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Original article

# The impact of a csDMARD in combination with a TNF inhibitor on drug retention and clinical remission in axial spondyloarthritis

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CLINICAL SCIENCE

## Abstract

**Objectives.** Many axial spondylarthritis (axSpA) patients receive a conventional synthetic DMARD (csDMARD) in combination with a TNF inhibitor (TNFi). However, the value of this co-therapy remains unclear. The objectives were to describe the characteristics of axSpA patients initiating a first TNFi as monotherapy compared with co-therapy with csDMARD, to compare one-year TNFi retention and remission rates, and to explore the impact of peripheral arthritis.

**Methods.** Data was collected from 13 European registries. One-year outcomes included TNFi retention and hazard ratios (HR) for discontinuation with 95% CIs. Logistic regression was performed with adjusted odds ratios (OR) of achieving remission (Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP $<1.3$ and/or BASDAI $<2$) and stratified by treatment. Inter-registry heterogeneity was assessed using random-effect meta-analyses, combined results were presented when heterogeneity was not significant. Peripheral arthritis was defined as $\geq 1$ swollen joint at baseline (=TNFi start).

**Results.** Amongst 24 171 axSpA patients, 32% received csDMARD co-therapy (range across countries: 13.5% to 71.2%). The co-therapy group had more baseline peripheral arthritis and higher CRP than the monotherapy group. One-year TNFi-retention rates (95% CI): 79% (78, 79%) for TNFi monotherapy *vs* 82% (81, 83%) with co-therapy ($P < 0.001$). Remission was obtained in 20% on monotherapy and 22% on co-therapy ($P < 0.001$); adjusted OR of 1.16 (1.07, 1.25). Remission rates at 12 months were similar in patients with/without peripheral arthritis.

**Conclusion.** This large European study of axial SpA patients showed similar one-year treatment outcomes for TNFi monotherapy and csDMARD co-therapy, although considerable heterogeneity across countries limited the identification of certain subgroups (e.g. peripheral arthritis) that may benefit from co-therapy.

**Key words:** spondylitis, ankylosing, MTX, SSZ, TNF inhibitors, epidemiology

**Rheumatology key messages**

- Amongst 24 171 axial spondylarthritis patients treated with a first TNF inhibitor, 32% received csDMARD co-therapy.
- AxSpA patients treated with co-therapy had more baseline peripheral arthritis and higher CRP levels.
- Co-therapy patients demonstrated higher TNFi retention and remission rates, although the clinical relevance is doubtful.

## Introduction

TNF inhibitors are the mainstay biologic for axial spondylarthritis (axSpA), but the value of combination therapy (co-therapy) with conventional synthetic DMARD (csDMARD) remains unclear. According to current international recommendations for the management of axSpA, csDMARDs are not indicated for axial disease, although the potential benefit of combining a csDMARD with a TNFi is on the research agenda [1–3]. Recent results from the EuroSpA collaboration, including 22 196 axSpA patients across 13 European countries, found that 31% of patients were treated with a csDMARD in combination with a TNFi at the time of biologic treatment start [4].

In PsA, the use of a csDMARDs with TNFi is associated with improved remission rates, specifically with methotrexate in combination with either adalimumab or infliximab [5]. In RA, a TNFi in combination with a csDMARD, such as methotrexate, is consistently associated with improved efficacy and a lower risk of TNFi discontinuation compared with TNFi monotherapy [6]. In contrast, some observational and pharmacokinetic studies have not demonstrated any added benefit of csDMARD combination therapy in axSpA [7–11], although other cohort studies reported improved drug retention for TNFi when given in combination with a csDMARD, particularly methotrexate [12–15].

Considering the relatively frequent use of csDMARD co-therapy in axSpA, an improved understanding of the role of csDMARDs in combination with TNFi in axSpA is a key aspect of management, potentially leading to improved patient outcomes. We therefore aimed to explore whether the co-administration of a csDMARD with a TNFi improved treatment outcomes compared with TNFi monotherapy, for either TNFi retention or the attainment of clinical remission, in a large international cohort of axSpA patients.

## Methods

An observational study based on routine care axSpA registries from 13 European countries, with data aggregated through the EuroSpA collaboration (www.eurospa.eu) as previously described [4].

### Data sources

AxSpA patients ≥18 years of age, initiating a first TNFi between 2006 and 2017, and registered in one of the following countries (registries): Czech Republic (ATTRA), Denmark (DANBIO), Finland (ROB-FIN), Iceland (ICEBIO), Italy (GISEA), Norway (NOR-DMARD), Portugal (Reuma.pt), Romania (RRBR), Slovenia (biorx.si), Spain (BIOBADASER), Sweden (SRQ), Switzerland (SCQM) or Turkey (TURKBIO).

### Follow-up, time-points and treatment group definitions

Patients were followed from the date of their first registered TNFi start (baseline) for 12 months or until treatment discontinuation, loss to follow-up, end of participation in the registry or death, whichever occurred first. Biosimilars were not distinguished from their originator products, and switches between the two were disregarded.

The methods of registration of csDMARD use (methotrexate, sulfasalazine, leflunomide or other) varied across the registries, with some recording start/stop dates, while others recorded treatment status (use/no use) at specific time points (clinical visits). Exposure to co-therapy at baseline (date of TNFi start) was based on start/stop dates for the csDMARDs when available, or otherwise on csDMARD status (use/no use) at the visit closest to baseline (time-window of −100 to +30 days). The 6- and 12-month follow-up visits were defined as the date of the visit closest to the time-point, within the ranges: days 151–270 and days 271–545, respectively.

The *monotherapy group* included patients starting a first TNFi without any concurrent use of a csDMARD at baseline. The *co-therapy group* included patients starting a first TNFi and either: (i) beginning csDMARD at the TNFi start date, (ii) adding TNFi to an ongoing (and continued) csDMARD-treatment, or (iii) csDMARD subsequently added within 30 days after the initiation of TNFi.

### Descriptive statistics

Results from descriptive statistical analyses of the two treatment groups, including baseline data are presented both pooled for the whole study population and by individual country, and compared with t-tests for continuous and $\chi^2$ tests for categorical variables.

### Comparative statistics, pooling and adjustment

Results from comparative statistical analyses (regression models, as specified below), per country, were combined in a meta-analysis using a random-effects approach, utilizing the Cochran Q-test and the $I^2$ statistic to assess the statistical heterogeneity between countries to evaluate the proportion of the total variation that was due to the between-country variation [16]. Pooled comparative estimates for retention or remission were only reported if the heterogeneity was below 50%. Models were adjusted for age, sex, calendar year of TNFi start, baseline BASDAI (in quartiles) and disease duration (in quartiles). For BASDAI and disease duration, we included a fifth category including missing values in the regression models.

### TNFi retention

The overall proportion of study patients remaining on TNFi at 12 months in the monotherapy and co-therapy groups was described with Kaplan–Meier curves. Hazard ratios (HR) with 95% CI of TNFi discontinuation (with monotherapy as the reference) were calculated using crude and adjusted Cox regression models. We defined discontinuation as cessation of TNFi due to either lack of efficacy or occurrence of an adverse event. Patients discontinuing for other reasons (e.g. pregnancy, remission) were censored.

### Clinical remission

Remission at 12 months after TNFi treatment start was defined as either the Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) <1.3 and/or the BASDAI<2 (0–10 scale) [17, 18]. Patients discontinuing TNFi treatment before 12 months because of remission were considered to be in remission if they had not initiated a second TNFi treatment within the 12-month period. For patients missing clinical data at 12 months and still on the same TNFi, ASDAS-CRP and BASDAI values at six months were carried forward ($n = 15$). Patients discontinuing TNFi treatment within the first year with lack of effectiveness or adverse events as the registered reason for discontinuation were considered as not attaining remission. Remission status in patients discontinuing for an unknown reason were considered missing. In sensitivity analyses, we examined BASDAI<2 and ASDAS-CRP<1.3 separately as criteria for achieving remission. Furthermore, we calculated the difference between 12-month and baseline values (deltas) of ASDAS-CRP and BASDAI.

We performed logistic regression to obtain the odds ratios (OR) of achieving remission at 12 months (with monotherapy as reference), stratified by country, with crude and adjusted models. A pooled OR, adjusted for country, in addition to the variables mentioned above, was calculated. To model the 12-month deltas for BASDAI and ASDAS-CRP, we utilized linear regression in each registry and overall, to compare the monotherapy and the co-therapy groups.

### Secondary analyses

The overall proportion of patients remaining on TNFi at 5 years in the monotherapy and co-therapy groups was examined. Stratified analyses were performed according to type of TNFi. Furthermore, stratification was performed according to type of csDMARD co-therapy, with the two most common csDMARDs: methotrexate and/or sulfasalazine. This was done either for all TNFi combined or in separate models for the five different TNFi. Further secondary analyses were performed based on stratification by peripheral joint involvement (28 joints) at

**Table 1** Baseline characteristics of patients initiating their first TNFi as monotherapy or in combination with csDMARD

| | Overall population | Missingness (%) | Co-therapy | TNFi monotherapy |
|---|---|---|---|---|
| Total number (%) | 24 171 | 0 | 7812 (32.3) | 16 359 (67.7) |
| Age (years) | 42.5 (12.4) | 0 | 43.3 (12.5) | 42.2 (12.4) |
| Gender, *n* (% male) | 14 284 (58) | 0 | 4484 (57) | 9800 (60) |
| Disease duration (years) | 5.9 (8.1) | 22.6 | 6.4 (7.9) | 5.6 (8.2) |
| Body mass index | 26.5 (6.3) | 53.8 | 26.8 (5.3) | 26.4 (6.8) |
| Year of TNFi start | 2012 (3) | 0 | 2012 (3) | 2012 (3) |
| BASDAI (/10) | 5.6 (2.2) | 38.3 | 5.7 (2.3) | 5.6 (2.1) |
| ASDAS-CRP | 3.5 (1.1) | 57.1 | 3.6 (1.1) | 3.4 (1.1) |
| BASFI (/10) | 4.5 (2.5) | 51.2 | 4.5 (2.5) | 4.4 (2.5) |
| Tender joints (*n*) | 2.0 (3.9) | 55.6 | 2.6 (4.2) | 1.7 (3.8) |
| At least 1 tender joint, *n* (%) | 4569 (42.6) | 55.6 | 2059 (56.3) | 2510 (35.5) |
| Swollen joints (*n*) | 0.8 (2.0) | 49.6 | 1.3 (2.6) | 0.5 (1.7) |
| At least 1 swollen joint[a], *n* (%) | 3092 (25.4) | 49.6 | 1665 (41.2) | 1427 (17.5) |
| VAS global health (/10) | 6.1 (2.5) | 34.8 | 6.0 (2.5) | 6.1 (2.5) |
| VAS pain (/10) | 6.0 (2.5) | 38.6 | 6.0 (2.5) | 6.1 (2.5) |
| CRP (mg/L) | 16.0 (22.9) | 23.9 | 20.5 (26.6) | 13.9 (20.9) |
| Corticosteroid use, *n* (%) | 2513 (12) | 15.6 | 1558 (21) | 955 (7) |
| csDMARD before TNFi, *n* (%) | 11 130 (61) | 24.2 | 5042 (77) | 6088 (52) |
| Type of TNFi | | | | |
| Adalimumab, *n* (%) | 7553 (31) | 0 | 2408 (31) | 5145 (31) |
| Etanercept, *n* (%) | 5883 (24) | 0 | 1757 (22) | 4126 (25) |
| Infliximab, *n* (%) | 6061 (25) | 0 | 2356 (30) | 3705 (23) |
| Golimumab, *n* (%) | 3515 (15) | 0 | 983 (13) | 2532 (16) |
| Certolizumab pegol, *n* (%) | 1159 (5) | 0 | 308 (4) | 851 (5) |
| Type of csDMARD | | | | |
| Methotrexate, *n* (%) | — | 0.9 | 4371 (56) | — |
| Sulphasalazine, *n* (%) | — | 0.5 | 3538 (45) | — |
| Leflunomide, *n* (%) | — | 4.3 | 260 (3) | — |
| Other, *n* (%) | — | 2.3 | 344 (4) | — |

Values represent the mean (SD) for continuous variables. Otherwise, numbers and percentages are indicated for categorical variables. Percentages were calculated from the total number of patients with available values. [a]Peripheral arthritis was defined as ≥1 swollen joint at baseline. ASDAS-CRP: AS disease activity score using CRP; Co-therapy: TNFi in combination with a csDMARD; *n*: number; VAS: visual analogue score.

baseline [swollen joint count (SJC) = 0, SJC ≥ 1 or SJC unknown].

### Patient and public involvement

Patients were not involved in the study planning.

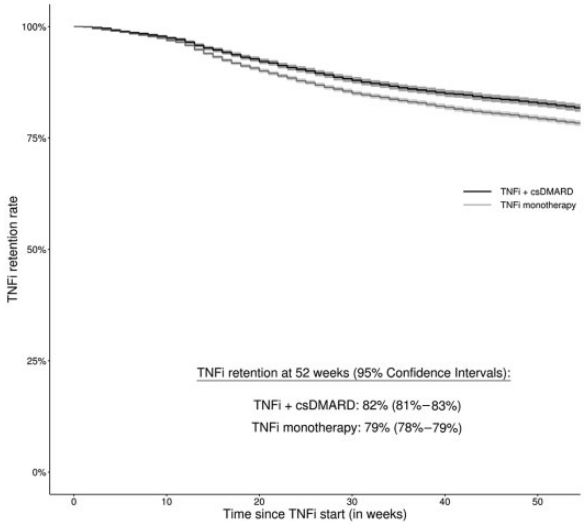
## Results

We included 24 171 axSpA patients from 13 countries. Baseline characteristics of the study cohort are presented in Table 1. The co-therapy group had significantly higher baseline values for CRP, tender/swollen joint counts, and percentages of patients with ≥1 tender/swollen joint, when compared with the monotherapy group, whereas disease activity scores such as BASDAI and ASDAS-CRP were similar. The proportion of patients on co-therapy ranged from 14% (Italy) to 71% (Finland). Percentages of patients on co-therapy: infliximab 38.9%, adalimumab 31.9%, etanercept 29.9%, golimumab 28.0% and certolizumab 26.6%. Baseline characteristics differed markedly between countries, with a mean BASDAI/ASDAS-CRP of 7.4/4.6 in Romania, compared with 3.6/2.7 in Finland (Supplementary Table S1, available at *Rheumatology* online). Similarly, large inter-country differences were observed in the proportions of patients treated with each specific medication: infliximab use varied from 1% (Slovenia) to 84% (Iceland), while among patients on co-therapy, methotrexate use varied from 12% (Romania) to 80% (Slovenia). The baseline rate of infliximab use was higher in the co-therapy group *vs* the TNFi monotherapy group (30% *vs* 23%) as was the use of corticosteroids (21% *vs* 7%).

### TNFi retention

TNFi retention at 12 months differed substantially between countries and varied from 70% (95% CI 68%, 71%) in Denmark to 94% (92%, 96%) in Romania (Supplementary Figs S1 and S2, available at *Rheumatology* online). Overall, among the 16 359 patients starting their first TNFi as monotherapy, 79%

**Fig. 1** TNFi retention rates to 12 months in TNFi monotherapy *vs* TNFi + csDMARD co-therapy groups




The shaded zone represents 95% CIs for pooled data from 13 European registries.

(78%, 79%) remained on the same TNFi treatment after 12 months, while the corresponding percentage for the 7812 patients starting their first TNFi in combination with csDMARD was 82% (81%, 83%) (Fig. 1). At 12 months, the proportions of patients who had discontinued their TNFi in the monotherapy/co-therapy groups due to an adverse event were 7%/6% and for lack of effectiveness were 12%/10%, respectively. Among patients in the co-therapy group who remained on a TNFi at 12 months and had known csDMARD status at 12 months, 97% (5070/5232) remained on a csDMARD. Reasons for TNFi discontinuation in each registry are displayed in Supplementary Table S2, available at *Rheumatology* online.

In analyses of TNFi retention stratified by country, the HR favoured co-therapy in Denmark, Norway, Switzerland and Sweden, while the HR favoured monotherapy in Italy and Turkey (Fig. 2). Due to marked heterogeneity ($I^2 = 79.4\%$, $P < 0.001$), a pooled HR was not estimated.

## Clinical remission

Overall numbers and percentages of patients in remission in the treatment groups are displayed in Table 2, demonstrating significantly higher proportions of remission in patients on co-therapy compared with TNFi monotherapy for each type of remission, although the numerical differences were small. Despite variations in the proportions of remission across countries (Supplementary Table S3, available at *Rheumatology* online), there was no statistically significant heterogeneity in the ORs estimates ($I^2 = 0\%$, $P = 0.658$). In Fig. 3, the adjusted ORs comparing the probability of attaining remission at 12 months, with TNFi monotherapy as reference, are presented for each country, as well as the meta-analysis. More than three-quarters of the registries demonstrated an OR higher than 1 (favouring co-therapy, although the majority were not statistically significant), which translated to a pooled adjusted OR of obtaining remission for the co-therapy group of 1.16 (1.07–1.25). Using only BASDAI<2 to define remission status provided a pooled OR that was slightly larger [OR = 1.29 (1.12–1.48)].

The improvements in ASDAS-CRP and BASDAI over 12 months are displayed in Supplementary Fig. S3A and B, respectively, for both the individual registries and the overall pooled data (available at *Rheumatology* online). For the pooled data, crude analyses showed a statistically significant difference between the two treatment groups in favour of co-therapy (*P*-values <0.001). Following adjustment, the overall delta-ASDAS-CRP remained highly significant ($P = 0.008$), although this was not the case for the overall delta-BASDAI ($P = 0.48$).

## Secondary analyses

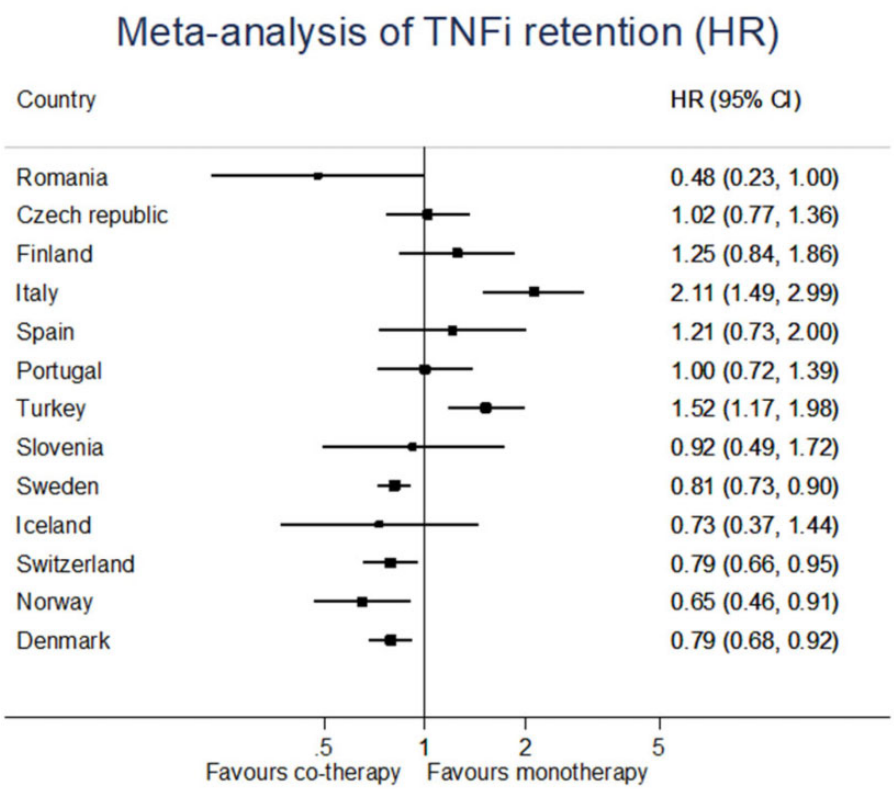
Overall, among the patients starting their first TNFi as monotherapy, 60% (59%–61%) remained on the same TNFi treatment after 5 years, while the corresponding percentage for co-therapy was 65% (63%–66%) (Supplementary Fig. S4, available at *Rheumatology* online). Retention rates for TNFi monotherapy *vs* co-therapy groups out to 5 years stratified by country are depicted in Supplementary Fig. S5, available at *Rheumatology* online. Secondary analyses of pooled data for TNFi retention are not presented due to marked heterogeneity.

Results of the secondary analyses for remission are displayed in Table 3. In adjusted analyses, co-therapy with any csDMARD compared with TNFi monotherapy was associated with statistically significant increases in the OR of remission for infliximab [1.21 (1.01–1.46)], etanercept [1.28 (1.06–1.56)] and golimumab [1.25 (1.00–1.55)], but not adalimumab [1.08 (0.93–1.27)] or certolizumab [0.96 (0.64–1.44)].

Regarding the individual csDMARDs, for all TNFi combined, co-therapy with either methotrexate or sulfasalazine individually improved the rates of remission compared with TNFi monotherapy [OR: 1.24 (1.10–1.38) and 1.26 (1.13–1.41) respectively] in adjusted analyses (Table 3). For the individual TNFi, co-therapy with methotrexate significantly improved the proportions of remission with both infliximab and etanercept, but not the other TNFi; while co-therapy with sulfasalazine significantly improved the proportions of remission with infliximab, etanercept and golimumab, but not adalimumab or certolizumab. Comparing TNFi monotherapy to TNFi combined with both methotrexate and sulfasalazine ($n = 868$, 11% of co-therapy group), we observed a similar pattern with an overall adjusted OR for attaining remission of 1.67 (1.37–2.04) with the combination of the three agents.

In patients with both known baseline peripheral joint status and known 12-month remission status ($n = 8218$),

FIG. 2 Meta-analysis of TNFi retention (HR)




Meta-analysis of adjusted hazard ratios (HR) and 95% CIs (95% CI) for discontinuation of TNFi based on the presence or absence of co-therapy with a csDMARD by country. Weights are from a random effects analysis. Overall estimate was not presented due to statistically significant heterogeneity ($I^2 = 79.4\%$, $P < 0.001$).

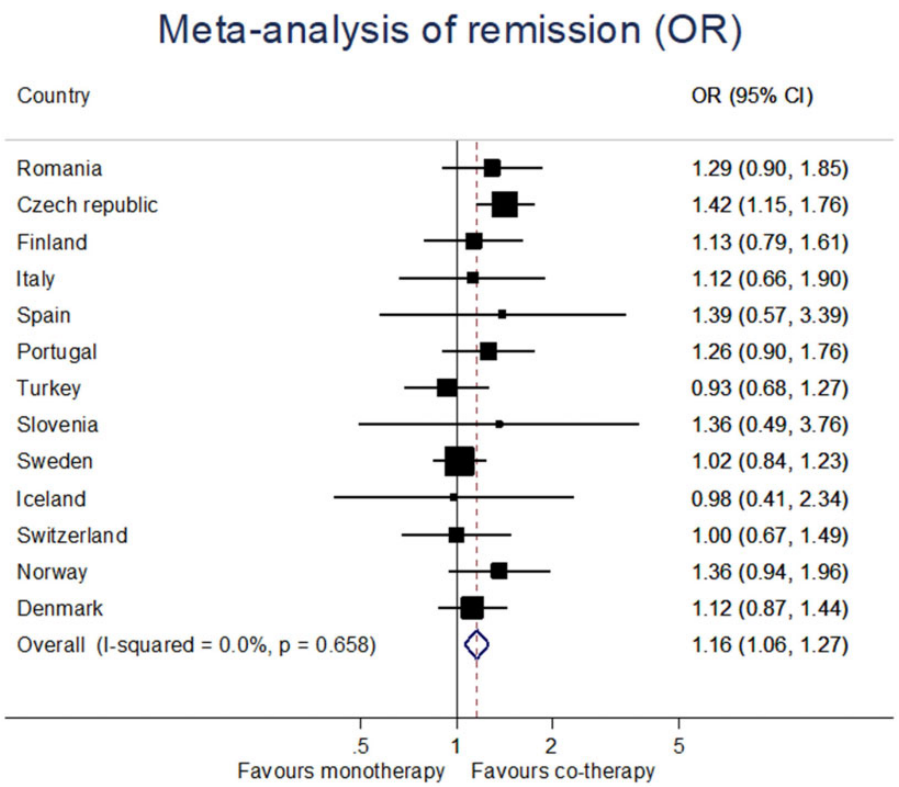
TABLE 2 Percentages and numbers of patients achieving clinical remission at 12 months

| | | Remission[a], % (number) | *P*-value (mono- vs. co-therapy) | No remission[a], % (number) | Unknown[b],% (number) | NNT |
|---|---|---|---|---|---|---|
| Any remission | TNFi monotherapy | 19.5 (2265) | | 80.5 (9371) | 28.9 (4723) | |
| | Co-therapy | 21.8 (1188) | $P < 0.0001$ | 78.2 (4255) | 30.3 (2369) | 43 |
| ASDAS remission (ASDAS-CRP $< 1.3$) | TNFi monotherapy | 21.8 (2091) | | 78.2 (7502) | 41.3 (6766) | |
| | Co-therapy | 23.7 (1063) | $P = 0.011$ | 76.3 (3418) | 42.6 (3331) | 53 |
| BASDAI remission (BASDAI $< 2$) | TNFi monotherapy | 5.9 (679) | | 94.1 (10 902) | 29.2 (4778) | |
| | Co-therapy | 7.7 (418) | $P < 0.0001$ | 92.2 (4993) | 30.7 (2401) | 56 |

Any remission was defined as either BASDAI $< 2$ and/or ASDAS-CRP $< 1.3$. [a]Percentages are calculated disregarding patients with unknown remission status. [b]Percentages are calculated on the total number of patients, including those with unknown remission status. $\chi^2$ tests were used to compare percentages of patients achieving clinical remission at 12 months between groups. ASDAS-CRP: AS disease activity score using CRP; NNT: number need to treat (for one additional patient obtaining remission with co-therapy over treatment with monotherapy).

23% had a SJC $\geq 1$ at baseline. SJC status was unknown for 50% of patients with available remission status. In adjusted analyses, the OR for remission at 12 months was higher for co-therapy in the SJC unknown group [1.3 (95% CI: 1.1, 1.5)] but was comparable in the SJC $= 0$ and the SJC $\geq 1$ subgroups (Supplementary Table S4, available at *Rheumatology* online). Secondary analyses in the subgroups of patients

Fig. 3 Meta-analysis of remission (OR)




Meta-analysis of remission (defined as either an ASDAS-CRP <1.3 and/or a BASDAI<2) at 12 months after TNFi treatment start by country, demonstrating the adjusted odds ratios (OR) and 95% CI based on the presence or absence of co-therapy (reference) with a csDMARD.

with known classification criteria (ASAS or modified New York) were not possible due to the high proportion of missingness (56% and 75%, respectively).

## Discussion

In this study of 24 171 patients with axial SpA treated with a first TNFi, co-therapy with a csDMARD was observed in a third of patients and was associated with the presence of swollen joints and higher CRP levels at baseline, compared with patients on TNFi monotherapy. Although patients on co-therapy demonstrated statistically higher TNFi retention and remisison rates compared with monotherapy, the differences were numerically small and potentially influenced by residual confounding, and thus unlikely to be of clinical relevance. This is further demonstrated by a number need to treat (NNT) of 43 in order to obtain remission in one additional patient treated with a csDMARD.

Despite marked variability between countries, overall, a higher proportion of patients on co-therapy (compared with those on TNFi monotherapy) remained on TNFi at 12 months. Our findings suggest that a benefit from concomitant csDMARD therapy on TNFi retention was more apparent in countries in the northern part of Europe (particularly Denmark, Norway, Iceland and Sweden) and Switzerland. Interestingly, these countries had considerably lower 12-month TNFi retention rates of around 75% and thus the potential for an additional beneficial effect from a csDMARD could be greater than in countries with retention rates around 90%.

Our findings regarding the impact of co-medication on TNFi retention are consistent with previous studies of axSpA patients in the southern European countries of Greece and Portugal, which did not demonstrate an advantage of csDMARD co-therapy [19, 20], and are similarly consistent with studies from Sweden and Switzerland that described a benefit with co-therapy [12, 13]. Conversely, a study of axSpA patients in the DANBIO registry from 2010 found that the use of methotrexate had no effect on TNFi retention [7]. Several differences between the included countries could potentially have an impact on TNFi retention. For example, Switzerland and the Scandinavian countries have approximately three-fold higher gross domestic products (GDP), compared with most of the other countries in the EuroSpA collaboration and this may have an impact on a multitude of factors, including access to healthcare and imaging (such as MRI), as well as the availability of certain medications. GDP has been associated with disease activity and treatment retention in

**Table 3** Secondary analyses of the medication-specific differences for TNFi and csDMARD regarding clinical remission

| | Total number (mono-/co-therapy) | Clinical remission at 12 months | | |
|---|---|---|---|---|
| | | Missingness[a] (%) (mono-/co-therapy) | Adjusted OR[b] (95% CI) | % achieving remission[c] (monotherapy vs co-therapy) |
| **Any csDMARD** | | | | |
| Infliximab | 3705/2356 | 27/33 | **1.21 (1.01, 1.46)*** | **17 *vs* 18** |
| Adalimumab | 5145/2408 | 30/29 | 1.08 (0.93, 1.27) | 20 *vs* 23 |
| Etanercept | 4126/1757 | 35/35 | **1.28 (1.06, 1.56)*** | **18 *vs* 22** |
| Golimumab | 2532/983 | 22/21 | **1.25 (1.00, 1.55)*** | **22 *vs* 27** |
| Certolizumab | 851/308 | 18/25 | 0.96 (0.64, 1.44) | 24 *vs* 23 |
| **Methotrexate** | | | | |
| Infliximab | 3705/1605 | 27/36 | **1.37 (1.11, 1.70)**** | **17 *vs* 19** |
| Adalimumab | 5145/1204 | 30/34 | 1.19 (0.96, 1.47) | 20 *vs* 22 |
| Etanercept | 4126/922 | 35/40 | **1.35 (1.04, 1.75)*** | **18 *vs* 20** |
| Golimumab | 2532/478 | 22/24 | 1.25 (0.93, 1.67) | 22 *vs* 26 |
| Certolizumab | 851/162 | 18/26 | 1.24 (0.73, 2.07) | 24 *vs* 25 |
| Any TNFi | 16 359/4371 | 29/34 | **1.24 (1.10, 1.38)***** | **20 *vs* 21** |
| **Sulfasalazine** | | | | |
| Infliximab | 3705/851 | 27/28 | **1.32 (1.03, 1.69)*** | **17 *vs* 22** |
| Adalimumab | 5145/1210 | 30/24 | 1.18 (0.97, 1.43)[t] | 20 *vs* 28 |
| Etanercept | 4126/848 | 35/28 | **1.38 (1.08, 1.74)**** | **18 *vs* 25** |
| Golimumab | 2532/493 | 22/17 | **1.45 (1.10, 1.91)***** | **22 *vs* 32** |
| Certolizumab | 851/136 | 18/23 | 0.75 (0.41, 1.31) | 24 *vs* 21 |
| Any TNFi | 16 359/3538 | 29/25 | **1.26 (1.13, 1.41)***** | **20 *vs* 26** |
| **Methotrexate + Sulfasalazine** | | | | |
| Infliximab | 3705/276 | 27/33 | **1.95 (1.32, 2.85)***** | **17 *vs* 30** |
| Adalimumab | 5145/260 | 30/30 | **1.85 (1.27, 2.67)**** | **20 *vs* 37** |
| Etanercept | 4126/197 | 35/28 | 1.45 (0.92, 2.24) [t] | 18 *vs* 26 |
| Golimumab | 2532/112 | 22/19 | **1.69 (1.01, 2.78)*** | **22 *vs* 36** |
| Certolizumab | 851/23 | 18/22 | 1.01 (0.28, 3.15) | 24 *vs* 28 |
| Any TNFi | 16 359/868 | 29/29 | **1.67 (1.37, 2.04)***** | **20 *vs* 32** |

Analyses based on the presence or absence of co-therapy (reference) with a csDMARD. HR: hazard ratio; OR: odds ratio. Odds ratios (OR) are provided with the 95% CI in brackets. [a]Proportions of patients missing data on remission status at 12 months. [b]Analyses adjusted for age, gender, calendar year, BASDAI (in quartiles) and disease duration (in quartiles). [c]Percentages calculated from the group of patients with available remission status. t = trend = $0.05 \leq P < 0.10$, *$P < 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$. Figures in bold represent significantly better outcomes ($P < 0.05$) with co-therapy compared to TNFi monotherapy.

RA [21, 22]. Moreover, the use of a csDMARD prior to starting a TNFi is mandatory in some countries for axSpA, such as Finland, where we observed 71% use of csDMARD at TNFi initiation. Local recommendations/guidelines regarding the use of csDMARD and TNFi vary across countries, as does their reimbursement. For example, Iceland demonstrated the highest proportion of infliximab use (84%), where a tender process exists for the cheapest TNFi.

A potential role for csDMARD use with a TNFi in axSpA has been hypothesized due to a reduced clinical response to infliximab being correlated with the formation of anti-infliximab antibodies [23]. Studies in SpA have demonstrated that csDMARDs (particularly methotrexate) improve the retention of infliximab more than other TNFi [13, 24]. Moreover, a study of a US administrative claims database reported that in 3812 AS patients, concomitant use of methotrexate, in contrast to other csDMARDs, was associated with a lower adjusted HR (95% CI) for TNFi discontinuation [0.79 (0.67, 0.93)] [25]. Methotrexate was evaluated in three RCTs, with a Cochrane review concluding insufficient evidence to support any benefit in the treatment of AS [26]. A Cochrane review of sulfasalazine concluded a statistically significant benefit in reducing the erythrocyte sedimentation rate and easing spinal stiffness, although the effect size was not clinically meaningful and there was no effect on pain or other measures of disease activity [27].

Previous studies in axSpA patients looking at clinicial effectiveness, including remission, have not demonstrated an overall benefit for csDMARD co-therapy over TNFi monotherapy [7, 13, 14, 28]. Although, a Swiss study found a significantly higher proportion of patients

with an ASDAS clinically important improvement with co-therapy in the subgroup of patients treated with infliximab and Shimabuco *et al.* found a higher rate of ASDAS remission in patients treated with sulfasalazine ($P = 0.037$), but not methotrexate [13, 28]. Our study found significantly higher proportions of clinical remission with co-therapy compared with TNFi monotherapy, both overall and individually with methotrexate and sulfasalazine. This difference could be partly explained by the large sample size. The numerical differences between groups were small (e.g. ASDAS-CRP remission proportions of 22% and 24%, in the two treatment groups), thus questionning the clinical relevance at the individual patient level.

In the current study, co-therapy with a csDMARD significantly improved the remission rates with infliximab, etanercept and golimumab compared with TNFi monotherapy, but not with adalimumab or certolizumab. While it is generally assumed that there are no significant differences between the various TNFi in terms of efficacy in axSpA, no head-to-head trials have compared them directly. A change in prescribing habits over time could also explain this to some extent, with infliximab and etanercept representing the first TNFi on the market, while adalimumab is currently the most prescribed TNFi. Similarly, TNFi retention rates may vary over time [4], although all analyses were adjusted for calendar year of TNFi start. Despite previous studies describing no benefit of co-therapy with etanercept, our findings in a much larger cohort seem robust as in adjusted analyses similar results were found regardless of the csDMARD utilised. Moreover, given that both BASDAI and ASDAS include patient reported disease outcomes not specific to axial disease (ie 'fatigue' and 'overall discomfort' with BASDAI and 'patient global' with ASDAS), there may be some patients who respond better with etanercept in combination with a csDMARD, compared with etanercept monotherapy which is not so efficient on several extra-musculoskeletal manifestations. Finally, it is difficult to make firm conclusions with regard to certolizumab given the relatively small number of patients.

Regarding the individual csDMARDs, we demonstrated that both methotrexate and sulfasalazine had a beneficial role on TNFi remission rates. Several studies have suggested that sulfasalazine might be superior to methotrexate in terms of TNFi retention [12, 14]. Based on the literature in other indications, particularly PsA, one could hypothesize that methotrexate and sulfasalazine may be useful in axSpA patients with peripheral synovitis or extra-articular manifestations such as psoriasis or uveitis [5, 29, 30].

Our study has several limitations to consider. Similar to many prospective cohort studies, we observed high proportions of missingness for many variables, although information on concomitant csDMARDs was almost complete. The missingness of variables was comparable in both exposure groups and therefore is unlikely to have influenced the results. The high missingness of variables such as peripheral joint involvement, psoriasis, uveitis and BMI prevented their inclusion as potential confounders in adjusted analyses. Much of this missingness was structural, as this data is not explicitly collected in several of the registries. We chose a combined remission score due to the relatively high proportion of missingness in ASDAS-CRP remission data. When comparing patients missing the remission outcome to patients having the outcome, there were no clinically relevant differences (data not shown).

Another potential limitation is residual confounding by factors influencing the use of a csDMARD, such as local regulations, alcohol intake, desire for pregnancy and the presence of comorbidities such as hepatic impairment. Most registries did not include details that allowed the distinction between patients with and without peripheral joint involvement. We attempted to analyse the effect of peripheral joint involvement with examination of the SJC at baseline; however, channelling bias towards concomitant csDMARD use in certain patient groups and the risk of residual confounding could have influenced the results. In addition, the relatively high rates of missingness for peripheral arthritis of around 50% may have prevented more conclusive results. For a limited number of patients from Finland ($n < 50$) in 2017 a systematic recording error may have occurred for BASDAI scores, which would not have the power to effect either the direction or the magnitude of the overall results.

The use of alternative statistical methods, such as propensity scoring, were considered, but ultimately we concluded that it was not feasible considering the high rates of missing data and risk of residual confounding. Furthermore, multiple imputation was considered, but because this would need to be performed separately for each country, and would thus be impacted by the pattern of missingness that was very closely related to the country variable (very high missingness in some countries and almost zero missingness in others), it was deemed inappropriate. Finally, we were not able to explore drug-related adverse events, which may be more common in the co-therapy group.

In conclusion, this large study of 24 171 axSpA patients demonstrated that csDMARD co-therapy was unlikely to have a clinically meaningful effect on neither TNFi retention nor treatment response. Our results do not support the routine use of csDMARD co-therapy with a TNFi. However, we cannot rule out an additional beneficial effect of co-therapy in certain subgroups, such as those with peripheral joint synovitis or extra-articular manifestations, where further studies may be warranted.

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All co-authors have contributed significantly in accordance with contributorship guidelines.

## Data availability statement

The data underlying this article were accessed from the EuroSpA Research Collaboration Network (https://eurospa.eu/#registries). The derived data generated in this research could be shared on reasonable request to the corresponding author but would require approval from all contributing registries.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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