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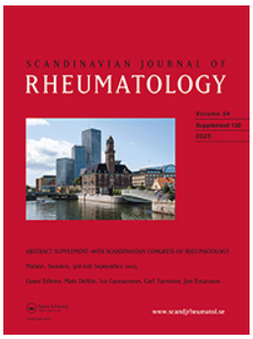

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Ratio between biological and targeted synthetic disease-modifying anti-rheumatic drugs and glucocorticoid use in various countries: results from METEOR

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Objective: To investigate globally the ratio between biological and targeted synthetic disease-modifying anti-rheumatic drugs (btsDMARDs) and glucocorticoid (GC) use in patients with rheumatoid arthritis (RA), in relation to country-level socioeconomic status (SES).

Method: Data on btsDMARD and GC use between 1 January 2007 and 13 September 2021 were extracted from the international observational METEOR RA registry. The ratio between the proportion of patients who had ever used a btsDMARD and those who had ever used a GC and never a btsDMARD, during 2 years of follow-up, was calculated per country. Associations between the btsDMARD/GC ratios and country-level indicators of SES were assessed with linear regression.

Results: Data from 10 856 patients covering eight geographically spread countries, of whom 8484 were from India, showed a wide range of drug use during 2 years of follow-up: btsDMARD (with or without GC), from 1% (South Africa, India) to 26% (Massachusetts, USA); GC and never btsDMARD use, 19% (UK) to 92% (South Africa). Higher country-level SES was related to a higher btsDMARD/GC ratio. For every additional 10 000 International $, GDP per capita, household net adjusted disposable income, and health expenditure per capita, the estimated increase in btsDMARD/GC ratio (range 0–1) was 0.1 (95% CI 0.05;0.1), 0.2 (95% CI 0.08;0.3), and 0.6 (95% CI 0.4;0.8), respectively.

Conclusion: In this analysis based on eight different countries, we show that the btsDMARD/GC ratio varies widely across countries. This was strongly associated with general country-level indicators of level of wealth, i.e. greater wealth was associated with a higher ratio.

The prognosis of rheumatoid arthritis (RA) has significantly improved since the introduction of biologic and targeted synthetic disease-modifying anti-rheumatic drugs (btsDMARDs). Correspondingly, current European Alliance of Associations for Rheumatology (EULAR) recommendations advise initiating btsDMARD therapy once first line conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy has failed and poor prognostic factors are present (1). However, despite the availability of an increasing number of biosimilars, btsDMARDs remain costly, which perpetuates the inequality in access to btsDMARD treatment around the world (1, 2). Several articles, including a publication from the Measurement of Efficacy of Treatment in the 'Era of Outcome' in Rheumatology (METEOR) registry, have demonstrated cross-country differences in btsDMARD prescription and suggest the possible influencing role of both a country's socioeconomic status (SES) and prescription and reimbursement rules (2–2).

A study based on the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) database, which included

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4363 patients with RA from 15 different countries, who were enrolled between January 2005 and October 2006, showed that the ratio between biological disease-modifying anti-rheumatic drug (bDMARD) and GC use strongly differed between countries (6). Since GCs have a rapid anti-inflammatory effect and cost considerably less than btsDMARD treatment, it may be hypothesized that in countries with lower SES, physicians are more likely to prescribe GCs instead of btsDMARDs owing to their better affordability. However, current international recommendations only advise short-term GCs as bridging treatment, because of the risk of adverse events attributed to long-term, especially high-dose, use of GCs (1).

Since in recent years more btsDMARDs, including less expensive biosimilars, have become available, and more studies on the effects of GC use have been published, patterns in btsDMARD and GC prescription may have changed (1, 7–9). Therefore, we aimed to investigate more recent data on the ratio between btsDMARD and GC use across different countries, and to assess whether the ratio between btsDMARD and GC use is indeed related to each country's SES.

Method

Data selection

Data on patient characteristics, disease activity, and medication use were collected from the METEOR registry (10). This is an international registry capturing non-protocolized data from daily clinical practice for patients with a clinical RA diagnosis. Except for a clinical RA diagnosis, there were no additional inclusion or exclusion criteria. Data can be entered into the registry by the treating rheumatologist. The registry follows all EULAR guidelines for data capture. For the current study, data were selected from patients newly diagnosed with RA (defined as patients starting treatment within 3 months of diagnosis), selected from countries that had contributed a minimum of 60 patients with a new diagnosis of RA between 1 January 2007 and 13 September 2021, with available data on medication use and a minimum follow-up duration of two visits. Data were gathered non-protocolized and anonymously, and complied with local protection and security regulations in all participating countries. Therefore, medical ethics board approval was not required.

Outcome measures

For each country, the proportion of patients who (i) had used a btsDMARD (with or without a GC) or (ii) had used GCs, with and without using a btsDMARD, at some time during 2 years of follow-up, was calculated. The btsDMARDs that were considered, based on availability for routine treatment during the indicated period, included etanercept, adalimumab, infliximab, rituximab, certolizumab, tocilizumab, abatacept, golimumab, tofacitinib, and baricitinib. The GCs that were considered were those given orally or systemically, and included deflazacort, methylprednisolone, dexamethasone, triamcinolone acetonide, prednisone, and prednisolone. Intra-articular injections were not considered because of irregularities and missing data on such injections. Owing to a lack of data on dosage and duration of GC use, these were not taken into account. A ratio between the proportion of patients with btsDMARD use (with or without GC) and with GC use (without a btsDMARD) was calculated for each country (btsDMARD/GC ratio) and compared with different publicly available country-level indicators of SES, similar to those used in previous reports (4, 5). The indicators for SES were derived from web-based sources (for which the access dates have been intentionally retained to match the timing of registry data extraction, ensuring consistency in the temporal alignment of all data sets used in the analysis) (11–14), and included gross domestic product (GDP) per capita, household net adjusted disposable income, health expenditure per capita, and average annual minimum wage. To ensure comparability, the indicators were expressed in international dollars (Intl $) through purchasing power parities. These are the rates of currency conversion that equalize the purchasing power of different currencies by eliminating the differences in price levels between countries (15). csDMARD use was not considered when calculating the ratio because it was not assumed to contribute to the difference in use of GCs and btsDMARDs in newly diagnosed RA patients, during the first years of treatment, at a country level. btsDMARD and GC costs were derived from filled out questionnaires sent to at least two rheumatologists based in the countries included (Supplementary Data S1), as previously described by Putrik et al (5). The figures reflected the official prices of the industry, and for each country the lowest prices were used, converted to Intl$ at the rate given on 9 November 2021. For each btsDMARD and GC, the annual costs were calculated, which reflect the most common treatment schemes (Supplementary Data S2) (2). From these annual costs, the minimum working months required to afford 30 days of btsDMARD therapy and the minimum working hours required to afford 30 days GC treatment were calculated per country.

Based on the answers to these questionnaires, a composite score for clinical eligibility to start a btsDMARD and access to btsDMARDs, similar to that described by Putrik et al, was calculated, by categorizing (i) the total number of reimbursed btsDMARDs, (ii) the total score for perceived access to medication, and (iii) the annual average btsDMARD costs into quartiles, and scoring them from 0 to 3, with an optimum score of 9 indicating 'highest level of access' (Table 1) (2). In addition, a composite score was computed per country regarding clinical eligibility for initiating a btsDMARD, by categorizing (i) minimal

Table 1. Composite scores for (A) clinical eligibility criteria for the start of btsDMARDs and (B) access to btsDMARDs.

	0	1	2	
(A) Clinical eligibility for btsDMARDs				
Is there any requirement for disease duration?	Any requirement	No requirement	na	
Number of DMARDs to be failed	> 2	2	< 2	
Level of DAS28	> 3.2	≤ 3.2	No requirement	
	0	1	2	3
(B) Accessibility to btsDMARDs				
Number of reimbursed btsDMARDs	0	1–6	7–8	10
Average annual price of all reimbursed btsDMARDs	Highest quartile	Second quartile	Third quartile	Lowest quartile
Average score on the six acceptability questions	Highest quartile	Second quartile	Third quartile	Lowest quartile

These composite scores are calculated on a country level. For each of the three items in the clinical eligibility score, 2 points can be gained. For each of the three items in the accessibility score, 3 points can be gained. When scores are based on quartiles, quartiles are defined based on data from all available countries. An additional explanation has been published previously (2).
btsDMARD, biological andtargeted synthetic disease-modifying anti-rheumatic drug; DAS28, Disease Activity Score based on 28-joint count; na, not applicable.

disease duration, (ii) number of csDMARDs to be failed (including type, number, and length of treatment), and (iii) clinical criteria such as level of disease activity [Disease Activity Score based on 28-joint count (DAS28)], and scoring them from 0 to 2. The composite score comprised the simple sum of the scores on the individual criteria, with a higher score indicating easier access (Table 1).

Statistical analysis

Patient characteristics and disease activity were analysed descriptively, based on complete cases. Data on medication use were not missing, by definition. The year 2007 was chosen as the baseline to analyse a potential change over time compared to the observations from the QUEST-RA database, which included data from patients until 2006 (6). At a country level, data were compared through descriptive statistics. Associations between the indicators of SES and the btsDMARD/GC ratio were assessed using univariable linear regression analyses at a country level, and selecting the indicators of SES as a predictor. We chose to present unadjusted models because differing patient characteristics within a country were not assumed to act as a confounder for the investigated associations at a country level. For example, it is difficult to imagine how differences in the proportion of anti-citrullinated protein antibody (ACPA)-positive patients could influence both the dependent (btsDMARD/GC ratio) and independent (country-level SES) variables. Other potential confounders at a country level, such as life expectancy or out-of-pocket payments, and their relationship with country-level SES, seem complex and unlikely to be unidirectional. In other words, life expectancy could influence country-level SES, but country-level SES may also influence life expectancy. To avoid overadjustment, these variables were not considered as potential confounders. Sensitivity analyses were performed including all patients using btsDMARDs, irrespective of whether they were new users or not. All analyses were performed using Stata SE version 16 (StataCorp, College Station, TX, USA).

Results

Country and database characteristics

Data from eight countries were analysed, contributing a total of 10 856 patients. The majority of patients were from India (state of Maharashtra). Other included countries were Mexico (Monterrey, Nuevo León), Portugal, South Africa, Spain, the Netherlands, the UK, and the USA (state of Massachusetts). Table 2 displays an overview of average baseline characteristics per country. Sixteen countries including 283 patients were excluded as they did not contribute a minimum of 60 patients as of 1 January 2007, and one country was excluded because it included patients from a bDMARD registry only (Figure 1).

The average number of included patients was 1357 [ranging from 64 (Spain) to 8484 (India)], with a median follow-up duration of 1.4 [interquartile range (IQR) 0.5–3.3] years. In addition, the average baseline characteristics varied between countries. The average baseline DAS28 was 5.2 [ranging from 4.5 (Netherlands) to 6.3 (India)]. In most countries, the average disease activity at baseline was high (DAS28 > 5.1). Patients treated in the Netherlands and Spain had moderate disease activity (DAS28 between 3.1 and 5.1). The average age at diagnosis was 52 years [ranging from 46 (India) to 58 years (UK)]. The average symptom duration before diagnosis was 2.3 years [ranging from 1.1 (UK) to 5.5 years (India)]. Overall, patients from the Netherlands and the UK had a shorter symptom duration and a higher age at diagnosis (Table 2).

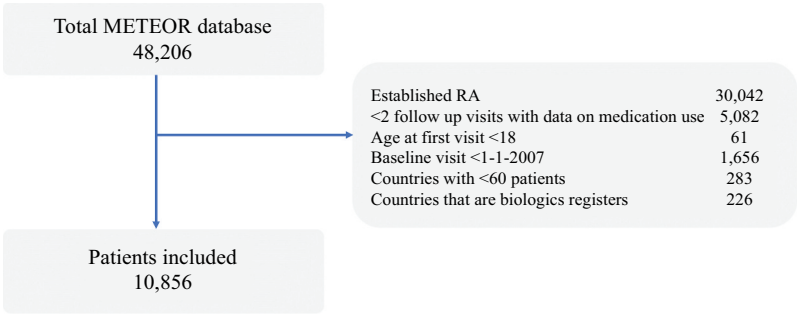

Figure 1. Patient selection flowchart. RA, rheumatoid arthritis.

Table 2. Baseline characteristics per country.

	USA	NL	PT	SA	ES	UK	IN	MX
Included patients, n (%)	215 (2)	369 (3)	334 (3)	754 (7)	64 (1)	466 (4)	8484 (78)	170 (2)
Female (%)	74	68	73	82	86	64	85	84
RF^+ (%)	44	49	61	93	83	66	82	48
$ACPA^+$ (%)	39	46	51	75	81	62	51	28
Current or ever smoker (%)	47	27	24	24	36	55	2	14
Age at diagnosis (years), mean ± sd	53 ± 14	57 ± 16	55 ± 15	50 ± 13	52 ± 15	58 ± 15	46 ± 12	48 ± 14
Symptom duration before diagnosis (years), mean ± sd	2.0 ± 3.8	1.5 ± 4.0	1.7 ± 3.1	3.6 ± 4.6	2.1 ± 10.7	1.1 ± 2.3	5.5 ± 6.1	1.4 ± 3.3
DAS28, mean ± sd	5.1 ± 1.4	4.5 ± 1.5	5.1 ± 1.5	5.5 ± 1.4	4.8 ± 1.5	5.1 ± 1.3	6.3 ± 1.3	5.1 ± 1.6

Number of sites from which data were collected per country: USA (State of Massachusetts) 1; NL, 6; PT, 16; SA, 2; ES, 7; UK, 3; IN (State of Maharashtra), 3; MX (State of Nuevo Léon), 2. (Sites are displayed per country in Supplementary Table S10.)
Missingness per baseline characteristic (%): female (0.3); RF+ (1.5); ACPA+ (33.0); Current or ever smoker (7.5); age at diagnosis (0.7); symptom duration before diagnosis (4.1); DAS28 (26.0).
ACPA, anti-citrullinated protein antibody; DAS28, Disease Activity Score based on 28-joint count; RF, rheumatoid factor; ES, Spain; IN, India; MX, Mexico; NL, Netherlands; PT, Portugal; SA, South Africa; UK, United Kingdom; USA, United States of America.

Countries also showed considerable differences in indicators of SES. GDP per capita ranged from 6454.2 Intl$ in India to 63543 Intl$ in the USA. The number of months required to work in order to afford 30 days of btsDMARD treatment ranged from 0.1 in the Netherlands to 8.7 in India. Furthermore, the number of hours required to work in order to afford 30 days GC treatment ranged from 0.6 in the Netherlands and the UK to 24.9 in Mexico (Supplementary Table S1).

btsDMARD and GC use per country

The btsDMARD/GC ratio differed between high- and low-income countries. Within 2 years of follow-up, the btsDMARD/GC ratio was the highest in the USA (0.6) and the lowest in South Africa (0.08) and India (0.1) (Table 3). Overall, the percentage of patients using a GC (without using a btsDMARD) during 2 years of follow-up was greater than the percentage of patients using a btsDMARD (Figure 2). The proportion of patients using a btsDMARD was the highest in the USA (26%) and the lowest in South Africa (1%), whereas the proportion of patients using a GC (without using a btsDMARD) was the highest in South Africa (92%) and the lowest in the UK (19%).

The majority of patients initiated a btsDMARD or GC within the first year of follow-up (Supplementary Table S3). Overall, countries had a similar proportion of

Table 3. btsDMARD/GC ratio per country, during maximum 2 years of follow-up.*

	USA	NL	UK	ES	PT	MX	SA	IN
btsDMARD/GC ratio baseline	0.105	0.070	0.012	0	0.026	0	0	0.002
btsDMARD/GC ratio within 1 year	0.409	0.263	0.058	0.123	0.073	0.015	0.009	0.008
btsDMARD/GC ratio within 2 years	0.549	0.429	0.125	0.217	0.123	0.023	0.009	0.010

*Overall median follow-up duration was 1.1 years (interquartile range 0.5–1.7 years). Not all countries had a median follow-up duration of more than 1 year (Mexico and South Africa). (Follow-up duration per country is provided in Supplementary Table S9.)
btsDMARD, biological and targeted synthetic disease-modifying anti-rheumatic drug; GC, glucocorticoid; MTX, methotrexate; ES, Spain; IN, India; MX, Mexico; NL, Netherlands; PT, Portugal; SA, South Africa; UK, United Kingdom; USA, United States of America.

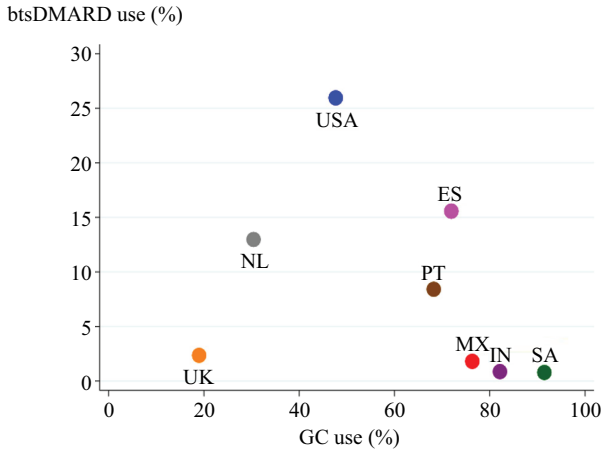

Figure 2. Proportion of newly diagnosed patients who used either a btsDMARD (with or without a GC) or a GC (without using a btsDMARD) during a maximum period of 2 years of follow-up. btsDMARD, biological and targeted synthetic disease-modifying anti-rheumatic drug; GC, glucocorticoid; ES, Spain; IN, India; MX, Mexico; NL, Netherlands; PT, Portugal; SA, South Africa; UK, United Kingdom; USA, United States of America.

GC use; however, countries did differ with regard to the proportion of patients using a GC without a btsDMARD. Of those who started btsDMARD therapy, the majority had previously initiated a GC. Although GC use was among the lowest in the UK and the Netherlands, in these countries a relatively low number of patients had used a btsDMARD. Moreover, Spain and Portugal had a similar number of patients using a btsDMARD compared to the Netherlands, while also having a higher number of patients using a GC (without using a btsDMARD) (Supplementary Table S2). In all included countries, when a GC was prescribed during the 2 year follow-up, it was, for the majority, part of the initial treatment strategy (started within 3 months of diagnosis). In Supplementary Table S13, the median (IQR) GC starting dose at baseline is described per country. Detailed information on GC doses over time was lacking. Over all countries, for patients who had used a btsDMARD during 2 years of follow-up and were prescribed a GC not as part of the initial treatment strategy, the time to initiating a btsDMARD was shorter (Supplementary Tables S11 and S12). In the Netherlands and the UK, the majority of patients were treated with a csDMARD (or csDMARDs) only. The proportion of patients not treated with a btsDMARD or with a GC throughout the first 2 years of follow-up ranged from 8% in South Africa to over three-quarters of the total number of included patients in the UK (79%) (Supplementary Table S2).

In countries with a median follow-up duration of more than 1 year, the btsDMARD/GC ratio increased during follow-up (Table 3), indicating an increase in the number of patients using a btsDMARD (with or without a GC) over time.

Country's SES and ratio of btsDMARD/GC use

The btsDMARD/GC ratio was found to have a significant positive association with several indicators of SES (Figure 3). For every additional 10 000 Intl$ GDP per capita, the estimated increase in btsDMARD/GC ratio (range 0 to 1) was 0.1 [95% confidence interval (CI) 0.05;0.1, p = 0.001]. Specifically, with increasing country wealth, the number of patients being prescribed a btsDMARD increased and/or the prescription of GCs decreased. Moreover, an increase of 10 000 Intl$ in household net adjusted disposable income and health expenditure per capita resulted in an estimated increase in btsDMARD/GC ratio by 0.2 (95% CI 0.08;0.3, p = 0.005) and 0.6 (95% CI 0.4;0.8, p = 0.001).

The btsDMARD/GC ratio was not statistically significantly associated with the composite score for accessibility to btsDMARD treatment (β = 0.01,

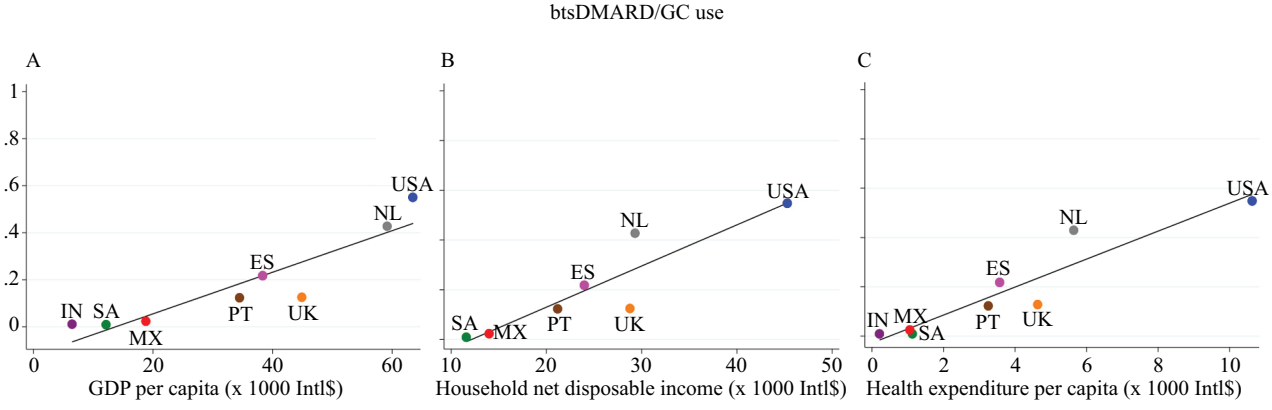

Figure 3. Associations between (A) GDP per capita (Intl$), (B) household net disposable income (Intl$), and (C) health expenditure per capita (Intl $) and the ratio between the proportion of newly diagnosed patients using a btsDMARD (with or without a GC) or using a GC (without btsDMARD use) during 2 years of follow-up. btsDMARD, biological and targeted synthetic disease-modifying anti-rheumatic drug; GC, glucocorticoid; GDP, gross domestic product; ES, Spain; IN, India; MX, Mexico; NL, Netherlands; PT, Portugal; SA, South Africa; UK, United Kingdom; USA, United States of America.

95% CI −0.1;0.1, p = 0.79) or with the composite score for clinical eligibility to btsDMARD treatment (β = 0.1, 95% CI −0.02;0.2, p = 0.09) (Supplementary Figure S4). The USA had the highest btsDMARD/GC ratio despite having the lowest composite score for perceived accessibility to btsDMARDs. India had one of the lowest btsDMARD/GC ratios despite having a similar composite score for clinical eligibility to start btsDMARD treatment to the USA. Sensitivity analyses, including all patients using btsDMARDs, irrespective of whether they were new users or not, produced similar results to the primary analyses (Supplementary Figures S1–3 and Supplementary Tables S7 and S8).

Discussion

In this study, we provide evidence of ongoing differences in btsDMARD and GC prescription across eight different countries during 2 years of follow-up, associated with a country's SES. As hypothesized, we found that countries with lower SES had a lower btsDMARD/GC ratio, through both lower rates of btsDMARD use and higher GC use. This was most marked in the countries with the lowest GDP per capita (India, South Africa, Mexico). The relatively infrequent use of btsDMARDs in low-income countries has been reported previously (2, 5). Similarly to the QUEST-RA study, which compared the bDMARD/GC ratio in 15 different countries from longitudinal data until 2006, GC use remains the lowest in the Netherlands and the UK, and bDMARD use has stayed the lowest in lower income countries (6). To suppress disease activity, GCs seem to be needed more often in these lower income counties. In South Africa and India, nearly all patients used a GC, without ever having used a btsDMARD, during the first year of follow-up. In these countries, not being able to switch to btsDMARDs, patients possibly use GCs for longer durations than those recommended in international clinical guidelines. GCs have been demonstrated to be effective in the majority of patients and discontinuation of GCs has been associated with disease flares (16). However, continued GC use, particularly in higher doses and/or for longer periods, may lead to more unwanted side effects or serious adverse events (17–23). Therefore, current treatment recommendations advise tapering GCs within 3 months (1). Unfortunately, owing to incomplete data on GC duration and dosage, these were not considered in this study and warrant further investigation. Of note, the proportion of GC use was generally higher in the QUEST-RA cohort than in this METEOR cohort, which could be attributable to differences in inclusion criteria, such as disease duration. Furthermore, the median follow-up duration in Mexico and South Africa was only 1 year, which could have led to a misleading representation of the overall ratio between btsDMARD and GC use in these countries. Nevertheless, the number of patients who start GCs in the first year of follow-up remains greater than in the other included countries with a higher level of wealth.

Previous studies have shown that lower SES is associated with worse disease activity (3, 4, 24, 25). Access to bDMARDs is influenced by factors such as SES, affordability, and restrictions due to prescription and reimbursement rules. Thus, lower SES contributes to difficulties in adhering to international treatment recommendations and to an inverse relationship between access to bDMARDs and disease activity (3, 2,4–6, 24). We were unable to observe an association between the btsDMARD/GC ratio and restrictions due to prescription and reimbursement rules about btsDMARDs themselves. However, in line with previous publications, these restrictions were approximated by the composite scores based on questionnaires for access to btsDMARDs, regarding btsDMARD costs and reimbursement rules and clinical eligibility criteria guiding btsDMARD therapy. As a result, these composite scores are a simplified depiction and may not capture real-world practice. Previous studies also indicate that there is likely to be a complex interplay of factors that play a role, beyond the accessibility and affordability of btsDMARDs, in poorer health outcomes (24, 26). These factors were not captured in the current study.

This is the first study to look at the ratio between btsDMARDs and GCs in newly diagnosed patients from the start of treatment, using more recent data, across eight countries, including a large number of 10 856 patients followed in daily clinical practice, from different healthcare systems. Furthermore, we were able to include data from countries such as South Africa, Mexico, and India, that are not regularly included in similar studies. However, this study also holds several limitations, stemming from the use of real-life observational data (e.g. case ascertainment, completeness, and reliability of data without case validation) and geographical representation. Only a limited number of hospitals contributed per country, which may introduce selection bias, and we cannot verify the extent to which they are representative of the entire country (4). Depending on how healthcare is organized locally, the type of hospital (e.g. private or public) may impact btsDMARD and GC prescribing behaviour. The prescription rates observed in this cohort may therefore differ from those observed in other cohorts, and caution should be applied regarding the generalizability of the observed results (27, 28). In addition, general country indicators may not fully reflect social welfare as they do not account for factors that influence well-being on an individual level, which may have influenced the magnitude of the observed inequalities. Also, similarly to other studies, the composite score for accessibility was not derived using real prices but by using official industry prices, as the former were not readily available. Nevertheless, in

this study, indicators of SES were similar to those used in previous studies, and they were converted to Intl$ to ensure comparability across different countries (2,4,5). Additional limitations were that a ratio was used to compare rates of prescribing btsDMARDs to GCs without factoring in the role of prescription of other drugs, such as csDMARDs. Furthermore, the ratio does not display the dosage, duration of use, rate of discontinuation, and reasons for certain treatment choices during the follow-up period. These time-dependent factors may also be influenced by patient-specific factors (disease activity, adherence to treatment, adverse effects, and comorbidities), which are also not reflected in the ratio. Furthermore, outliers may have influenced the observed associations, which were based on a limited number of countries. Lastly, follow-up was limited to 2 years, and it is unknown whether these results can be extrapolated beyond this follow-up period.

Conclusion

This study provides evidence of persisting disparities in btsDMARD and GC use across countries, despite recent positive developments in treatments and treatment strategies. This finding endorses the view that additional steps are urgently required in order to offer equal treatment opportunities for patients in countries with different levels of wealth.

Disclosure statement

Sytske Anne Bergstra has received a grant from Pfizer and speaker fees from Benecke. The remaining authors declare that they have no competing interests relevant to this study.

Data availability statement

The data set used and analysed during the current study is available from the corresponding author upon reasonable request.

Supplemental material

Supplemental data for this article can be accessed online at https://doi.org/10.1080/03009742.2025.2515730

Ethics and informed consent

The METEOR registry contains anonymized data which were gathered during daily practice. Treatment, timing of follow-up visits, and measurements were non-protocolled and complied with local protection and security regulations in all participating countries. Therefore, medical ethics board approval was not required.

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