes	[b]			[b]		

This stratified analysis was only conducted for the physician-centred models, as the PhGA (involved in the interaction PhGA*ASDAS) was not considered for the patient-centred models.
[a] ASDAS not included, as participants were stratified by ASDAS.
[b] Factor not included in multivariable analysis, as it was not potentially associated with the outcome in univariable analysis ($P \geq 0.20$).
[c] PhGA not included in final multivariable model, as it was not significantly associated with the outcome in multivariable analysis (if retained in the model: $OR_{PhGA} = 1.32$, 95% CI 0.84–2.08, $P = 0.23$).
[d] ASAS HI not included in multivariable model, as it was not potentially associated with the outcome in univariable analysis. If it was forced in the model, it was not associated with the outcome (Group A: ASDAS ≥2.75: $OR_{ASAS\ HI} = 1.02$, 95% CI 0.85–1.22, $P = 0.87$; Group B: 2.1 ≤ ASDAS < 2.75: $OR_{ASAS\ HI} = 0.99$, 95% CI 0.80–1.22, $P = 0.93$). ASAS HI: Assessment of SpondyloArthritis international Society Health Index; ASDAS: Ankylosing Spondylitis Disease Activity Score; N/A, not applicable; OR: odds ratio; PhGA: physician global assessment of disease activity; TI: treatment intensification.

seems unlikely, as correlations between physician-centred and patient-centred factors were low.

There has been much discussion about the concept of T2T in axSpA [19]. Although the rationale behind T2T seems sound (for example, given the relationship between disease activity and progression of structural damage [20, 21]), several key aspects remain uncertain. The only recommendations to date suggest remission (of both musculoskeletal disease and EMMs), or alternatively low disease activity, as the target [4]. However, the ASDAS—the preferred instrument to measure axSpA disease activity [1]—does not capture EMMs. Also, it is unclear whether ASDAS scores above the current cut-off for HDA (2.1) correspond to active disease. Almost 60% of patients in this study (who all had ASDAS ≥2.1) still considered their current state as acceptable, a finding that challenges this cut-off. Also, from the rheumatologist's perspective, disease activity scores such as the ASDAS do not always reflect actual disease activity [8, 18, 22–24]. Finally, the only trial to date on T2T in axSpA—which used an ASDAS-based target—was negative, although results on several secondary outcomes did favour a T2T strategy [25]. Altogether, these uncertainties likely make rheumatologists hesitant to adopt an ASDAS-based T2T strategy in current practice. Still, although our findings seem to challenge the clinical utility of the ASDAS in this population, this does not mean we should abandon this measure. There are several other potential explanations for our findings. Disease activity in axSpA fluctuates over time, and rheumatologists could delay TI in case of HDA, to see if spontaneous recovery occurs. In a previous study in our registry, 20% of patients with HDA were in an LDA state at a consecutive measurement without treatment modification [7]. There could also be patient-related factors, such as comorbidities or age, that could limit treatment options and TI. Importantly, patients might be hesitant to change treatment, despite being in an HDA state. They could be worried about ineffectiveness of other treatments or about adverse events [26]. Although patients' satisfaction with their current health state and their willingness to change therapy seem strongly linked [13], a substantial number of patients are not open to considering a change in treatment, even when the impact of disease is high [27]. None of these explanations invalidate the ASDAS. Additional research should focus on how rheumatologists consider this measure in the decision-making process, and why.

We need to emphasize that, if treatment is only intensified in some—but not all—patients with HDA, this is not

necessarily a negative outcome. Changing treatment every time that a disease activity score is high will result in overtreatment, lead to rapid cycling through treatment options, and negatively affect both patients (disappointment about inefficacy, side effects) and society (b/tsDMARD costs). The risk of overtreatment needs to be carefully weighed against the risk and consequences of suboptimal treatment if T2T recommendations are not adhered to. A substantial proportion of patients is not able to achieve the T2T targets of remission or low disease activity. Alternative targets might be considered instead of (or in addition to) disease activity, such as focusing on both control of inflammation and control of disease impact [28]. Such a strategy might also allow for a more personalized approach to T2T with a choice of treatment target based on a shared decision.

The current study has several strengths. First, SpA-Net is a web-based monitoring system used in daily rheumatology practice. Our results reflect current Dutch practice, from both an academic and a general hospital, and are likely generalizable. Second, in SpA-Net, the ASDAS is readily calculated and presented to the rheumatologist and patient in an understandable way, which facilitates implementation of ASDAS-driven disease management and T2T. Third, due to the wide variety of information collected in SpA-Net using validated instruments, we were able to explore both patient-centred and physician-centred factors.

Some limitations need to be discussed. First, no information was available on the reasons for (non-)TI. As discussed above, there can be many reasons why no TI is conducted despite HDA. Although we can make inferences based on our results, interpretation has to be done with caution. Second, data on primary determinants was sometimes missing, reducing our sample size for the regression analyses. This could have led to selection bias and has likely affected the power to detect statistically significant associations. However, when interpreting the analyses, we mainly considered the effect sizes (OR), and we also conducted several sensitivity analyses where statistical significance was not used as part of modelling strategy (i.e. forcing and retaining primary factors in the models). Third, due to our analytical approach, we only included one observation per patient in the regression analyses. As such, information was discarded. Fourth, we did not consider non-pharmacological treatment in this study. Finally, for our primary analysis, we included glucocorticoids in our definition of TI. Although short-term use could be warranted, these should not be used long-term [1, 29]. A sensitivity analysis without glucocorticoids yielded similar results to the primary analysis.

Going forward, future studies need to explore the reasons for (non-)TI in these patients. This requires researchers to take mixed-methods approaches, bringing together quantitative and qualitative data, capturing both rheumatologists' and patients' perspectives. The latter will be essential to fully understand the process behind the decision-making in daily practice, and the role that patients have in this context.

In conclusion, in the majority of patients with axSpA and HDA, treatment is not intensified. The decision to intensify treatment is mainly associated with physician-centred factors, and not with patient-centred factors or ASDAS. Further research is needed to better understand these treatment decisions, and ultimately optimize axSpA disease management.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Contribution statement

A.v.T. and C.W. designed the study. C.W. and R.N.E. conducted the analyses. All authors interpreted the results, revised the manuscript critically for important intellectual content and approved the final manuscript.

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