**INEQUITY IN BIOLOGIC DMARD PRESCRIPTION FOR SPONDYLOARTHRITIS ACROSS THE GLOBE: RESULTS FROM THE ASAS COMOSPA STUDY**

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**Abstract**

**Objectives:** The value of biologic DMARDs (bDMARDs) in SpA is well recognized but global access to these treatments can be limited due to high costs and other factors. This study explores country-variation in the use of bDMARDs in SpA in relation to country-level socio-economic factors.

**Methods:** Patients fulfilling the ASAS SpA criteria in the multi-national, cross-sectional ASAS COMOSPA study were studied. Current use of bDMARDs or conventional synthetic DMARDs (csDMARDs) was investigated, in separate models, with multilevel logistic regression analysis, taking the country level into account. Contribution of socio-economic factors including country health expenditures, gross domestic product (GDP) and human development index (HDI) as independent country-level factors, was explored individually, in models adjusted for socio-demographic as well as clinical variables.

**Results:** In total, 3370 patients from 22 countries were included (mean[SD] age 43[14] years; 66% male; 88% axial disease). Across countries, 1275 (38%) were bDMARD users. Crude mean bDMARD-use varied between 5% (China) to 74% (Belgium). After adjustment for relevant socio-demographic and clinical variables, important variation in bDMARD-use across countries remained ($p<0.001$). Country-level socio-economic factors, specifically higher health expenditures were related to higher bDMARD uptake, though not meeting statistical significance (OR 1.96;95%CI 0.94,4.10). csDMARD uptake was significantly lower in countries with higher health expenditures (OR 0.32;95%CI 0.15,0.65). Similar trends were seen with the other socio-economic variables.

**Conclusions:** There remains important residual variation across countries in bDMARD uptake of patients with SpA followed in specialized SpA centers. This is independent of well-known factors for bDMARD use such as clinical and country-level socio-economic factors.

## INTRODUCTION

The role of biological disease-modifying anti-rheumatic drugs (bDMARDs) in Spondyloarthritis (SpA) has been extensively studied and robust scientific evidence supports their efficacy in reducing disease activity and improving functional ability, spinal mobility and quality of life.[1] bDMARDs are therefore recommended for use in the presence of active disease and following failure of two non-steroidal anti-inflammatory drugs (NSAIDs).[2] However, an important barrier to their use is their high cost which also influences the development of national guidelines and prescribing patterns.

On the other hand, the use of conventional synthetic DMARDs (csDMARDs) in SpA, unlike rheumatoid arthritis (RA) and other inflammatory arthritides with peripheral joint involvement is less-well established. Currently there is a general lack of evidence on their role in axSpA,[3] and the existing evidence consistently shows no efficacy[4–6] making their role debatable[7] and resulting in the Assessment in SpondyloArthritis international Society (ASAS) and the European League Against Rheumatism (EULAR) not supporting their use in patients with only axial disease.[2]

Existing literature supports inequity in bDMARD prescription in RA, both at an individual and country level,[8–13] but the evidence for this is lacking in SpA. Increasing insight into patterns of treatment use across countries and potential differential access to biologic drugs can help highlight potential sources of inequity and drive change through informing service delivery, refining drug reimbursement criteria and access to these treatments nationally, in line with international recommendations. This is particularly important, since access and use of healthcare services that prevent and treat disease is one of the key determinants of health.[14]

This study aimed to explore individual and country-level variation in the uptake of DMARDs in patients with SpA and unravel gaps in literature regarding how they are used and possible factors that could influence this. The ASAS COMOrbidities in SPondyloArthritis (COMOSPA) study, an international study including patients from 22 countries and initially designed to estimate the prevalence of comorbidities in SpA,[15] provided an ideal setting to answer these questions.

## METHODS

### Study design and patient recruitment

ASAS-COMOSPA is a multi-centre cross-sectional observational study with 22 participating countries across four continents (Africa, America, Asia and Europe).[15] Consecutive patients (age 18 years or over) with a clinical diagnosis of SpA according to the treating rheumatologist, either axial or peripheral, were included in ASAS-COMOSPA, provided they were able to understand and complete the questionnaires. For the present study, analyses were restricted to patients fulfilling the ASAS criteria for SpA, either axial or peripheral.[16] The study was conducted according to guidelines for good clinical practice in all countries with all local ethics committees approving the ASAS-COMOSPA study protocol. Written informed consent was obtained from all subjects before enrolment.

**Data collection**

Data collection in the ASAS-COMOSPA ranged from patient demographic variables to disease-related variables and treatment data, including: treatment with non-steroidal anti-inflammatory drugs (NSAIDs) with computation of the ASAS NSAID score (0-400)[17] reflecting NSAID-use over the past 3 months; current and past use of csDMARDs and bDMARDs (see below).

**Outcome measures**

The main outcome of interest was current bDMARD uptake, studied as a binary variable to indicate current bDMARD use versus all other (including csDMARD use and/or NSAIDs). In addition, current csDMARD uptake as a binary variable to indicate current csDMARD use versus all other (including bDMARD use with or without csDMARDs and/or NSAID use) was also examined in separate models as another outcome measure.

**Individual-level variables**

Variables of interest potentially influencing the uptake of DMARDs, aside from age and gender, included socio-demographic factors such as educational status (secondary and university education vs primary education); HLA B27 status (positive vs negative); measures of disease activity such as the Ankylosing Spondylitis Disease Activity Score calculated with CRP (ASDAS); measures of functional ability (Bath Ankylosing Spondylitis Functional Index [BASFI], range 0-10); presence of axial vs peripheral disease (yes for axial disease); radiographic sacroiliitis (yes vs no); presence of peripheral enthesitis, dactylitis or extra-articular manifestations (uveitis, psoriasis or

inflammatory bowel disease), (yes vs no) and comorbidity burden using the Rheumatic Disease Comorbidity Index (RDCI, range 0-9).[18]

**Country-level variables**

Country socio-economic variables were studied as the main independent variables of interest and included: country health expenditures per capita[19] (adjusted for purchasing power parity [PPP], measured in international dollars); gross domestic product (GDP)[20] (adjusted for PPP, measured in international dollars); Gini index[21,22], as a measure of income inequality across a country (range 0 [absolute equality]-100 [absolute inequality]); human development index (HDI)[23], a composite measure of average achievement in key dimensions of human development used to rank countries based on their performance in these. These variables were split into tertiles with the top two compared to the bottom tertile in regression analyses: for country health expenditures, GDP and Gini, high/medium versus low. For HDI, an external classification system was used[23] as opposed to creating a new dichotomization, with categories compared being high/very high versus medium. All country-level socioeconomic variables are presented in ~~the~~ supplementary table 1. The country health expenditures variable was *a priori* chosen as the main independent variable of interest, as the outcome refers to uptake of a drug, falling into health expenditures. Therefore, we hypothesized that country health expenditures would be the most relevant socio-economic variable in the context of health spending and a good reflection of country wealth.

**Data analysis**

Multilevel modeling analyses were conducted in order to account for patients being recruited from different countries. Multilevel models take into account the dependency of the observations, in this instance by accounting for the two-level structure in the data, namely patients at the 'lower' level are nested within countries at the 'higher' level.[24] Multi-level mixed effects logistic regression models with random intercept for country were constructed with current use of bDMARDs and current use of csDMARDs as the dependent variables, in separate models. Odds ratios (ORs) and 95% Confidence Intervals (CI) were estimated. Variations in impact of patient-level socio-demographic variables (age, gender and educational status) on DMARD use across countries were first tested by incorporating random slopes for the variable, which is comparable to testing for interactions in a simple regression model. The effect of level of

education was found to vary significantly ($p<0.001$) across countries in relation to bDMARD uptake; therefore, education was included with a random slope in multivariable models where bDMARD was the outcome to control for potential confounding at the country as well as individual level. Potential confounders were entered in the models in a manual forward procedure (cut-off $p<0.05$) provided they were meaningful in the univariable analyses (defined as $p<0.10$) or if considered clinically relevant. In a final step, the contribution of country health expenditures, GDP, Gini and HDI as independent country level factors, was individually explored in models adjusted for socio-demographic (age, gender, education level) as well as clinical variables (presence of axial vs peripheral disease, disease activity, sacroiliitis on X-ray, history of extra-articular manifestations, total NSAID score, past cs/bDMARD use) known to determine bDMARD-use (or csDMARD use, respectively) in SpA. All analyses were conducted with the statistical software Stata v13.

## RESULTS

### Patient, disease characteristics and treatment

From a total of 3984 patients included in ASAS-COMOSPA across 22 countries, 3370 (85%) fulfilled the ASAS SpA criteria for axial or peripheral disease and were included in this study. The majority of patients were male (66%); mean age was 43 years (SD 14), mean disease duration 8.4 years (SD 9.5) and 88% had axial disease. Table 1 summarizes the patient demographics, clinical characteristics and type of treatment used. Results by individual country are shown in supplementary table 2. Across countries, 1275 (38%) patients were bDMARD users, 1168 (35%) csDMARD users (25% without bDMARDs). Crude mean bDMARD and csDMARD uptake varied considerably across countries (see figure 1).

### *bDMARD uptake*

Table 2 shows the model with bDMARD uptake as the outcome. Higher country health expenditure was associated with higher bDMARD uptake (OR 1.96; 95%CI 0.94,4.10), though without reaching statistical significance. In the same models, past b/csDMARD use was associated with almost double odds of using bDMARDs. Similarly, male gender, presence of axial (vs peripheral) disease, sacroiliitis on X-ray and presence of extra-articular manifestations were all significantly associated with higher bDMARD use. The results also suggest an association between lower disease activity with lower bDMARD use, likely to be a reflection of the cross-sectional

nature of the study (i.e. simply an observation of less disease activity in those already on bDMARDs). Figure 1 shows the crude and adjusted percentage of bDMARD uptake by country. The model demonstrated significant variation in bDMARD use by country ($p<0.001$) despite full adjustment.

***csDMARD uptake***

Table 3 shows the model with csDMARD uptake as the outcome. Higher country health expenditure was associated with lower csDMARD uptake (OR 0.32; 95%CI 0.15,0.65). The results of the csDMARD model are complimentary to those of the bDMARD model, with the same variables demonstrating an association with csDMARD uptake in the opposite direction to those of bDMARD uptake. In other words, male gender, axial disease and sacroiliitis on X-ray and past csDMARD use were all significantly associated with lower csDMARD use. Higher disease activity was associated with higher csDMARD use, again likely to be a reflection of the cross-sectional nature of the study (i.e. higher disease activity in those using csDMARDs). Figure 2 shows the crude and adjusted percentage of csDMARD uptake by country. A significant variation across countries was also seen in relation to csDMARD uptake ($p<0.001$) and also independent of adjustment for socio-demographic, clinical and socio-economic relevant variables.

***Other country-level socio-economic variables***

Across other socio-economic variables studied, the only significant association in univariable analyses was between HDI and csDMARD uptake. Replacing country health expenditures in the final adjusted models with other country-level socio-economic variables revealed higher use of bDMARDs and lower use of csDMARDs with higher GDP and HDI, although significance was only reached for GDP and csDMARD use (OR 0.44; 95%CI 0.21,0.91) (Table 4). Higher country-income inequality as measured by Gini was associated with lower bDMARD than csDMARD uptake, although no statistical significance was reached (Table 4).

## DISCUSSION

The ASAS-COMOSPA study enabled the systematic study of b- and cs-DMARD uptake across 22 countries. It demonstrates important residual variation, which is not explained by socio-demographic and clinical characteristics. The study suggests that country-level socio-economic indicators may in part, but not entirely, explain some of the differences. The csDMARD findings are supportive of the bDMARD results, highlighting that higher country welfare seems to be

associated not only with higher bDMARD use (although not reaching statistical significance), independent of all other characteristics including country of residence, but also with lower csDMARD use. Given the lack of evidence for efficacy of csDMARDs in axSpA[3] and the available evidence consistently showing no efficacy,[2,4–7] this reflects an unjust selection of treatment for patients in countries of lower socio-economic welfare, based on decisions other than clinical indication.

bDMARD use was almost double in countries with higher compared to lower country health expenditures. Although not reaching statistical significance, the effect is of interest, since power to detect country level predictors is driven largely by the number of countries. The number of countries included in ASAS-COMOSPA, though impressive for a multinational study with the logistic challenges it represents, is relatively small in statistical terms and a limiting factor when analyzing country-level variables. This, in turn, is reflected in a lack of power to identify potentially significant relationships.

To date, only few studies have systematically studied access to biologics across countries and these have been mainly in RA.[8–13] Our study observations find support in the existing literature of bDMARD use in RA which suggests country-level socioeconomic factors to play a role.[11,13,25,26] In particular, existing evidence shows that patients living in countries with a higher welfare have lower disease activity states, likely to be at least in part mediated by a higher likelihood of receiving bDMARDs.[13] The high costs of these drugs have undoubtedly influenced reimbursement but also national recommendations and guidelines across countries, in order to regulate access to these treatments while keeping a balance between clinical and economic demands.[27,28] Indeed, costs of bDMARDs vary widely by country, driven by socio-economic welfare among other factors [10] with countries of lower socio-economic welfare ~~have been shown to have~~ demonstrating stricter eligibility criteria for bDMARDs ~~in RA~~.[12]

The existence of international recommendations in SpA[29] encourage comparable management in these patients. In fact, evidence suggests that most national recommendations follow the international ASAS recommendations and despite some countries requiring, for example, additional objective signs of inflammation and/or more pre-treatment, limiting access, general consensus exists about the use of, for example, TNF-inhibitor therapies.[30] Still, there could be

'hidden' barriers across individual countries limiting access to these drugs, ranging from differences in the funding of health-care provision, to local/regional variation in budget availability and feasibility of access to these more expensive, albeit more effective treatments, through to differences in guideline interpretation and personal approach as well as preference by the treating rheumatologist. It may be, for example, that knowledge about the potential side effects of bDMARDs poses resistance to their use by some individuals, who may in turn seek out to alternative treatments. This may explain the differences observed even between countries with comparable health expenditures. We can only speculate on the reasons for the residual degree of variation in bDMARD uptake in our study, despite adjustment for patient, disease and country-level characteristics. It is also possible that patient selection at inclusion into the study may have played a role in these observations. For example, preferential review of patients on bDMARDs by some centers would not provide an accurate reflection of the wider practice at a specific clinical setting and less so across the entire country. Furthermore, it is possible that not always consecutive patients may have been selected for inclusion into the study. The fundamental issue though remains that, assuming the patient needs for bDMARD use are similar across countries, differential access to these treatments raises concerns regarding the risk of inequity.

Male patients, presence of axial disease, sacroiliitis on X-ray and presence of extra-articular disease were all associated with higher bDMARD use. In the csDMARD model, these associations were reversed and therefore supportive of the bDMARD findings. These observations are reassuring, since all these factors are indicators of worse disease or better response and justify higher bDMARD use.[31–33]

The study has some important limitations. Firstly, selection bias cannot be excluded and the uptake of bDMARDs in the group of patients included per country may not be fully representative of the general bDMARD uptake across all SpA patients. More specifically, the study has been conducted in centers that are associated with ASAS and this may be a bias towards higher bDMARD prescription, independent of the country and related socio-economic factors. Better selection of patients for bDMARD use is possible in ASAS centers. This reflects potential sources of bias to the findings of the study. However, consecutive patients were included in the study and the disease characteristics of the population studied is reflective of a typical SpA population. Secondly, it was not possible to explore all possible reasons for barriers to access of bDMARDs

and as mentioned above, explanations for the residual variation seen in bDMARD use after adjusting for socio-economic, socio-demographic and clinical variables remain speculative. The aim, however, was to investigate whether differential access could be a problem and potentially leading to inequities. Further research should unveil possible other explanations for treatment choices. Furthermore, the cross-sectional nature of ASAS-COMOSPA precludes the study of causal links; instead, it only allows for associations to be seen. Finally, the cross-sectional nature of the analysis prevents the adjustment of disease activity before the start of bDMARDs, another important limitation.

Important strengths of the study include the large patient numbers and the uniqueness of ASAS-COMOSPA as one of the largest multi-national SpA datasets to date, which includes a wealth of information ranging from socio-demographic, to disease-related clinical and radiographic measures of disease as well as country-level macro-economic data. The study population is typical and representative for SpA, characterized by predominantly male patients with an average age in the early 40s. The occurrence of disease at the peak of the productive lifespan of young individuals[34,35] with the known considerable impact on work ability[36] makes it imperative that access to treatments that are known to be effective in suppressing inflammation is feasible and unrestricted. This, alone, makes our study particularly relevant.

In conclusion, this study provides insights into complex contributions between patient and disease-related factors and country-level socio-economic factors, raising concerns regarding equity in access to effective (biologic) treatments in SpA. The findings suggest unequal and unjust selection of treatment for SpA independent of clinical indication, an observation that necessitates urgent attention on the health equality and public health agenda.

**COMPETING INTERESTS:**

The authors declare they have no conflicts of interest relating to this study.

**CONTRIBUTORSHIP:**

The authors take responsibility for the integrity of the work , from inception to published article and they should indicate that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Table 1.** Patient demographics, clinical characteristics and treatment in patients with SpA fulfilling the ASAS classification criteria.

| | Mean (SD) or n (%)<br>N = 3370 |
|---|---|
| Age, n=3334 | 42.9 (13.7) |
| Disease duration (years), n=3342 | 8.4 (9.5) |
| Male gender | 2221 (66) |
| HLA B27 positive, n=2733 | 2082 (76) |
| Education level, n=3364 | |
| -Primary school or less | 421 (13) |
| -Secondary school | 1497 (44) |
| -University | 1446 (43) |
| BMI ($kg/m^2$), n=3325 | 26.1 (5.7) |

| | |
|---|---|
| Current or previous smoker, n=3365 | 1565 (46) |
| Sacroiliiis on X-ray, n=3190 | 2406 (75) |
| Sacroiliitis on MRI, n=1782 | 1249 (70) |
| History of enthesitis, n=3367 | 1281 (38) |
| History of dactylitis, n=3368 | 463 (14) |
| CRP (mg/L), n=3208 | 0.51 (11) |
| Patient Global (0-10), n=3336 | 4.1 (2.5) |
| BASDAI (0-10), n=3352 | 3.7 (2.4) |
| BASFI (0-10), n=3349 | 31 (2.7) |
| ASDAS (CRP), n=3155 | 2.0 (1.1) |
| Axial involvement (+/- peripheral) | 2955 (87.7) |
| History of uveitis, n=3368 | 724 (21) |
| History of psoriasis, n=3369 | 643 (19) |
| History of IBD, n=3366 | 194 (6) |
| Extra-articular manifestations (uveiitis, IBD, psoriasis) | 1369(41) |
| RDCI (0-9) | 0.7 (1.1) |
| Treatment | |
| -NSAID intake, n=3363 | 3025(90) |
| -NSAID total score (past 3 months) | 37 (46) |
| -current b/csDMARD | 2114 (63) |
| -current bDMARD | 1275 (38) |
| -current csDMARD | 1168 (35) |
| -current csDMARD only | 839 (25) |

*BMI=Body mass index; MRI=Magnetic Resonance Imaging; CRP=C-reactive protein; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS= Ankylosing Spondylitis Disease Activity Score calculated with CRP; IBD=Inflammatory Bowel Disease; RDCI= Rheumatic Disease Comorbidity Index; NSAID=Non-Steroidal Anti-inflammatory Drug; bDMARD=biologic Disease-Modifying Anti-Rheumatic Drugs; csDMARD= conventional synthetic Disease-Modifying Anti-Rheumatic Drug.*

**Table 2.** Uptake of bDMARDs: association with socio-demographic, clinical and treatment variables as well as indicators of the country socio-economic welfare.

| Independent predictors | Univariable analysis OR (95% CI) | Multivariable analysis OR (95% CI) n=2792 |
|---|---|---|
| Country health expenditure (high/medium vs low) | 1.71 (0.84,3.50) | 1.96 (0.94,4.10) |
| Age (years) | 1.01 (1.00,1.01) | 1.00 (0.99,1.01) |
| Male gender (vs females) | 1.18 (1.01,1.39) | 1.26 (1.04,1.53) |
| Axial (vs peripheral) disease | 1.48 (1.16,1.89) | 1.62 (1.15,2.28) |
| ASDAS | 0.82 (0.76,0.89) | 0.80 (0.73,0.87) |
| Sacroiliitis on X-ray | 1.75 (1.44,2.12) | 1.41 (1.12,1.78) |
| History of extra-articular manifestations | 1.46 (1.25,1.70) | 1.31 (1.08,1.58) |
| Total NSAID score (0-400), last 3 months | 0.99 (0.99,1.00) | 0.99 (0.99,1.00) |
| Past csDMARD use | 2.31 (1.96,2.73) | 2.08 (1.72,2.52) |
| Past bDMARD use | 2.64 (2.13,3.28) | 2.48 (1.93,3.19) |
| Education (secondary/university vs primary) | 0.79 (0.62,1.00) | 0.76 (0.52,1.13) |

**Table 3.** Uptake of csDMARDs: association with socio-demographic, clinical and treatment variables as well as indicators of the country socio-economic welfare

| Independent predictors | Univariable analysis OR (95% CI) | Multivariable analysis OR (95% CI) n=2792 |
|---|---|---|
| Country health expenditure (high/medium vs low) | 0.52 (0.26,1.03) | 0.32 (0.15,0.65) |
| Age (years) | 1.01 (1.00,1.02) | 1.00 (1.00,1.01) |
| Male gender (vs females) | 0.73 (0.61,0.87) | 0.76 (0.62,0.94) |
| Axial (vs peripheral) disease | 0.30 (0.24,0.39) | 0.31 (0.23,0.44) |
| ASDAS | 1.17 (1.07,1.27) | 1.16 (1.06,1.28) |

| | | |
|---|---|---|
| Sacroiliitis on X-ray | 0.53 (0.43,0.65) | 0.74 (0.58,0.94) |
| History of extra-articular manifestations | 1.39 (0.00,1.16) | 1.53 (1.23,1.90) |
| Total NSAID score (0-400) in last 3 months | 1.00 (1.00,1.01) | 1.00 (1.00,1.01) |
| Past csDMARD use | 0.39 (0.32,0.48) | 0.36 (0.28,0.45) |
| Past bDMARD use | 0.55 (0.42,0.73) | 0.73 (0.53,1.00) |

**Table 4**. Relationship between country-level socio-economic factors and bDMARD and csDMARD use, all tested individually in separate models (each cell represents a different model)

| | **bDMARD use** | | **csDMARD use** | |
|---|---|---|---|---|
| | **Univariable analysis** OR (95% CI) | **Multivariable analysis§** OR (95% CI) | **Univariable analysis** OR (95% CI) | **Multivariable analysis±** OR (95% CI) |
| GDP (high/medium vs low) | 1.57 (0.78,3.15) | 1.93 (0.91,4.06) | 0.59 (0.30,1.15) | 0.44 (0.21,0.91)* |
| Gini (high/medium vs low) | 0.84 (0.38,1.87) | 0.73 (0.31,1.72) | 0.76 (0.35,1.65) | 0.96 (0.39,2.37) |
| HDI (very high/high vs medium) | 2.16 (0.64, 7.27) | 2.12 (0.62, 7.31) | 0.32 (0.11,0.98)* | 0.29 (0.08,1.07) |

**p<0.05*

*GDP= Gross Domestic Product; Gini= measure of income inequality; HDI=Human Development Index*

*§ Refers to the multivariable model presented in table 2 and in which the variable health expenditures was replaced by the other country-level socio-economic factors, in separate models*

*± Refers to the multivariable model presented in table 3 and in which the variable health expenditures was replaced by the other country-level socio-economic factors, in separate models*

**Figure 1:** bDMARD uptake (%) by country. Crude and adjusted percentage use shown along with 95% CI based on models with socio-economic, socio-demographic and clinical variables. Countries ranked based on health expenditure: low (left) to high (right).

**Figure 2.** csDMARD uptake (%) by country. Adjusted and crude percentage use shown along with 95% CI based on models with socio-economic, socio-demographic and clinical variables. Countries ranked based on health expenditure: low (left) to high (right).